MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2-Epoxy-4-vinylcyclohexane (CAS # 106-86-5)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level for 1,2-Epoxy-4-vinylcyclohexane (CAS # 106-86-5)

DATE: November 28, 2016

The initial threshold screening level (ITSL) for 1,2-epoxy-4-vinylcyclohexane is 6.0 µg/m³ based on an annual averaging time.

1,2-Epoxy-4-vinylcyclohexane (CAS # 106-86-5) also known as 3-vinyl-7-oxabicyclo (4.1.0) heptane, 4-vinylcyclohexene monoxide, or VCMX is a colorless liquid with a molecular weight of 124.18 g/mol. It is mainly used as a chemical intermediate in coatings, composites, and adhesives in the electronics industry.

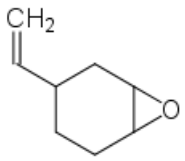

Figure 1. Structure of 1,2-epoxy-4-vinylcyclohexane.

A literature review was conducted to determine an ITSL for 1,2-epoxy-4-vinylcyclohexane. The following references and databases were searched to derive the screening level: Chemical Criteria Database (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) 2012 Guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), AQD's Acute Database, Chemical Abstract Service (CAS) Online (searched 10/19/16), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, and EPA Toxic Substance Control Act Test Submission Database (TSCATS).

The ITSL is based on a 13-week inhalation study (NTIS, 2001) in male and female Sprague-Dawley rats and CD-1 mice (10 animals/sex/species for low and mid exposure levels; 20 animals/sex/species for the air control and high exposure levels). Groups were exposed via whole body exposure to either 0, 20, 80, and 200 (mice) or 400 (rats) ppm of 1,2-epoxy-4-vinylcyclohexane for 6 hours/day, 5 days/week, for 13 weeks. Following the 13-week treatment period, 10 animals/sex/species from the air control and the high exposure levels were held for a 4-week recovery period before sacrifice. All survivors were sacrificed immediately after treatment or after the recovery period. All mice and rats in all dosage groups showed exposure-

related increases in nasal epithelium degeneration without recovery. “In the respiratory mucosa, loss of epithelial cilia (minimal to moderate) occurred in 1/10 males and 6/10 females in the 200 ppm group; overall severity was greatest in the females. A similar finding of slight severity in 1/10 females from the Air Control group was considered to be incidental. Focal thinning (slight) of the respiratory epithelium occurred in 1/10 males and 1/10 females in the 200 ppm group. Eosinophilia with blebbing (minimal to marked) of the respiratory epithlium occurred only in mice exposed to the test material (4/10 males each from the 80 and 200 ppm groups and 3/10, 7/10, and 2/10 females in the 20, 80, and 200 ppm groups respectively). Intracytoplasmic eosinophilic material similar to that seen in this study has been seen in mice in air control groups and in groups exposed to various test materials from other inhalation studies conducted in this facility. The exact nature of this material, presumed to be secretory, and reasons for its increase following exposure to a variety of test materials are uncertain but probably represents a nonspecific response to the inhalation of the test material” (NTIS, 2001). Female mice showed degeneration of ovarian follicles starting at 200 ppm without recovery. Male and female mice and male rats at both the 200 ppm and 400 ppm dosage groups showed dose dependent decrease in body weight gains, and urine changes which included a decrease in pH, and an increase in ketone levels. “Inhalation exposure of rats and mice to VCMX at concentrations of 20 ppm and higher, for 13 weeks, resulted in an exposure-level-related increase in nasal epithelium changes in both species, which were not completely reversible in high-concentration animals (mice, 200 ppm; rats, 400 ppm) held for a 4- week recovery period. These nasal effects were seen without any corresponding lung changes indicating a localized effect of test material exposure within the respiratory tract” (NTIS, 2001). Based on the study findings, the LOAEL for mice and rats is 20 ppm due to nasal epithelium degeneration (NTIS, 2001).

A conversion factor from ppm to mg/m^3 was determined using the molecular weight of 1,2-epoxy-4-vinylcyclohexane of 124.18 g/mol, assuming 25°C and 760 mmHg.

$$LOAEL\ {}^{mg}/_{m^3} = \frac{20\ ppm\ \times 124.18\ {}^{g}/_{mol}}{24.45} = 101.5787\ {}^{mg}/_{m^3}$$

$$LOAEL_{ADJ} = 101.5787321\ \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} =\ 18.1391\ {}^{mg}/_{m^3}$$

The $LOAEL_{HEC}$ was calculated for a gas:respiratory effect in the Extrathoracic (ET) region because the most sensitive effect is nasal epithelium degeneration. The EPA (2012) states that for the ET region, “strong evidence indicating that in the absence of modeling the default dosimetric adjustment factor (DAF) = 1.” Since the dose in animals equals the dose in humans.

$$LOAEL_{HEC} =\ LOAEL_{ADJ}$$

$$LOAEL_{HEC} = 18.1391\ {}^{mg}/_{m^3}$$

ITSL Using Sprague-Dawley Rat or the CD-1 Mouse data:

$$LOAEL_{HEC} =\ LOAEL_{ADJ}\ = 18.1391\ {}^{mg}/_{m^3}$$

$$ITSL = \frac{LOAEL_{HEC}}{UF_H\ \times\ UF_A\ \times\ UF_S\ \times\ UF_L}$$

Where:

UF = The uncertainty factor used to account for differences between the available data and the possible effects in the human population, usually expressed as factors of 10.

UF_H = Uncertainty factor used to account for the variation in sensitivity among individuals of the human population.

UF_A = Uncertainty factor used to account for the extrapolation from animal data to humans; the application of an uncertainty factor of 3 due to the use of dosimetric adjustment factors.

UF_S = Uncertainty factor used to account for the extrapolation from less than chronic NOAELs to chronic NOAELs. A factor of 10 is applied because the study duration was 13 weeks.

UF_L = Uncertainty factor used to account for the extrapolation from a LOAEL to a NOAEL; the application of an uncertainty factor of 10 is due to the frequency and severity of the nasal epithelium degeneration.

$$ITSL = \frac{18.1391\ {}^{mg}/_{m^3}}{10\ \times 3\ \times 10\ \times 10} = 0.006046\ {}^{mg}/_{m^3} = 6.046\ {}^{\mu g}/_{m^3}$$

According to Rule 336.1232(1)(a) the proposed ITSL for 1,2-epoxy-4-vinylcyclohexane equals the RfC, if the RfC can be determined from the best available information sources. The potential rat RfC and ITSL of 6.0 µg/m^3 is the same as the potential mouse RfC and ITSL of 6.0 µg/m^3. According to Rule 232(2)(b) a 24-hour averaging time period should be used; however, this ITSL is based on a 13-week inhalation study and an uncertainty factor of 10 was used for a subchronic to chronic study, therefore it is appropriate to utilize an annual averaging time. The initial threshold screening level (ITSL) for 1,2-epoxy-4-vinylcyclohexane is 6.0 µg/m³ 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. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. U.S. Environmental Protection Agency, Washington, DC. EPA/600/R-12/044.

NTIS. 2001. 8EHQ-0101-14257. National Technical Information Service. Springfield, VA 22161. Vinyl Cyclohexene Monoxide (VCMS): A 13-Week Inhalation Toxicity Study in Mice and Rats Via Whole-Body Exposures 12-Crown-4: A 4-Week Inhalation Toxicity Study in Rats Via Whole-Body Exposures; Report Number 97U1660, October 20, 2000; Huntington Life Sciences.

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