MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 4,4'-Methylenedianiline (CAS # 101-77-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: April 29, 2016

SUBJECT: Screening Level for 4,4'-Methylenedianiline (CAS# 101-77-9)

The initial risk screening level (IRSL) for 4,4'-methylenedianiline (CAS # 101-77-9) is 0.022 $\mu g/m^3$ annual averaging time and the secondary risk screening level (SRSL) is 0.22 $\mu g/m^3$ annual averaging time.

4,4'-Methylenedianiline (MDA) is also known as bis(4-amino)methane, 4,4'-diaminodi-phenylmethane, and diphenylmethanediamine is a pale brown, crystalline solid with a faint, amine-like odor and a molecular weight of 198.27 g/mol. It is used: for making polyurethane foams; as hardeners in epoxy resins and adhesives; and in the production of high-performance polymers. The International Agency for Research on Cancer (IARC) lists MDA is a class 2B carcinogen, which means *possibly carcinogenic to humans*. An accidental mass poisoning occurred near Epping, Essex, United Kingdom in 1965 where 84 individuals ate bread made with flour that was contaminated with MDA. The compound caused reversible hepatotoxicity evidenced by jaundice of the affected individuals (Kopelman et al., 1966).

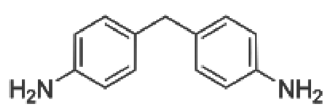

Figure 1. Structure of 4,4'-Methylenedianiline (MDA).

A literature review was conducted to determine an initial risk screening level (IRSL) for MDA. The following references and databases were searched to derive the above screening level: 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 (SciFinder) [CAS search performed on 4/5/16], National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, and EPA Toxic Substance Control Act Test Submission Database (TSCATS).

IRSL Derivation:

A study by the National Toxicology Program (NTP, 1983) used male and female F344 rats and B6C3F_1 mice (50 per sex, species, and exposure group) exposed to 4,4'-methylenedianiline hydrochloride via drinking water. 4,4'-Methylenedianiline dihydrochloride was used because 4,4'-methylenedianiline is not stable in feed or water also, as 4,4'-methylenedianiline dihydrochloride is not stable in feed, it was decided to perform this experiment in water. The dosage of 0, 150, or 300 ppm methylenedianiline dihydrochloride was administered in tap water, *ad libitum*; drinking water of controls adjusted to pH of the 300 ppm formulation for 103 weeks. The dose of MDA was calculated to determine the amount consumed per day per kilogram of body weight. For male F344 rats the dose groups were 0, 9, and 16 mg/kg bw/day. For female rats the dose groups were 0, 10, and 19 mg/kg bw/day. For B6C3F_1 mice the calculated dose groups were 0, 25, and 57 mg/kg bw/day for males and 0, 19, and 43 mg/kg bw/day for females. "No significant differences in survival were observed between any groups of either sex of rats" (NTP, 1983). "In mice the survival of the high dose group of male mice was significantly reduced when compared with both that of the low dose and the control groups. No other significant differences in survival were observed between any groups of either sex" (NTP, 1983). "Under the conditions of these studies, 4,4'-Methylenedianiline dihydrochloride was carcinogenic for F344/N rats and B6C3F_1 mice of each sex, causing significantly increased incidences of thyroid follicular cell carcinomas in male rats, thyroid follicular cell adenomas in female rats and in mice of each sex, C-cell adenomas of the thyroid gland in female rats, neoplastic nodules in the liver of male rats, hepatocellular carcinomas in mice of each sex, adenomas of the liver and malignant lymphomas in female mice, and adrenal pheochromocytomas in male mice" (NTP, 1983). The table below gives a summary of the tumor incidences in mice and rats.

