MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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February 6, 2017

TO: File for Methyl Isocyanate (CAS No. 624-83-9)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Derivation of Initial Threshold Screening Level

The initial threshold screening level (ITSL) for methyl isocyanate is 1 µg/m^3, with annual averaging time.

Previously, the averaging time (AT) assigned to the methyl isocyanate ITSL was 24 hours (2 April 2014; see attached memo). The ITSL was based on a chronic Reference Exposure Limit (REL) derived by California Office of Environmental Health Hazard and Assessment (OEHHA). OEHHA calculated the REL using methodology specifically for chronic (long-term) exposures. Also, OEHHA specifies that the REL is given an annual AT. Therefore, the ITSL is assigned an annual AT. An updated literature review was not performed at this time.

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TO: File for Methyl Isocyanate (CAS # 624-83-9)

FROM: Doreen Lehner

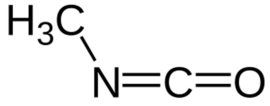
SUBJECT: Screening level for Methyl Isocyanate

DATE: April 2, 2014

The Initial Threshold Screening Level (ITSL) for methyl isocyanate is 1 µg/m³ based on 24-hour averaging time.

Methyl isocyanate [MIC] is also known as isocyanatomethane and methyl carbylamines. MIC is a colorless, flammable liquid with a sharp, pungent odor that reacts with water to form hydrogen chloride gas. It has a molecular weight of 57.051 g/mol. MIC is used: an as intermediate in the production of carbamate pesticides (such as carbaryl, methomyl, and aldicarb); and in the production of rubbers and adhesives. The structure of methyl isocyanate is shown in the figure below.

Figure 1. Structure of methyl isocyanate



MIC is a highly toxic and irritating material; it is extremely hazardous to human health. The uncontrolled release of approximately 93,000 lbs of MIC from an underground tank at the Union Carbide India Limited (UCIL) factory in Bhopal, India on December 3, 1984, released a cloud of the gas; the exposure was short-term (30-45 minutes) and no measurements were taken, but the air concentration was estimated at 13-100 ppm (Cal EPA, 2001; Wikipedia, 2014). The exposure killed nearly 5,000 people within five days of the initial exposure and approximately 6,000 people died during the following decade with another 10,000 people affected with blindness (Cal EPA, 2001). The initial symptoms among the population living near the Union Carbide plant were irritation and difficulty breathing. Deaths were due mainly to respiratory system effects, such as pulmonary edema, bronchospasm, and electrolyte imbalance. Other causes of death were due to tissue anoxia, gastrointestinal symptoms, and muscular weakness. Within one year of exposure, survivors exhibited damage to the eyes and lungs, with fibrosis of the lungs as the most common lung damage. Reproductive toxicity was observed in women exposed to MIC in Bhopal; 43% of women pregnant at the time of exposure had

poor birth outcomes. Among live births, 14% of the infants died within 30 days, whereas a 3% death rate was recorded in the years before the incident (Cal EPA, 2001). In summary, the lung is the critical target organ, for long-term effects from acute exposure, although adverse effects on other organs (e.g., eye, reproductive, and gastrointestinal) also exist. acute exposure suggest an immunological component, which could involve several systems al EPA, 2001).

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), Registry for Toxic Effects of Chemical Substances(RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) - Online (searched 2/11/2014), National Library of Medicine, and the EPA Aggregated Computational Toxicology Resource (ACToR) Database.

ITSL Discussion and Derivation

There are many short term studies on MIC, most performed after the Bhopal, India incident, to determine the effects of acute exposure. The EPA does not have an inhalation RfC because the available data were considered inadequate for the derivation of an inhalation RfC, and there is no oral RfD available. California EPA does have a chronic inhalation reference exposure level (REL) of 1 µg/m^3 based on a study by Dodd and Fowler (1986). Groups of male and female Fischer 344 rats were exposed to 0.0, 0.15, 0.6, or 3.1 ppm MIC vapor 6 hrs per day for two 4-day sessions separated by a 2-day rest. . The rats were killed the morning following the last exposure day. The 3.1 ppm exposed rats had decreased body weight and food consumption, and a 26% decrease in blood oxygen saturation (males only). A 38% increase in hemoglobin concentration (males only) and increase in lung weights were also observed in the 3.1 ppm exposure group of rats. Multiple histologic lesions consisted of necrosis, suppurative inflammation, squamous metaplasia, and intraluminal and submucosal fibroplasia (bronchi and bronchioles only) which extended from the anterior nasal cavity to the terminal bronchioles (Dodd and Fowler, 1986). “Decrease in liver, kidney, and testes absolute weights were observed in this exposure group, but the authors interpreted these data as a reflection of the body weight losses... These data suggest a NOAEL of 0.6 ppm MIC, based on weight gain loss, absolute lung weight, and lung histopathology in rats, immediately following cessation of exposure.” (Cal EPA, 2001).

