MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Isobutene (CAS No. 115-11-7)

FROM: Robert Sills, Toxics Unit Supervisor, Air Quality Division

SUBJECT: ITSL Basis

DATE: September 12, 2017

The Initial Threshold Screening Level (ITSL) for isobutene (a.k.a., isobutylene) is 110,000 ug/m^3 with annual averaging time (AT).

This assessment utilized recent toxicological literature reviews by OECD (2003) and TCEQ (2015), and the findings of key studies including a chronic inhalation bioassay (NTP, 1998). Occupational Exposure Limits for isobutene are not available from ACGIH, NIOSH or OSHA.

OECD (2003) developed an assessment of isobutene as part of their High Volume Chemicals Programme. Isobutene has a low order of acute toxicity. Inhalation of isobutene can produce CNS depression, anesthesia (narcosis), and/or asphyxiation , but only at very high concentrations, i.e., approximately 20% or higher. Repeated dose studies for 14 weeks or 2 years at concentrations of up to 8,000 ppm did not result in exposure related adverse effects in mice or rats. Minimal effects on kidney weights and liver weights were not exposure concentration related or not adverse and significant (OECD, 2003; TCEQ, 2015). 13-Week and 14-week inhalation bioassays (NTP, 1998) found minimal effects in rats and mice exposed up to 8,000 ppm. No significant toxicological effects were observed at any concentration. The toxicological effects of an observed increase in ketone bodies is unknown (OECD, 2003). Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in exposed male and female rats but not in mice. In 2-year inhalation bioassays (NTP, 1998), rats and mice had exposure concentration-related increases in hyaline degeneration of the olfactory epithelium of the nose. “The accumulation of these protein globules is considered a nonspecific adaptive response to prolonged inhalation of irritant material and has no adverse effect on affected animals (NTP, 1998; OECD, 2003). Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats, however no nasal neoplasms were observed and this finding was not regarded as significant or adverse (OECD, 2003). The

frequency of the finding of minimal hypertrophy of goblet cells was as follows (TCEQ, 2015) at 0 ppm, 500 ppm, 2,000 ppm and 8,000 ppm, respectively: in male rats, 43/49; 45/49; 46/50; and, 49/49; in female rats, 44/50; 47/50; 48/50; and, 47/49. (It may be noted that previously, AQD (1994) based an ITSL on the 13-week inhalation bioassay finding of minimal hypertrophy of goblet cells in the nasopharyngeal duct, considering this to represent a subchronic LOAEL.)

Regarding potential reproductive/developmental effects, OECD (2003) found that, "Under the conditions of this prenatal developmental toxicity study, the inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity, prenatal or developmental toxicity, or teratogenicity at all tested concentrations up to 8,000 ppm. There was no effect of isobutylene on the number, growth or survival of the fetuses *in utero* and no effect on fetal development. These findings, along with the findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in repeated dose inhalation studies in two species, and the lack of significant effects on reproductive parameters (except for a minor weight increase in epididymis weight and decreased sperm motility in male rats exposed at 8,000 ppm) leads to a conclusion of low concern for reproductive toxicity.

OECD (2003) also considered any evidence of a carcinogenicity concern for isobutene. They determined that isobutene is not mutagenic or genotoxic. Isobutene exposure did cause in increased incidence of thyroid follicular cell carcinoma in the 8,000 ppm group male rats. However, there were no concurrent increases of thyroid gland follicular cell hyperplasia or adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the chamber controls, and the carcinomas appeared to be morphologically similar to spontaneously developing adenoma in male rats (NTP, 1998; OECD, 2003). "Based on the results of the NTP studies, isobutylene has a low potential for carcinogenicity. Although isobutylene produced an increase in follicular cell carcinomas of the thyroid, this effect occurred only in male rats at the highest dose, i.e., 8000 ppm. Thyroid tumors did not occur in female rats nor did they occur in male or female mice. As isobutylene is not genotoxic and as the thyroid tumors occurred in male rats at the highest dose, i.e., 8000 ppm, the mechanism for the formation of the thyroid tumors most likely has a threshold. Overall, this data suggests that isobutylene has a low potential for carcinogenicity." (OECD, 2003).

TCEQ (2015) developed a chronic Reference Value (ReV) of 110,000 ug/m^3 based on a free-standing NOAEL in rats and mice after chronic exposure (NTP, 1998). Their assessment of the key studies concurs with that of OECD (2003) described above; the free-standing NOAEL from the subchronic, chronic, and reproductive/developmental studies was identical at 8,000 ppm. They derived their chronic ReV assuming that isobutene is a category 3 gas (inducing systemic effects, notably, CNS effects, rather

than point-of-entry effects), and thus used an RGDR = 1. They applied a total uncertainty factor UF_T = 30, consisting of UF_H = 10, UF_A = 3 and UF_D = 1. A UF_A = 3 was used because a default dosimetric adjustment from animal-to-human exposure was conducted which accounts for toxicokinetic differences but not toxicodynamic differences. They applied dosing adjustments to account for the exposure schedule of 6 hrs/24 hrs and 5 days/7 days. They utilized the analytical exposure level of 7,960 ppm for the free-standing NOAEL, rather than the nominal value of 8,000 ppm. Their adjusted Point of Departure (POD) and ReV calculation are as follows:

POD_{ADJ} = POD (7960 ppm) X (6/24) X (5/7) = 1,421 ppm

POD_{HEC} = POD_{AQJ} X RGDR = 1,421 ppm X 1 = 1,421 ppm

$$\text{Chronic ReV} = \frac{POD_{HEC}}{UF_H \times UF_A \times UF_D} = 1{,}421 \text{ ppm} / (10X3X1) = 47.37 \text{ ppm} = 47{,}370 \text{ ppb}$$

Conversion factor: 1 ppb = 2.29 ug/m^3 (TCEQ, 2015)

Therefore, the Chronic ReV = 110,000 ug/m^3 (after rounding 108,477 ug/m^3 to two significant figures).

The AQD concurs with the TCEQ (2015) chronic ReV basis and derivation and is adopting this same value as the ITSL. An annual averaging time will be used with this ITSL.

References:

AQD. 1994. File for Isobutylene (CAS # 115-11-7). Screening Level for Isobutylene. Memo to file from George Eurich.

Organization for Economic Cooperation and Development (OECD). 2003. Screening Information Dataset (SIDS). Isobutylene. Date of last update: October 31, 2003. United Nations Environment Programme (UNEP) Publications.

Texas Commission on Environmental Quality (TCEQ). 2015. Development Support Document. Isobutene. Last revised: September 14, 2015. Prepared by: Roberta L. Grant, Ph.D., Toxicology Division.