	Control	**Low Dose**	**High Dose**
Male Rats			
Neoplastic nodules in the liver	1/50	12/50	25/50
Thyroid follicular cell carcinomas	0/49	0/47	7/48
Female Rats			
Thyroid follicular cell adenomas	0/47	2/47	17/48
C-cell adenomas of the thyroid gland	0/47	3/47	6/48
Male Mice			
Thyroid follicular cell adenomas	0/47	3/49	16/49
Hepatocellular carcinomas	10/49	33/50	29/50
Adrenal pheochromocytomas	2/48	12/49	14/49
Female Mice			
Thyroid follicular cell adenomas	0/50	1/47	13/50
Hepatocellular carcinomas	1/50	6/50	11/50
Adenomas of the liver	3/50	9/50	12/50
Malignant lymphomas	1/46	1/47	3/49

Each tumor incidence was run on the EPA's Benchmark Dose Software (version 260.1) using the multi-stage cancer model. A linear extrapolation from the lower 95% confidence limit on dose as the point of departure to zero response at zero dose. The cancer slope factor was then calculated from this benchmark dose lower confidence limit (BMDL) and the benchmark dose associated with 10% extra risk (BMR) as shown below:

$$Cancer\ slope\ factor = \frac{BMR}{BMDL} = q_1^*$$

After reviewing the results, the best statistical fit was for the male rat neoplastic nodules in the liver giving a benchmark dose lower confidence limit (BMDL) of 2.33437 mg/kg bw/day as the point of departure and a cancer slope factor of 0.0428381 when BMR is 0.1. Rule 231(3)(f) can be used to derive an inhalation slope factor from an oral slope factor by using the following equation:

$$q_1^*({}^{\mu g}/_{m^3})^{-1} = q_1^*\,({}^{mg}/_{kg\ bw/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{a}{b}$$

Where:
a = absorption efficiency by inhalation route of exposure.
b = absorption efficiency by oral route of exposure.

In the absence of absorption efficiency data the value for a/b = 1. To determine q_1^* (${}^{mg}/_{kg\ bw\ /day}$), the oral slope factor for humans, the following equation is used:

$$q_1^*\ animal\ \times T = q_1^*\ human$$

To determine T, the interspecies scaling factor, the following equation is used:

$$T = (\frac{W_H}{W_A})^{\frac{1}{4}} = (\frac{70\ kg}{0.399\ kg})^{\frac{1}{4}} = 3.6394$$

Where:
W_H = Average weight of an adult human and assumed to be 70 kilogram.
W_A = Body weight of male rat in kilogram.

The mean body weight for the male F344/N rat in this study was 0.399 kg. Adding the information to the above equation gives a T of 3.6394. The T value from the above equation and the q_1^* animal value (which is the multi-stage cancer slope factor of 0.0428381 in mg/kg bw/day from the BMDS multi-stage cancer model) were to determine the q_1^* for humans as follows:

$$q_1^*\ human = 0.0428381\ {}^{mg}/_{kg\ bw/day} \times 3.6394 = 0.1559\ {}^{mg}/_{kg\ bw/day}$$

Inserting the value of q_1^* human oral slope factor in mg/kg bw/day into the equation to determine the q_1^* inhalation in $(\mu g/m^3)^{-1}$ found in Rule 231(3)(f) above gives:

$$q_1^*\,({}^{\mu g}/_{m^3})^{-1} = 0.1559\,({}^{mg}/_{kg/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1} = 0.00004454({}^{\mu g}/_{m^3})^{-1}$$

Rule 231(1) was used in the equation below to develop the IRSL:

$$IRSL = \frac{1\ \times 10^{-6}}{Unit\ Risk}$$

Where:
Unit Risk = Additional lifetime cancer risk occurring in a population in which all individual are exposed continuously for life to a concentration of 1 microgram per cubic meter of the chemical in the air they breathe.
Unit Risk = q_1^*.

$$IRSL = \frac{1 \times 10^{-6}}{0.00004454({}^{\mu g}/_{m^3})^{-1}} = 0.02245\,{}^{ug}/_{m^3} = 0.022\,{}^{\mu g}/_{m^3}$$

The initial risk screening level (IRSL) for 4,4'-methylenedianiline (CAS# 101-77-9) is 0.022 μg/m^3 annual averaging time and the secondary risk screening level (SRSL) is 0.22 μg/m^3 annual averaging time.

References:

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

Kopelman H, Robertson MH, Sanders PG, and Ash I. 1966. The Epping jaundice. Brit. Med. J. 1:514-516.

NTP. 1983. NTP Technical Report on the Carcinogenesis Studies of 4,4'-Methylenedianiline Dihydrochloride (CAS No. 13552-44-8) In F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies). National Toxicology Program. Box 12233 Research Triangle Park, North Carolina 27709. NTP Publication No. 83-2504. NTP TR 248.

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