STATE OF MICHIGAN
Rick Snyder, Governor

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AIR QUALITY DIVISION

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Response to Public Comments for Propylene oxide (CAS # 75-56-9)

Summary:

Based on public comments, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD), has reviewed the Initial Risk Screening Level (IRSL) for propylene oxide. The AQD does not agree with the commenter. The IRSL of 0.3 µg/m^3 continues to be appropriate and defensible to assess public health risks from exposures to propylene oxide. The Initial Threshold Screening Level (ITSL) for propylene oxide will also remain at 30 µg/m^3 (annual averaging time).

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the AQD published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994. PA 451, as amended (NREPA).

Comments and Responses:

Comment #1:

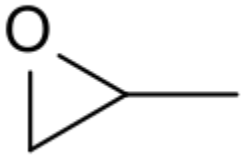
The AQD's ITSL, IRSL and secondary risk screening level (SRSL) for propylene oxide are based on the United States Environmental Protection Agency's (EPA) IRIS database RfC value. This EPA IRIS assessment was published in 1994 and considered the only data available before that time. Since then, significant research has been performed to inform on the mode of action of the rodent nasal tumors observed with chronic high exposure concentrations of propylene oxide, therefore the EPA IRIS assessment is outdated. The propylene oxide research results and a risk assessment were published in Sweeney et al. (2009. Derivation of inhalation toxicity reference values for propylene oxide using mode of action analysis: Example of a threshold carcinogen. *Critical Reviews in Toxicology. 39(6):462-486*). This assessment concluded from the available mode of action information that cancer induction by propylene oxide at the site of contact in rodents has a practical threshold. This information supports human risk reference values from the rat and mouse of 0.7 and 0.5 ppm propylene oxide, respectively. More detailed information on propylene oxide's genotoxicity is published in a review by Albertini and Sweeney (2007). Additional details and information on the published articles and unpublished studies is also available as summaries prepared for the EU REACH registration of propylene oxide and are available at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances.

Response:

Upon reviewing the submitted documents, the AQD noted that the EPA IRIS website contained a reregistration eligibility decision (RED) document for propylene oxide dated July 31, 2006 (EPA, 2006). In this document, the EPA reviewed the comments submitted by Dr. Sweeney and colleagues during the open comment period of the propylene oxide review. The EPA accepted the comments but continued to use the EPA (1990) cancer slope factor for the inhalation rate of exposure of 3.5×10^{-6} $(\mu g/m^3)^{-1}$ for propylene oxide assessment. The value listed in EPA RED (2006) is slightly different than the inhalation unit risk listed in EPA IRIS (1990) of 3.7E-6 $(\mu g/m^3)^{-1}$. The AQD used the EPA IRIS (1990) value of 3.7E-6 $(\mu g/m^3)^{-1}$ in the original IRSL derivation. The AQD does not use an EPA inhalation reference concentration (RfC) for carcinogenic effects, but uses the EPA (1990) inhalation unit risk (IUR) of 3.7E-6 $(\mu g/m^3)^{-1}$ for propylene oxide. The AQD will continue to use the EPA (1990) inhalation cancer slope factor of 3.7×10^{-6} $(\mu g/m^3)^{-1}$ for the derivation of the IRSL, as discussed further below. The ITSL basis is discussed below in Comment and Response #2.

The Albertini and Sweeney (2007) review article compares toxicities of propylene oxide to ethylene oxide which is structurally similar. In the Sweeney et al. (2009) review article, the authors then compare propylene oxide to formaldehyde in a hypothesis that propylene oxide is a threshold carcinogen. As formaldehyde is not structurally similar,

the comparison of propylene oxide to formaldehyde is a questionable comparison. The structures of the three compounds are shown in Figure 1, below:



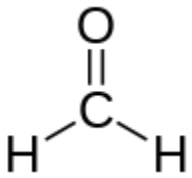


Figure 1. Propylene oxide **Ethylene oxide** **Formaldehyde**

The Sweeney et al. (2009) article discusses propylene oxide as a potential threshold carcinogen and uses the benchmark dose software (BMDS) dichotomous gamma model to determine a point-of-departure calculation. The authors did not use the multistage cancer model and did not show data on the comparison of the two models to show model discrepancies to support their claim that propylene oxide is a threshold carcinogen. The EPA states that the most appropriate model for determining carcinogenicity is the multistage cancer model as this model is the most appropriate for focusing on the low end of the dose-response curve. The Gamma model was developed for non-carcinogenic effects. Without data using the established multistage cancer model, no detailed comparisons can be made on the suitability of their model choice. It is not convincing to use an inappropriate model because it fits the data better as an adequate reason to change an established EPA inhalation unit risk factor of 3.7E-6 $(\mu g/m^3)^{-1}$. No new cancer bioassay was performed that was not already evaluated by the EPA (2006) for the Sweeney et al. (2009) assessment that propylene oxide may be a threshold carcinogen. The Sweeney et al. (2009) review is simply applying a different model to substantiate a theory.

