MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: 1,2-Dibromoethane File (CAS# 106-93-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

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SUBJECT: Screening Level for 1,2-dibromoethane (CAS# 106-93-4)

The initial threshold screening level (ITSL) for 1,2-dibromoethane (CAS # 106-93-4) [also known as ethylene dibromide] is 9 µg/m^3 based on an annual averaging time. The initial risk screening level (IRSL) is 0.002 µg/m^3 and the SRSL is 0.02 µg/m^3 based on an annual averaging time. The ITSL was established in 2004 and was based on the EPA (2004) RfC of 9 x 10^{-3} mg/m^3 derived from nasal inflammation in a mouse chronic inhalation study by NTP (1982). The averaging time for the ITSL was originally set at the default of 24 hours, but is now being set at annual as supported by the key study and critical effect. The IRSL was also established in 2004 and was based on EPA's (2004) Inhalation Unit Risk (IUR) of 6 x 10^{-4} per µg/m^3 (95% upper bound) derived from nasal cavity tumors (including adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, and mesotheliomas from male Fisher 344 rats in a chronic inhalation study by NTP (1982).

1,2-Dibromoethane (CAS# 106-93-4), also known as ethylene dibromide (EDB) and glycol dibromide, is an organobromine compound with a molecular weight of 187.88 g/mol. It can be found naturally in the ocean in trace amounts and may be formed by algae and kelp.
1,2 Dibromoethane is colorless liquid with a sweet odor, with an odor threshold of 10 ppm.
1,2 Dibromoethane is used: as a fumigant on logs for termites and beetles; as a fumigant to control moths in beehives; as a pesticide in soil and on citrus, vegetable, and grain crops; as a preparation for dyes and waxes; and as an intermediate in the production of vinyl bromide (ATSDR, 2011).

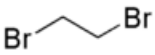

Figure 1. Structure of 1,2-Dibromoethane.

ITSL Derivation:

A study by the National Toxicology Program (NTP, 1982) used male and female F344 rats and B6C3F1 mice (50 per sex, species, and exposure group) exposed via inhalation to either 0, 10, or 40 ppm (0, 77, or 307 mg/m^3) 1,2-dibromoethane for 6 hours/day, 5 days/week, for 103 weeks. "However, high-exposure rats of both sexes and female mice exhibited high mortality (84-90%) beginning at about 60 weeks, resulting in early termination (between 78 and 91 weeks) of these exposure groups. The low exposure groups were not terminated until the end of the study (104-106 weeks) although low-exposure female mice displayed high mortality (62%)

relative to controls (20% mortality). The male mouse study was not considered as relevant for derivation of an RfC because of high mortality in control and exposed groups due to complications from urinary tract infections that were not exposure-related" (EPA, 2004).

The noncarcinogenic effects observed in the NTP (1982) study are hepatic necrosis (male and female rats), testicular degeneration (male rats), retinal atrophy (female rats), adrenal cortical degeneration (female rats), splenic hematopoiesis (female mice), and inflammation of the nasal cavity (female mice). Because the NTP study demonstrated adequate spacing of exposure levels with increasing responses at increasing exposure levels, the inhalation toxicity of 1,2-dibromoethane was evaluated by EPA (2004) using benchmark dose (BMD) analysis. To derive an RfC, the BMDL values derived from the NTP (1982) study were adjusted to equivalent continuous exposures, converted to human equivalent concentrations (HECs), and then divided by uncertainty factors. For systemic (liver, testicular, retinal, adrenal, and splenic) effects, the EPA RfC method for Category 3 gases (EPA, 1994) was used to convert BMDLs to BMDL(HEC)s. The EPA RfC method for Category 1 gases was used to convert the BMDL for nasal effects to a BMDL(HEC). As shown in Table 1, the NTP (1982) data for nasal effects in female mice resulted in the lowest BMDL(HEC) of 2.8 mg/m^3. This BMDL(HEC) was then divided by an overall uncertainty factor of 300 to obtain the RfC of 9 E-3 mg/kg-day" (EPA, 2004).

