MICHIGAN DEPARTMENT OF NATURAL RESOURCES & ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: File for 1,2-Epoxybutane (CAS# 106-88-7)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 23, 2017

SUBJECT: 1,2-Epoxybutane (CAS# 106-88-7) change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for 1,2-epoxybutane is 20 µg/m^3 based on an annual averaging time. The ITSL was originally established on 10/31/2012 and was set at 20 µg/m^3 based on a 24-hour averaging time. The ITSL was based on an EPA (1992) reference concentration (RfC) of 20 µg/m^3 which was derived from an NTP (1988) 2-year carcinogenicity bioassay in which mice and rats were exposed via inhalation to 1,2-epoxybutane. As the key study used to derive the ITSL is a 2-year inhalation study, the averaging time is appropriately set at annual. Therefore, the averaging time is being changed from 24 hours to annual at this time.

References:

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

EPA. 1992. Integrated Risk Information System. 1,2-Epoxybutane (EBU) (CASRN 106-88-7). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=630

NTP. 1988. Toxicology and carcinogenesis studies of 1,2-epoxybutane (CAS No. 106-88-7) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 329. U.S. Department of Health and Human Services, National Toxicology Program, Research Triangle Park, NC.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2-Epoxybutane (CAS No. 106-88-7)

FROM: Cathy Simon, Air Quality Division

DATE: October 31, 2012

SUBJECT: Review of Screening Levels for 1,2-Epoxybutane

An updated review and evaluation of the existing screening levels for 1,2-epoxybutane has been completed. Based on this evaluation, no changes to the existing screening levels are recommended at this time. The screening levels remain as follows:

Initial Threshold Screening Level (ITSL) = 20 µg/m^3 (24-hour averaging time)
Initial Risk Screening Level (IRSL) = 1.2 µg/m^3 (annual averaging time)
Secondary Risk Screening Level (SRSL) = 12 µg/m^3 (annual averaging time)

The background information, relevant data and basis for this conclusion are summarized below.

Background

In 1986, the National Toxicology Program (NTP) released a draft report on a cancer bioassay in which mice and rats were exposed via inhalation to 1,2-epoxybutane. The results of this bioassay showed a statistically significant increased incidence of tumors of the nasal cavity and lung in male rats. In female rats, no tumors were significantly increased over control animals, although tumors of the nasal cavity were observed in two rats in the high dose group. No evidence of carcinogenicity was found in male or female mice. The NTP report was released in final form in 1988, with a conclusion that there was clear evidence of carcinogenicity in male rats as shown by an increased incidence of papillary adenomas of the nasal cavity and alveolar/bronchiolar adenomas or carcinomas. In addition, there was a finding of equivocal evidence in female rats as shown by presence of papillary adenomas in two rats in the high dose group (NTP, 1988).

As a results of the release of the draft NTP report, the Michigan Air Pollution Control Commission (MAPCC) convened an advisory committee in 1987 to evaluate the carcinogenic potential of 1,2-epoxybutane. This compound was of special concern as it was used as a stabilizer in commercial grade methyl chloroform, and at the time, the MAPCC was considering exempting methyl chloroform from the definition of volatile organic compound as listed in the Michigan Air Pollution Control Rules.

In July and September 1987, the MAPCC Special Advisory Committee on Methyl Chloroform Exemption for VOC Definition issued reports concluding that the finding of carcinogenicity in animals was relevant to the potential implications for human carcinogenicity, and that the linearized multistage model was appropriate to use in determining the upper plausible limit on risk from exposure to 1,2-epoxybutane (Wurzel et al, 1987a; 1987b).

In September 1987, the Michigan Department of Natural Resources (MDNR), Air Quality Division (AQD) derived a unit risk value of 8.17×10^{-7} $(\mu g/m^3)^{-1}$ for 1,2-epoxybutane using the linearized multistage model and the incidence of alveolar/bronchiolar carcinomas in male rats as reported in the 1986 NTP draft report (MDNR, 1987). Based on this unit risk value, the concentration of 1,2-epoxybutane in air resulting in an increased cancer risk of one in one million was determined to be 1.2 $\mu g/m^3$.

In December 1991, the AQD established an ITSL of 20 $\mu g/m^3$ (24-hour averaging time) for 1,2-epoxybutane. This ITSL was derived from an inhalation reference concentration (RfC) of 20 $\mu g/m^3$ developed by the US Environmental Protection Agency (US EPA).

In 1992, the AQD established an IRSL of 1.2 ug/m^3 and a SRSL of 12 ug/m^3, based upon the earlier risk assessment work done for 1,2-epoxybutane in 1987.

Review of the ITSL

The US EPA established an inhalation RfC for 1,2-epoxybutane in December 1991. This RfC was derived from the NTP (1988) carcinogenicity bioassay in which mice and rats were exposed to 1,2-epoxybutane by inhalation for two years. Mice were exposed to concentrations of 50 and 100 ppm, whereas rats were exposed to dose levels of 200 and 400 ppm. The critical effect identified by the US EPA was degenerative lesions of the nasal cavity, which occurred at all exposure concentrations in both sexes of both species. The LOAEL for this effect was 50 ppm (147 mg/m^3) in mice and 200 ppm (590 mg/m^3) in rats. No NOAEL was identified for either rats or mice. Since a lower LOAEL was identified for mice, this value was used in derivation of the inhalation RfC (EPA, 2012).