Physiologically based pharmacokinetic (PBPK) modeling was also used by Sweeney et al. (2009) to evaluate propylene oxide. Currently, the AQD does not have the expertise to evaluate the accuracy or appropriateness of the data used for the PBPK modeling.

A “mode of action” (MOA) can be used to support a threshold/non-threshold determination for carcinogenic properties of a chemical. When a MOA is not known, the default assumption is non-threshold according to the EPA (2005) cancer risk assessment guidance. Propylene oxide is a direct-acting alkylating agent and can induce gene and chromosome level genotoxic effects, which has been seen in in vitro tests. Propylene oxide is also a site-of-contact carcinogen in animal bioassays. Available information suggests that propylene oxide has a complex mode of action. Lynch et al. (1984) exposed Fischer 344 rats to 0, 100, or 300 ppm propylene oxide, which caused adenomas in the nasal cavity at the highest dose level. Renne et al. (1986) also exposed Fischer 344 rats to 0, 200, and 400 ppm propylene oxide and detected nasal cavity adenomas. Propylene oxide also induced inflammation in the respiratory nasal mucosa. “Metabolic elimination of propylene oxide is mediated by

epoxide hydrolase (EH) and by glutathione S-transferase (GST)" (Lee et al., 2005). GST catalyzed the conjugation of propylene oxide with glutathione (GSH):

> This process could cause a decrease in the cytosolic nonprotein sulfhydryl (NPSH) content of which GSH is the major contributor. GSH is involved in a multitude of cellular functions. Severe perturbation of GSH status can lead to cytotoxicity, apoptosis, and cell proliferation. Because of apoptotic or necrotic cell death, a regenerative proliferation of cells might be expected too. Following repeated propylene oxide inhalation exposure, induction of cell proliferation was observed in respiratory nasal mucosa (RNM) of rats. Also, propylene oxide adducts to DNA were detected in all tissues studied; by far the highest levels were found in the RNM, with up to 25-fold higher adduct levels than other systemically exposed tissues (Lee et al., 2005).

Propylene oxide can cause severe, sustained GSH depletion and can induce cell proliferation in the nasal respiratory epithelium. GSH depletion was also seen in the blood and liver, propylene oxide elimination was mainly through GST catalyzed reactions (81% in blood and 80% in liver) with some propylene oxide elimination through the EH dependent (9% in blood and 10 % in liver in rats) (as reported in Lee et al., 2005).

The rat data was assessed by Sweeney et al. (2009) in terms of an internal dosimetry measure area under the curve for propylene oxide (AUC PO) based upon a PBPK model while the mouse data was assessed in terms of continuous external concentration. The difference in evaluating rat and mouse data from the same study was not adequately explained by Sweeney et al. (2009).

The European Chemicals Agency (ECHA) has listed propylene oxide as a carcinogen and a mutagen. The EPA (1990) has listed propylene oxide as Class B2; probable human carcinogen, and has stated that there is also evidence of mutagenicity in a variety of test systems. Even though the EPA has stated that propylene oxide is mutagenic, they have not calculated or applied a default age dependent adjustment factor (ADAF) for early life stage exposures. The DEQ's Air Toxics Workgroup recommended that the DEQ not use ADAFs for a chemical until the EPA uses it in an Inhalation Unit Risk (IUR) or oral slope factor derivation for a substance. Also, propylene oxide is a hazardous air pollutant, and Table 1 (EPA, 2017) does not indicate a mutagenic mode of action.

