Michigan Department of Natural Resources and the Environment

Interoffice Communication

TO: File for 4,4'-Diaminodicyclohexylmethane (CAS# 1761-71-3)

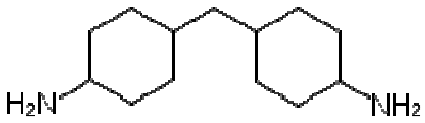
FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Review of Screening Level for 4,4'-Diaminodicyclohexylmethane (CAS# 1761-71-3)

DATE: March 9, 2011

The initial threshold screening level (ITSL) for 4,4'-diaminodicyclohexylmethane is 6 µg/m3 based on an annual averaging time.

4,4'-Diaminodicyclohexylmethane (CAS # 1761-71-3) also known as 1,4-bis(aminocyclohexyl)methane, 4-[(4-aminocyclohexyl)methyl]cyclohexylamine, and para-aminocyclohexyl methane (PACM) has a molecular weight of 210.363 and is a highly corrosive, clear to yellowish-white liquid or white to brownish solid depending on the ratios of isomers. The chemical can be a mixture of the following isomers: trans, trans isomer; cis, trans isomer (p-p PACM); cis, cis isomer, or o-p' PACM. It is insoluble in water and is sensitive to decomposition in air and light. 4,4'-Diaminodicyclohexylmethane is an optically clear material which is used in polyamide fibers and other synthetic fiber polymers, as a curing agent for the epoxy industry, in preparations of yellow azo pigments, and in resins.



4,4'-Diaminodicyclohexylmethane

A literature review was conducted to determine an initial threshold screening level (ITSL) for 4,4'-diaminodicyclohexylmethane. The following references and databases were searched to derive the above screening level: EPBCCD, United States Environ-mental 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) 2008 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (search performed 10/18/10), National Library of Medicine (NLM)-online, EPA

Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB). RfC or RfD values were unavailable. There is no NIOSH recommended exposure limit data available for this compound or a threshold limit value from ACGIH. No 7-day inhalation studies which would yield a LOAEL or NOAEL and no acute inhalation data where an LC_{50} can be derived.

There is a study by Kennedy, G.L. 1991, which investigated the acute and repeated oral toxicity of 4,4'-diaminodicyclohexylmethane in rats and dogs. An acute oral toxicity study was performed using a single oral dose of either 100, 200, 300, 450, 670, 1,000, or 1,250 mg/g administered by gavage to one rat at each dose level. Rats were weighed and examined for pharmacotoxic signs daily for up to 14 days post-dosing at which time, the rats were sacrificed and examined grossly for lesions. Lethality occurred in rats at 1,000 mg/kg or greater. These doses produced signs of discomfort, pallor, in coordination and death from acute gastritis within 24 hours. The rat treated at 670 mg/kg demonstrated all of the above signs but survived the 14-day dosing period. This rat showed continual weight loss for 10 days followed by recovery, but the animal still weighed 10 g less than pre-dosing when sacrificed. Pathological examination revealed healing gastritis with ulceration. The same changes were seen at 450 mg/kg, with the weight loss persisting for 7 days. No outward signs of response were seen in rats receiving 100-300 mg/kg, but gastric changes were seen at 200 and 300, but not at 100 mg/kg.

Kennedy also performed a repeated oral toxicity study on six Crl:CD rats using oral doses of 200 mg/kg 4,4'-diaminodicyclohexylmethane. Rats did not tolerate well repeated oral doses of 200 mg/kg. One rat died after the 10th dose and two others were sacrificed at the point of death on the first recovery day. During the first treatment week the rats showed increasing discomfort. Body weights showed a continual decline over the testing period. During the second treatment week the rats were generally inactive. Pathological examination revealed subchronic gastritis with ulceration. Liver injury, characterized by vacuolated cells in the centrilobular regions, was seen in three of the five rats examined at or near the 10th dose. One animal that was allowed a 10-day recovery period became more active (toward normal), began to gain weight and appeared to return to good condition. No pathological changes were detected in this rat following the recovery period.

