MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethylene oxide (CAS # 75-21-8)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Ethylene oxide IRSL

DATE: January 17, 2017

The Initial Risk Screening Level (IRSL) for Ethylene oxide (EtO) is 0.0002 ug/m^3, with annual averaging time (AT). The Secondary Risk Screening Level (SRSL) is 0.002 ug/m^3, with annual AT.

Previously, the IRSL was established on September 22, 1982 at 0.03 ug/m^3 (rounded from 0.026 ug/m^3) based on a unit risk estimate = 3.82 E-5 (ug/m^3)$^{-1}$, which was derived by AQD based on a rat inhalation bioassay demonstrating an increased incidence of mononuclear cell leukemia. An updated literature review and risk assessment by AQD on October 16, 1991 revealed additional animal carcinogenicity bioassay data, but no compelling reason to revise the previous unit risk estimate or screening levels.

The present update is based on an EPA (2016) assessment, which is currently at the EPA-IRIS “final assessment” stage, which provides the following summary:

“Basis:

- Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), ethylene oxide is "carcinogenic to humans" by the inhalation route of exposure, based on (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO. *Note: Application of ADAFs to the cancer inhalation unit risk is recommended in combination with appropriate exposure data when assessing risks associated with early-life exposure (see Section 4.4 of the Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide).*
- This may be a synopsis of the full weight-of-evidence narrative.

Inhalation Unit Risk: 3 x10^{-3} per µg/m^3
Extrapolation Method: Linear extrapolation. Two-piece linear spline model with knot at

1,600 ppm × days for lymphoid cancer. Two-piece linear spline model with knot at 5,750 ppm × days for breast cancer incidence in females. POD of 1% extra risk was used for both cancer types.
Tumor site(s): Reproductive, Immune
Tumor type(s): Lymphoid cancer, (female) breast cancer (Steenland et al., 2003, 2004)"

EPA (2016) did not provide an RfD or an RfC.

AQD's current review concurs with EPA's (2016) weight-of-evidence classification and unit risk estimate, and the appropriateness of applying age-dependent adjustment factors (ADAFs) to account for the mutagenic mode of action for lifetime exposure. It is noted that the EPA (2016) unit risk estimate was derived from the human data from the NIOSH study (Steenland et al., 2003, 2004). EPA (2016) concluded that there is a mutagenic mode of action for EtO, and noted that there are no chemical-specific data from which to assess early-life susceptibility; therefore, increased early-life susceptibility should be assumed as per EPA (2005a, 2005b). EPA (2016) thus applied ADAFs and derived an ADAF-adjusted cancer risk unit risk estimate (URE) of 5.0 E-3 per ug/m^3, and a corresponding 1E-6 lifetime cancer risk exposure level of 2E-4 ug/m^3 (0.0002 ug/m^3). Accordingly, the SRSL (1E-5 risk level) = 2E-3 ug/m^3 (0.002 ug/m^3). This is in agreement with the following calculation utilizing a cancer risk multiplier of 1.7 (MDEQ, 2012) to apply ADAFs for lifetime exposure as per EPA (2005b):

URE (adjusted with ADAFs) = 3E-3 per (ug/m^3) X 1.7 = 5.1E-3 per (ug/m^3).

$$\text{IRSL} = \frac{1\text{E-}6}{5.1\text{E-}3 \text{ per } (\text{ug}/\text{m}^3)} = 1.96\text{E-}4 \text{ ug}/\text{m}^3 \sim 2\text{E-}4 \text{ ug}/\text{m}^3$$

$$\text{SRSL} = \frac{1\text{E-}5}{5.1\text{E-}3 \text{ per } (\text{ug}/\text{m}^3)} = 1.96\text{E-}3 \text{ ug}/\text{m}^3 \sim 2\text{E-}3 \text{ ug}/\text{m}^3$$

References:

EPA. 2016. Integrated Risk Information (IRIS) database. Chemical file for ethylene oxide. Last updated 12/16/16. Retrieved 1/17/17. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025&forceAssessmentTab=true#fragment-2

EPA. 2005a. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B.

EPA. 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F.

MDEQ. 2012. Evaluation of Age-Dependent Adjustment Factors (ADAFs) Application. MDEQ Toxics Steering Group, Children's Environmental Health Subcommittee. February 9, 2012.