Sweeney et al. (2009) suggested that the carcinogenic mode of action for propylene oxide is that propylene oxide induces DNA reactive genotoxic effects due to glutathione depletion, which progresses to mutations leading to nasal tumors. Albertini and Sweeney (2007) states that propylene oxide is a threshold carcinogen and refers to studies where 10 to 30% glutathione depletion (when compared to controls) led to liver toxicity (Mitchell et al., 1973; Uhlig and Wendel, 1992; Younes and Sieger, 1981). Glutathione depletion was also seen by Lee et al. (2005) in respiratory nasal epithelium in animals exposed to propylene oxide. Glutathione is a critical molecule for cellular functions; it binds to exogenous chemicals for quick transport out of the cell and it helps

to buffer cells from internal oxidative stress. A reduction in a cell's buffering capacity can lead to an increase in cell proliferation, as well as a disruption of apoptosis (Albertini and Sweeney, 2007). There is not enough information available to determine whether glutathione depletion is a mechanism required for tumor formation. Sweeney et al. (2009) states that there is "negligible concern" for workers contracting "DNA-reactive genotoxicity" (nasal tumors) at the occupational exposure limit (OEL) of 2 ppm threshold limit value-time weighted average (TLV-TWA) based on animal data and epidemiology studies. However, OELs are not designed or intended to be health protective for susceptible populations, such as children, the elderly, and individuals with chronic conditions or illness. "Children may be at increased risk because nasal proliferation is likely to be greater at a younger age, as the proliferation must provide for both increasing nasal surface area as well as replacement of dying cells through natural turnover" (Sweeney et al., 2009). Decreased glutathione occurs in rapidly dividing cells. It would not be health protective to use an OEL when more appropriate data are available. Given the mutagenicity of propylene oxide, the induction of cell proliferation of nasal mucosa, and the extra-sensitivity of childhood exposures, and the unclear MOA and hypothesis for a threshold, the AQD will continue to assess propylene oxide cancer risk using the default non-threshold approach. This continues to be a prudent public health protective approach for AQD's permitting program to protect ambient air and public health.

In conclusion, the AQD will continue to use the EPA's inhalation unit risk of 3.7E-6 $(\mu g/m^3)^{-1}$ instead of the Sweeney et al. (2009) reference value of 0.7 and 0.5 ppm (for rat and mouse respectively). The IRSL of 0.3 $\mu g/m^3$ based on an annual averaging time is more appropriate and health protective for lifetime exposure to a population including children, the elderly, and sensitive individuals in the population.

Comment #2:

The non-cancer effects for propylene oxide were determined to occur at 0.4 ppm based on the non-neoplastic nasal effects in rats. Overall, the extensive database of toxicology information for propylene oxide provides a good understanding of its toxicity and supports that propylene oxide is a low concern to human and environmental health under its conditions of use.

We urge you to consider the current toxicity information available for propylene oxide and update your ITSL document to include this information. It is important that the basis for values accurately reflects the available information (provided in comment #1) on propylene oxide.

Response:

The propylene oxide ITSL of 30 $\mu g/m^2$ was based on an EPA (1990) RfC of 3E- 2 mg/m^3. The EPA derived the RfC from Kuper et al. (1988) two-year rat inhalation study where 100 Wistar rats/sex/group were exposed to either 0, 30, 100, or 300 ppm

(0, 71, 238, or 713 mg/m^3) propylene oxide for 6 hours/day, 5 days/week for 123 weeks (females) and 124 weeks (males). There were statistically significant extra-thoracic respiratory effects, the most sensitive of which were nest-like infolds of the nasal respiratory epithelium at 71 mg/m^3. The EPA "RfC is an estimate of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (EPA, 1990). The ITSL of 30 µg/m^3 based on an annual averaging time is more protective for a lifetime exposure to a population including children, the elderly, and sensitive individuals in the population.

Summary and Conclusions:

The information presented by the commenter was evaluated to determine the most appropriate screening levels for propylene oxide. The evidence for depletion of intracellular glutathione in nasal cells was not sufficient to conclude that propylene oxide causes cancer via a threshold mechanism. In summary, the IRSL of 0.3 µg/m^3 will continue to be based on the EPA (1990) inhalation unit risk of 3.7 E-6 (µg/m^3)$^{-1}$. The current ITSL of 30 µg/m^3 was calculated using Rule 232(1)(a) based on the EPA RfC. The IRSL, SRSL, and the ITSL continue to be appropriate and defensible to protect public health as AQD screening levels.

The primary AQD reviewer for these comments was Doreen Lehner, AQD Toxicologist. The secondary (peer) reviewer was Mike Depa, AQD Toxicologist.

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