"1,2-Dibromoethane is considered a Category 2 gas because it is relatively insoluble in water and demonstrates systemic toxicity. For Category 2 gases, HEC values are calculated using methods for Category 1 gases for portal-of-entry effects and Category 3 methods for systemic effects (EPA, 1994)" (EPA, 2004). "HEC values were calculated in accordance with EPA (1994) RfC methods. For extrarespiratory effects, a default adjustment factor of 1.0 was used for adjusting from ADJ to HEC values because 1,2-dibromoethane blood:air partition coefficients are not known for the experimental species and humans. For the respiratory effect (nasal inflammation) the HEC was calculated for an effect in the extrathoracic (ET) region. Minute volume$_{mouse}$ = 0.041 L/min, minute volume$_{human}$ = 13.8 L/min, Surface area (ET)$_{mouse}$ = 3 cm^2, Surface area (ET)$_{human}$ = 200 cm^2" (EPA, 2004).

$$Regional\ gas\ dose\ ratio_{ET} = \frac{\frac{minute\ volume_{mouse}}{surface\ area\ (ET)_{mouse}}}{\frac{minute\ volume_{human}}{surface\ area\ (ET)_{human}}} = \frac{\frac{0.41\ L/_{min}}{3\ cm^2}}{\frac{13.8\ L/_{min}}{200\ cm^2}} = 0.198$$

The BMDL$_{10}$ for nasal inflammation was determined to be 80.1088 mg/m^3 and was adjusted to a continuous exposure by using the following equation:

$$BMDL_{ADJ} = 80.1088\ {}^{mg}/_{m^3} \times \frac{5\ days}{7\ days} \times \frac{6\ hours}{24\ hours} = 14.3\ {}^{mg}/_{m^3}$$

$$BMDL_{HEC} = BMDL_{ADJ} \times Regional\ gas\ dose\ ratio_{ET} = 14.3\ {}^{mg}/_{m^3} \times 0.198 = 2.8\ {}^{mg}/_{m^3}$$

EPA used an uncertainty factor of 300 (3 for interspecies variability, 10 for intraspecies variability in sensitivity, and 10 for database uncertainty). "An uncertainty factor of 3 was applied for interspecies pharmacodynamics as a consequence of considering human equivalent dosimetry and due to the lack of data suggesting a more or less divergent response in humans. An uncertainty factor of 10 for intraspecies variability in sensitivity results was applied as well as a default value due to the lack of data indicating a different degree of variability in humans. An

uncertainty factor for less than lifetime exposure is considered to be unnecessary because the principal study was carried out for at least 88 weeks. A database uncertainty factor of 10 is applied. High mortality in the principal study (NTP, 1982) causes considerable uncertainty with respect to the exposures that the animals received and with respect to the responses that might have been observed had the animals survived to term. A 1-generation inhalation reproductive toxicity study is available, but no multi-generation study. The lack of the multi-generation study is of particular concern in light of the genotoxicity of 1,2-dibromoethane, because any genetic damage to the germ cells of the F1 generation would not be detected until the F2 generation. Furthermore, the absence of an evaluation of sperm in the reproductive toxicity study is of concern, in light of the effects observed in humans and bulls. Developmental toxicity studies covering major organogenesis (but not studies covering the entire period of gestation) are available in two species via the inhalation route, and inhalation systemic toxicity studies that evaluated the respiratory tract are available in two species. There is also some limited evidence for neurobehavioral developmental effects caused by 1,2-dibromoethane as well as endocrine disruption (based on effects on other endocrine organs as well as changes in hormone levels)" (EPA, 2004). This gives a Reference Concentration for chronic inhalation exposure (RfC) of 9×10^{-3} mg/m^3.

Rule 232(1)(a) states that a RfC can be used as an ITSL; therefore, the ITSL for acrylonitrile is 9 µg/m^3. Rule 232(2)(b) states that the default averaging time is 24-hours; however, in this case, the critical effect and study duration support an annual averaging time as allowed under Rule 229(2)(b).

