MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for ethylene (CAS # 74-85-1)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Ethylene ITSL change in the averaging time from 24 hrs to annual

DATE: December 5, 2016

The current ITSL for ethylene (6240 ug/m^3) was established on November 1, 1994 (see attached). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The basis was a chronic (2 year) rat inhalation bioassay No Observable Effect Level (NOEL). The current file review concludes that the AT for the ITSL may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

November 1, 1994

TO: File for Ethylene (CAS # 74-85-1)

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for Ethylene

The initial threshold screening level (ITSL) for ethylene is 6240 $\mu g/m^3$ based on a 24 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS Online and NLM/Toxline (1967 - October 3, 1994).

No RfC, RfD or NIOSH REL were available for ethylene. ACGIH (1993) lists no specific TLV or STEL for ethylene, as the chemical is considered a "simple asphyxiant", for which available oxygen, rather than a threshold concentration, is the critical limiting factor in precipitating health effects.

Of potential concern is the fact that a certain amount of the ethylene to which humans are exposed is metabolized to ethylene oxide, a chemical which is mutagenic and carcinogenic in mice (NTP, 1987) and probably carcinogenic in humans (IARC, 1985). Occupational studies (Törnqvist et. al., 1989) and pharmacokinetic studies in humans (Filser et. al., 1992) and Sprague-Dawley rats (Bolt and Filser, 1987) suggest that between 2 and 3% of the ethylene to which humans are exposed is metabolized to ethylene oxide. However, IARC (1987) considers ethylene itself "not classifiable as to carcinogenicity in humans", based on no data indicating carcinogenic effects in either animals or humans. A literature search did not locate any studies which indicated carcinogenic effects due to ethylene itself.

A chronic inhalation bioassay has been conducted for ethylene (Hamm et. al., 1984). Groups of Fischer-344 rats (6.5 weeks of age at initiation of the study), 120 per sex per group, were exposed to ethylene gas in air at target concentrations of 0, 300, 1000 and 3000 ppm, 6 hours per day, 5 days per week for up to 24 consecutive months. Time weighted average concentrations for the 2 years of exposure were 0, 301, 1003, and 3003 ppm (0, 352, 1174 and 3514 mg/m^3, respectively). The maximum tolerated dose was not used, as concentrations above 3000 ppm were considered hazardous because of the risk of explosion. Clinical observations, body and organ

weight measurements and ophthalmologic examinations were carried out on all studied animals; in addition, hematology, clinical chemistry and urinalysis were carried out on 5 randomly selected animals per sex per group at 6 and 12 months, and 10 rats per sex per group at 18 and 24 months. All animals were subjected to gross necropsy; 5 rats per sex per group were necropsied at 6 and 12 months, 20 rats per sex per group at 18 months, and all surviving animals at 106 weeks. All unscheduled deaths were necropsied as soon as they were found. Tissues for histopathologic exam were prepared for all rats; histopathologic exams were performed on all fixed tissues from the high dose and control animals. Unscheduled deaths were recorded for 151 of the 960 test animals (16%); these were evenly distributed across the dose groups. No consistent significant differences between groups were recorded for any of measured parameters; pathological lesions occurred with approximately equal frequencies across groups and were considered unrelated to ethylene exposure. The study did not reveal any chronic toxicity or oncogenicity associated with ethylene inhalation in F344 rats at any of the studied doses.

As this study comprised best data available for evaluation, it is selected as the key study and used to derive the ITSL, based on the methods described for calculation of RfCs by EPA (1990). Per section 4.1.1 (p. 4-8), since this study recorded No Observed Effect Levels at multiple dose response levels in the absence of additional data, NOAELs or LOAELs, the highest NOEL, i.e., 3003 ppm (3514 mg/m^3) is used to drive the RfC.