To derive the RfC, the mouse LOAEL of 147 mg/m^3 was adjusted for an exposure duration of five days per week and six hours per day to give a $LOAEL_{(ADJ)}$ of 26 mg/m^3. Because the effects in the nasal cavity were in the extrathoracic region, the $LOAEL_{(ADJ)}$ was multiplied by a $RGDR_{(ET)}$ of 0.183 to give a $LOAEL_{(HEC)}$ of 4.8 mg/m^3. A total uncertainty factor of 300 was then applied to the $LOAEL_{(HEC)}$ to derive the RfC of 20 $\mu g/m^3$. The uncertainty factor of 300 consisted of a factor of 10 for use of a LOAEL, a factor of 10 to protect sensitive individuals, and a factor of 3 for interspecies extrapolation (EPA, 2012).

While the inhalation RfC was established in 1991, a screening level review of the scientific literature conducted by an EPA contractor in September 2002 did not identify any critical new studies pertinent to derivation of the RfC. In addition, no occupational exposure levels have been established by the American Council of Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH), or the Occupational Safety and Health Administration (OSHA). No minimal risk levels (MRLs) for 1,2-epoxybutane have been set by the Agency for Toxic Substances and Disease Registry (ATSDR), nor has this agency published a *Toxicological Profile* for this compound.

The current ITSL for 1,2-epoxybutane of 20 $\mu g/m^3$ (24-hour averaging time) was established pursuant to Rule 232(1)(a) of the Michigan Air Pollution Control Rules. As no new data have been identified that would result in a change of this value, the ITSL remains at 20 $\mu g/m^3$ (24-hour averaging time).

Review of the Cancer Risk Screening Levels

No human epidemiology data were identified evaluating the carcinogenic potential of 1,2-epoxybutane. The only lifetime exposure animal studies available which did not involve combined exposure with other chemicals, were those done by the NTP (1988). As previously stated, the results of this inhalation bioassay indicated there was clear evidence of carcinogenicity in male rats as shown by an increased incidence of papillary adenomas of the nasal cavity and alveolar/bronchiolar adenomas or carcinomas. In addition, there was a finding of equivocal evidence in female rats as shown by presence of papillary adenomas in two rats in the high dose. No evidence of carcinogenicity was found in male or female mice.

Other data relating to the evaluation of the carcinogenic potential of 1,2-epoxybutane include a 77 week skin painting study in mice in which the incidence of skin tumors were not increased. Additionally, 1,2-epoxybutane has produced positive results in a number of genotoxicity assays including gene mutations in bacteria, fungi, mouse lymphoma cells (in vitro), and Drosophila melanogaster; increased frequency of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells; and cell transformation of Syrian hamster embryo cells and Fisher 344 rat embryo cells (IARC, 1999).

The International Agency for Research on Cancer (IARC) has reviewed and evaluated the data relating to the carcinogenic potential of 1,2-epoxybutane (IARC 1989; 1999). In their most recent evaluation, IARC identified 1,2-epoxybutane as possibly carcinogenic to humans (Group 2B). This conclusion is based upon the finding of limited evidence of carcinogenicity in animals, along with the determination that "1,2-epoxybutane is a direct-acting alkylating agent which is mutagenic in a range of test systems" (IARC, 1999).

The US EPA has not evaluated the data regarding the carcinogenic potential of 1,2-epoxybutane for its IRIS program (EPA, 2012), and has not made any determination on the carcinogenic classification of this compound.

The chemical, 1,2-epoxybutane, meets the definition of carcinogen found in Rule 103(c) of the Michigan Air Pollution Control Rules. The existing IRSL of 1.2 µg/m^3 (annual average) and SRSL of 12 µg/m^3 were established pursuant to the procedures specified in Rule 231. No new data have been identified which would change these findings, and therefore no changes are recommended to these screening levels.

References

EPA. 2012. Integrated Risk Information System. 1,2-Epoxybutane (EBU) (CASRN 106-88-7). Accessed on 9/17/2012. http://www.epa.gov/iris/subst/0630.htm

IARC (International Agency for Research on Cancer). 1989. 1,2-Epoxybutane. In *Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting.* IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Lyon, France. Volume 47, pp. 217-28.

IARC. 1999. 1,2-Epoxybutane. In *Re-evaluation of some organic chemicals, hydrazine, and hydrogen peroxide*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France. Volume 71, Part 2, pp. 629-40.

MDNR. 1987. *Memo from Catherine Simon to File. Subject: Risk Assessment for 1,2-Epoxybutane (CAS No. 106-88-7).* September 9, 1987. Michigan Department of Natural Resources, Air Quality Division.

NTP. 1988. Toxicology and carcinogenesis studies of 1,2-epoxybutane (CAS No. 106-88-7) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 329. U.S. Department of Health and Human Services, National Toxicology Program, Research Triangle Park, NC.

Wurzel, Kathryn, Rolf Hartung, and Rudolph Jaeger. 1987a. Evaluation of the Toxicity and Risk Assessment for 1,2-Butylene Oxide, A Stabilizer in Commercial Grade Methyl Chloroform. Final Report of the Special Advisory Committee on Methyl Chloroform Exemption for VOC Definition. Presented to the Michigan Air Pollution Control Commission on July 28, 1997.

Wurzel, Kathryn, Rolf Hartung, and Rudolph Jaeger. 1987b. Addendum to the Final Report. Evaluation of the Toxicity and Risk Assessment for 1,2-Butylene Oxide, A Stabilizer in Commercial Grade Methyl Chloroform. Final Report of the Special Advisory Committee on Methyl Chloroform Exemption for VOC Definition - Presented to the Michigan Air Pollution Control Commission on July 28, 1997. Date of Addendum: September 14, 1987.

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