Repeated oral toxicity dosing in 3 beagles was performed by Kennedy, who used an initial dose of 1,000 mg/kg 4,4'-diaminodicyclohexylmethane. This dose level caused loss of appetite so dosing was discontinued for 1 week. After doses of 500 mg/kg, the same loss of appetite was seen. The dose was further reduced to 50 mg/kg and then to 25 mg/kg to prevent both excess salivation and decreased food intake. After 15 treatments at 25 mg/kg, the dogs appeared in good condition, excess salivation was absent and food consumption appeared normal; the dose was raised to 50 mg/kg for the remainder of the study. After

153 treatments, excessive salivation was seen and the tongues were swollen and edematous. These conditions persisted for the remainder of the testing period. One dog became lethargic and responded slowly to external stimuli after 244 doses. Treatment was discontinued for 14 days without any improvement. Dosing on this dog was continued for 4 days after which the dog was sacrificed and pathological examination revealed gastric ulceration, nephritis, and fatty changes in the liver. One dog showed marked inflammation of the mouth after 316 doses and was sacrificed. Examination revealed chronic gastritis, nephritis, and marked infiltration of fat into the liver. The final dog continued to display a swollen tongue with marked salivation until sacrificed after 411 treatments. Examination detected only mild nephritis in this dog. Cytoscopic examination during the study showed an increasing engorgement of blood vessels as the treatment period continued. No evidence of bladder injury was found in two of the dogs, in the third dog, one small area on the lower ventral wall of the bladder showed evidence of hemorrhage which was likely caused by the examination procedure and not 4,4'-diaminodicyclohexylmethane.

The 18 month dog study used 3 dogs, and only one of which survived to the end of the study. The animal deaths (2/3) represent a Frank Effect Level, therefore the 18-month study was inappropriate to use to develop a screening level. No mention of controls were discussed. The 2 week rat study dosing with 200 mg/kg 4,4'-diaminodicyclohexylmethane was used for risk assessment as 6 rats were used and five of the rats survived until the 10th dose. This study also did not mention controls, but the rat that was allowed a 10 day recovery appeared to be normal with no pathological changes, which suggests that the effects of 4,4'-diaminodicyclohexylmethane are not permanent in cases of ingestion. Kennedy also performed eye irritation studies, which cannot be used as part of an air risk assessment , but due to the corrosive nature of this compound, corrosive effects of 4,4'-diaminodicyclohexylmethane causes permanent damage to eye tissue and eye protection is strongly suggested when working with this chemical.

Based on Rule 232(1)(e) the ITSL is determined as follows:

$$ITSL = \frac{LOAEL}{35 \times 100 \times UF} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

Where:
W_A = Body weight of experimental animal in kilograms (kg).
I_A = Daily inhalation rate of experimental animal in cubic meters/day.
b = Absorption efficiency by the oral route of exposure.
a = Absorption efficiency by the inhalation route of exposure.
UF = A value from 1 to 10 determined on a case-by-case basis, considering type and severity of effect.

The LOAEL is 200 mg/kg from the rat 10 day repeated oral toxicity study. The W_A is the default value for a non-gender rat is 0.395 kg. The I_A is determined by the following equation taken from EPA 1988 determined below:

$$I_A = 0.80 \times W^{0.8206}$$

Where:
I = Inhalation rates in m3/day
W = Body weight (kg)

$$I_A = 0.80 \times 0.395^{0.8206} = 0.373\, {}^{m^3}\!/_{day}$$

The value b/a is not known and therefore a default value of 1 is used. The UF of 10 is used to extrapolate from a rat to human. Using the above equation:

$$ITSL = \frac{200\, {}^{mg}\!/_{kg}}{35 \times 100 \times 10} \times \frac{0.395 kg}{0.373\, {}^{m^3}\!/_{day}} \times 1 = 0.006051\, {}^{mg}\!/_{m^3} = 6.051\, {}^{\mu g}\!/_{m^3}$$

The ITSL rounded to one significant figure is 6 µg/m^3. Based on rule 232(2)(c) the averaging time is annual.

Based on the above data, the ITSL for 4,4'-diaminodicyclohexylmethane is 6 µg/m^3 based on an annual averaging time.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

EPA. 1988. Recommendation for and documentation of biological values for use in risk assessment. PB 88-179874.

Kennedy, G.L. Jr. 1991. Toxicity of 1,4-Bis(aminocyclohexyl)methane. Journal of Applied Toxicology, vol 11(5):367-371.

DL:lh