Human Equivalent Dose (HED) Calculation:

a) The key study NOEL of 3003 ppm is converted to mg/m^3, using the chemical specific conversion factor (1 ppm = 1.17 mg/m^3) of Verschueren (1983). Thus, the NOEL = 3514 mg/m^3.

b) Dose adjustment is necessary to account for discontinuous exposure regimens used in the key study. Per EPA (1990), section 4.1.1.2, p. 4-13:

$$NOEL_{[ADJ]}(mg/m^3) = 3514\ mg/m^3 \times \frac{6\ hrs/day}{24\ hrs} \times \frac{5\ days/week}{7\ days}$$

$$= 3514\ mg/m^3 \times 0.25 \times 0.71$$

$$= 624\ mg/m^3$$

Pharmacokinetic data for ethylene in Sprague-Dawley rats (Bolt and Filser, 1987) indicate first-order kinetics at atmospheric concentrations < 80 ppm, with increasing saturation up to the maximum metabolic rate attained at concentrations higher than 1000 ppm.

c) Since the toxic action of ethylene is via asphyxiation, the HED is determined assuming extrarespiratory effects. Consequently,

$$NOEL_{[HEC]}\,(mg/m^3) = NOEL_{[ADJ]}\,(mg/m^3) \times \frac{\lambda_{animal}}{\lambda_{human}}$$

$$= 624\ mg/m^3 \times 1$$

$$= 624\ mg/m^3$$

where $\lambda_{animal}/\lambda_{human}$, the ratio of blood-to-air partition coefficients for rats to humans, assumes the EPA default value of 1 in the absence of data to the contrary.

Inhalation Reference Concentration (RfC) calculation:

Per EPA (1990), section 4.1.1, pp. 4-4 to 4-5:

$$RfC = NOEL_{[HEC]}/(UF \times MF)$$

$$= \frac{624\ mg/m^3}{([10 \times 10] \times 1)}$$

$$= 6.24\ mg/m^3$$

where the total UF of 100 is composed of 2 10-fold uncertainty factors to account for extrapolation from average healthy humans to sensitive humans, and for interspecies extrapolation from rats to humans. The MF assumes the default value of 1.

Using the EPA draft guidelines (Section 4.3, p. 4-42), level of confidence in the database for this RfC would be considered low, based on the availability of only one chronic toxicity study.

Derivation of the ITSL:

Per section R 336.1232, rule 232, subrule (1)(a) of Act 348, the ITSL for ethylene equals the inhalation RfC. Therefore:

$$\textbf{ITSL} = RfC = 6.24\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg} = \textbf{6240}\ \mu g/m^3$$ based on **24 hour averaging time**

REFERENCES

ACGIH (1993). Ethylene (74-85-1). Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices 1993-1994. American Conference of Governmental Industrial Hygienists, Cincinnati, pp. 7, 21.

Bolt, H.M., and Filser, J.G. (1987). Kinetics and disposition in toxicology; Example: Carcinogenic risk estimate for ethylene. Arch. Toxicol. 60(1-3):73-76.

EPA (1990). Interim Methods for Development of Inhalation Reference Concentrations (Review Draft). EPA Document No. 600/8-90/066A. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, N.C.

Filser, J.G., Denk, B., Törnqvist, M., Kessler, W. and Ehrenberg, L. (1992). Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene. Arch. Toxicol. 66(3):157-163.

Hamm, Jr., T.E., Guest, D. and Dent, J.G. (1984). Chronic toxicity and oncogenicity bioassay of inhaled ethylene in Fischer-344 rats. Fundam. Appl. Toxicol. 4(3, Pt. 1):473-478.

IARC (1985). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Allyl Compounds, Aldehydes, Epoxides and Peroxides, Volume 36. World Health Organization, International Agency for Research on Cancer, Lyon, pp. 189-226.

IARC (1987). Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7. International Agency for Research on Cancer, Lyon, p. 63.

NTP (1987). Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F, Mice (Inhalation Studies), NTP Technical Report 326, NIH Publication No. 88-2582. National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

Törnqvist, M., Alberg, J., Nilsson, S. and Osterman-Golkar, S. (1989). Ethylene oxide doses in ethene-exposed fruit store workers. Scand. J. Work Environ. Health 15:436-438.

Vershchueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd Ed. Van Nostrand Reinhold Company, New York, p. 632.

DO:ma
cc: A. Khan