A second rat study was performed using 3.0 ppm MIC, 6 hrs per day for either one or two 4-day sessions and animals were sacrificed on post-exposure days 1, 15, 43, and 85. survived the 4 or 8 day exposure regimen, although significant decreases in body weight and encrustation of the eyes, nose, or mouth area were observed. During the first 15 days post- exposure, male mortality was 63%: only 6% of the MIC-exposed females died. The cause of death was interpreted to be a combination of pulmonary vascular and inflammatory changes coupled with anorexia. For survivors, recovery from the necrotizing and irritating effects of MIC vapor was observed. Squamous metaplasia of respiratory epithelium, observed in rats sacrificed at the end of the exposure period,

was replaced by tall pseudostratified columnar (regenerative) epithelium beginning in the bronchi and bronchioles as well as the distal trachea. Collagen maturation and condensation of the intraluminal and submucosal fibroplasia occurred during the post-exposure period." (Dodd and Fowler, 1986). "In males, the intraluminal and submucosal fibroplasia changed in appearance during this interval, due in part to the maturation of fibrous tissue. Mucous plugs were also seen in the terminal bronchioles and alveoli in some rats. The importance of this observation is the progressive character of MIC induced lung disease. Such progression may be difficult to follow at lower doses, if the times involved are of insufficient duration." (Cal EPA, 2001).

For the derivation of a chronic inhalation Reference Exposure Level (REL), Cal EPA used the Dodd and Fowler (1986) study on male and female Fischer 344 rats with the critical effects of decreased weight gain and lung pathology immediately after cessation of exposure with a NOAEL of 0.6 ppm. Although the exposure was only for 10 days, the Dodd and Fowler (1986) study includes the longest exposure duration of the available investigations and also uses some of the lower exposure levels (down to 0.15 ppm). The microscopic findings of the respiratory tract were statistically analyzed, although the observation of the tabulated data at the four doses (0, 0.15, 0.6, or 3.1 ppm) clearly shows a NOAEL of 0.6 ppm. Other endpoints with the same NOAEL were increased hemoglobin and increased absolute lung weights. The symptomatic ramifications of the increased hemoglobin are unknown, although similar increases were reported for humans exposed to MIC in Bhopal (Srivastava et al., 1988)(Cal EPA, 2001).

Cal EPA calculated the average experimental exposure at 0.12 ppm for the NOAEL group (NOAEL of 0.6 ppm x 8 exposure days/10 days x 6 hour exposure/24 hours). Cal EPA then calculated a human equivalent concentration of 0.15 ppm for the NOAEL group (gas with pulmonary respiratory effects, RGDR = 1.23, based on BW = 152 g, MV= 0.12 L/min, SA = 225 cm^2). Cal EPA used an uncertainty factor of 300 (10 for subchronic to chronic), 3 for interspecies uncertainty factor, and 10 for intraspecies uncertainty factor), which gives a final inhalation reference exposure level of 0.5 ppb (1 $\mu g/m^3$)[see calculation below]:

REL = [0.15ppm(2.34 $\mu g/m^3$)/(ppm)]/(300) x 1000µg/mg
REL = 1.17 $\mu g/m^3$, or ~ 1 $\mu g/m^3$

As the Cal EPA chronic inhalation REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups, and since Cal EPA RELs are peer- reviewed, the value of 1 $\mu g/m^3$ is adopted as the initial threshold screening level (ITSL) for methyl isocyanate. According to Rule 232(2)(b), the default averaging time is 24 hours. This is an appropriate averaging time for this ITSL as this REL is based on a total of an 8 day exposure period, even with the application of an uncertainty factor of 10 for subchronic to chronic. The initial threshold screening level (ITSL) for methyl isocyanate (CAS# 624-83-9) is 1 $\mu g/m^3$ based on a 24-hour averaging time.

References:

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Cal EPA, 2001. Determination of Noncancer Chronic Reference Exposure Levels. Chronic Toxicity Summary. Methyl Isocyanate. CAS Number: 624-83-9. Available online at: http://www.oehha.ca.gov/risk/ChemicalDB/index.asp

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Srivastava RC, Gupta BN, Athar M, Behari JR, Dwivdei RS, Hasan SK, Bharti RS, Singh A, Misra M, and Ray pK. 1988. Effect of exposure to toxic gas on the population of Bhopal: Part III Assessment of toxic manifestations in humans hematological and biochemical studies. Ind. J. Exp. Biol. 26:165-172.

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