MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Dichlorodifluoromethane (CAS # 75-71-8)

FROM: Keisha Williams, Air Quality Division

DATE: February 22, 2019

SUBJECT: Screening Level Update for Dichlorodifluoromethane

The initial threshold screening level (ITSL) for acute exposure to dichlorodifluoromethane is 49,500 µg/m^3 (8-hour averaging time) (MDEQ, 2001). An ITSL for chronic exposure to trichlorofluoromethane is being adopted at this time. The chronic ITSL is 330 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD), Rule 336.1232 (1) (a).

This determination was based on an updated review by the MDEQ, Remediation and Redevelopment Division (MDEQ, 2015). Dichlorofluoromethane (CFC-12) is among the class of potential ozone-depleting compounds that have been banned from production and importation in the United States (USEPA). However, with the potential for use of existing stockpiles and the continued detectable levels observed at air monitoring stations in Michigan, these ITSLs will be retained.

Background Information

CFC-12 was used as a refrigerant, aerosol propellant, solvent and pesticide (HSDB, 2013). Figure 1 shows the chemical structure for CFC-12, and Table 1 shows some of its chemical properties.

Figure 1. Chemical structure of CFC-12

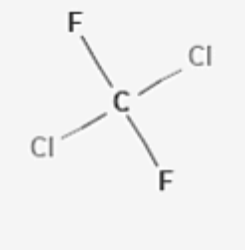

Table 1. Chemical and physical properties of CFC-12

Molecular weight (grams/mole)	120.908
Boiling point	-29.8°C
Vapor pressure	4850 mm Hg at 25 °C
Physical state at room temperature	Gas

Reference: NCBI

There have been oral studies conducted on rodents that were designed to investigate the carcinogenicity of CFC-12 (ACGIH, 2001). Based on these studies and a lack of information, CFC-12 is currently considered to not be classifiable as a carcinogen.

The acute ITSL is based on an occupational exposure limit which, in turn, is based on a no observable adverse effect level (NOAEL) from subchronic inhalation studies, where "Prendergast et al. (1967) exposed several species to 3997 ± 112 mg/m^3 CFC-12 continuously for 90 days" (MDEQ, 2001). The 1992 threshold limit value (TLV) that is cited as the basis for the ITSL has not changed (ACGIH, 2001). With an updated review of established benchmarks, the USEPA's provisional peer-reviewed toxicity value (PPRTV) was determined to be an appropriate basis for a chronic ITSL (MDEQ, 2015).

The USEPA's PPRTV is based on the same *in vivo* studies used to derive the occupational exposure limit (ACGIH, 2001; EPA, 2010). The exposure concentration in the squirrel monkey and beagle dog studies was used for the provisional inhalation reference concentration (p-RfC) derivation as shown in Equation 1. This exposure concentration, 985 mg/m^3, resulted in a lowest observable adverse effect level (LOAEL) of reduced body weight gain after 6 weeks of inhalation exposure for 8 hours/day, 5 days per week. In the PPRTV documentation, it was noted that the "confidence in the principle study…is low."

Equation 1.

$$Subchronic\ p-RfC = \frac{LOAEL}{UF} = \frac{985\frac{mg}{m^3}}{1000} = 1\frac{mg}{m^3}$$

Where uncertainty factors are 3 for interspecies extrapolation, 10 for intraspecies extrapolation, 10 for LOAEL to NOAEL extrapolation, and 3 for database limitations, because the database lacks reproductive and developmental toxicity studies.

Rather than using database uncertainty factors as a default policy, it has been AQD policy to only adopt database uncertainty factors when there is some chemical-specific evidence or rationale. As a result, the use of this uncertainty factor is further evaluated here. Based on the PPRTV documentation, "The database for inhalation exposure to dichlorodifluoromethane includes studies in humans, subchronic toxicity studies in several species of animals, a chronic study that presented only limited data on noncancer endpoints, and a limited developmental toxicity study in two species that tested a mixture containing 90% dichlorodifluoromethane in which no effects were seen at high doses. A factor of 3 ($10^{0.5}$) is applied for database inadequacies because data for evaluating reproductive and developmental toxicity via the inhalation route are inadequate." The rationale presented does not indicate chemical-specific

evidence for use of the database uncertainty factor. In as much, the uncertainty factor of 3 applied for database deficiencies will not be retained.