IRSL Derivation:

The EPA has determined that 1,2-dibromoethane is a Group B2, probable human carcinogen, "…based on the consistent findings of several studies reporting increased incidences of a variety of tumors in rats and mice of both sexes by different routes of administration at both the site of application and at distant sites, it can be concluded that there is strong evidence of the carcinogenicity of 1,2-dibromoethane in animals. The available evidence further supports a conclusion that 1,2-dibromoethane is a genotoxic carcinogen based on evidence from a variety of *in vitro* and *in vivo* test systems" (EPA, 2004).

The EPA derived a quantitative estimate of carcinogenic risk from inhalation exposure with an inhalation unit risk (IUR) of 6×10^{-4} (µg/m^3)$^{-1}$ using dose-response data from the NTP (1982) study. The inhalation IUR was based on nasal cavity tumors (which includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, and mesotheliomas in male Fischer 344 rats.

Administered concentration (ppm)	Equivalent continuous concentration (ppm)	Human equivalent continuous concentration (ppm)	Tumor incidence adjusted using poly-3* Procedure		
			Nasal tumors	Hemangiosarcomas	Mesotheliomas
0	0	0	1/46 (2%)	0/46 (0%)	1/46 (2%)
10	1.8	0.36	39/45 (86%)	1/43 (2%)	8/43 (19%)
40	7.1	1.42	41/43 (95%)	15/28 (54%)	25/35 (71%)

*Poly-3 procedure involves adjusting each animal represented in the denominator by $(t/104)^3$, where t is the time of final sacrifice in a given dose group. Source: NTP (1982).

The EPA used the "mulitstage Weibull method [using] linear extrapolation from the lower 95% confidence limit on dose associated with extra risk (adjusted for background) at point of departure at lower end of data range" (EPA, 2004). "EPA RfC methodology (EPA, 1994, 2002) was used to estimate human equivalent dose corresponding to the nasal (extra-thoracic) region. 1,2-Dibromoethane was considered a Category 1 gas for this analysis, due to its assumed portal-of-entry toxicity in this tissue. Assuming a temperature of 25°C, a barometric pressure of 760 mmHg, and a molecular weight for 1,2-dibromoethane of 187.88, one ppm equals 7.68 mg/m^3 (187.88/24.45). Minute volume$_{rat}$ = 0.21 L/min, minute volume$_{human}$ = 13.8 L/min, surface area (ET)$_{rat}$ = 15 cm^2, surface area (ET)$_{human}$ = 200 cm^2" (EPA, 2004).

$$Regional\ gas\ dose\ ratio\ (ET) = \frac{\frac{minute\ volume_{rat}}{surface\ area\ (ET)_{rat}}}{\frac{minute\ volume_{human}}{surface\ area\ (ET)_{human}}} = \frac{\frac{0.21\ ^{L}/_{min}}{15 cm^2}}{\frac{13.8\ ^{L}/_{min}}{200 cm^2}} = 0.20$$

"Each of the exposures adjusted for continuous exposure above were multiplied by the regional gas dose ratio of 0.20 to yield human equivalent exposure levels. This gives a calculated inhalation unit risk of 6 x10^{-4} (95% upper bound). Rule 231(1) was used to develop the IRSL, using the inhalation unit risk value derived by the EPA for 1,2-dibromoethane. The equation is below:

$$IRSL = \frac{1 \times 10^{-6}}{Unit\ Risk} = \frac{1 \times 10^{-6}}{6 \times 10^{-4}} = 0.00167\ ^{\mu g}/_{m^3} \cong 0.002\ ^{\mu g}/_{m^3}$$

Rule 231(4) states that the averaging time for IRSLs and SRSLs is an annual averaging time. The initial risk screening level (IRSL) for 1,2-dibromoethane (CAS# 106-93-4) is 0.002 µg/m^3 and the SRSL is 0.02 µg/m^3 based on an annual averaging time.

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