It is also AQD policy to derive either acute or chronic ITSLs as compared to adopting subchronic screening levels. In the PPRTV documentation, it was determined to not be appropriate to derive a chronic p-RfC, because "…no chronic duration human inhalation studies exists, and the few subchronic human inhalation studies identified are either of poor design, short-term exposure duration (e.g., 3−4 weeks), or involve exposure to mixtures of compounds containing dichlorodifluoromethane." However, a chronic screening level was derived by USEPA to assist risk assessors (USEPA, 2010). In this chronic screening value derivation, an uncertainty factor of 10 for subchronic to chronic extrapolation was applied to the subchronic p-RfC as shown in Equation 2.

Equation 2.

$$Screening\ Chronic\ p-RfC = \frac{LOAEL_{HEC}}{UF} = \frac{985\frac{mg}{m^3}}{10{,}000} = 1x10^{-1}\frac{mg}{m^3}$$

For the purposes of a chronic ITSL derivation, the database uncertainty factor will be removed, but the duration uncertainty factor will be retained as shown in Equation 3.

Equation 3.

$$chronic\ ITSL = \frac{LOAEL}{UF} = \frac{985\frac{mg}{m^3}}{3{,}000} = 0.3283\frac{mg}{m^3}x\frac{10^3\mu g}{mg} \approx 330\ \frac{\mu g}{m^3}, annual\ averaging\ time$$

Therefore, the ITSL for CFC-12 is 330 µg/m^3, annual averaging time.

References

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Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

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USEPA. Ozone Layer Protection-Science. Ozone-Depleting Substances. Class I Ozone-Depleting Substances. Accessed on January 15, 2019: http://www.epa.gov/ozone/strathome.html

KW:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 16, 2001

TO: File for dichlorodifluoromethane (CASRN 75-71-8)

FROM: Mary Lee Hultin, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The final Initial Threshold Screening Level (ITSL) for dichlorodifluoromethane (CFC-12; CASRN 75-71-8) is 49,500 µg/m^3 for an 8-hour averaging time. The Air Quality Division (AQD) staff initially evaluated this compound in 1993 using interim ITSL procedures to derive a permissible impact range of 49,500 ug/m^3 and 700 µg/m^3 for an 8-hour and 24-hour averaging time, respectively. In an effort to finalize all interim chemical screening levels, this chemical was re-reviewed to set a final ITSL. The following references or databases were searched to identify data to determine the ITSL: IRIS-online, HEAST, RTECS, EPB-CCD, MDEQ library, CAS-online, NLM-online, NIOSH Pocket Guide, and ACGIH Guide.

CFC-12 is used as a refrigerant, solvent, blowing agent, sterilant, an intermediates for plastics, and as an aerosol propellant (WHO, 1990). It may be abused when humans deliberately inhale volatile substances to achieve intoxication (Flanagan and Ives, 1994). People may also be exposed through industrial accidents and poor occupational practices (WHO, 1990). It is a colorless gas with and ether-like odor at extremely high concentrations. Its vapor pressure is 5.7 atm.

The American Council of Governmental Industrial Hygienists (ACGIH) listed an occupational exposure level of 1000 ppm (4950 mg/m^3) for CFC-12 (1992). This is based on a subchronic continuous-exposure study. Prendergast *et al.* (1967) exposed several species to 3997 ± 112 mg/m^3 CFC-12 continuously for 90 days. Hartley guinea pigs appeared to be the most sensitive species with one pig out of 15 dying, 1 showing a focal giant cell pneumonitis upon necropsy, and all liver sections examined from this species showing slight to extensive fatty infiltration, with several sections showing focal or submassive necrosis. These effects were also seen, with lower incidence and less severity, in guinea pigs receiving repeated exposures ($LOAEL_{ADJ}$ = 984.8 mg/m^3) for six weeks. This study was cited in the HEAST documentation as an adequate provisional value for an RfC, using the repeated-exposure, lower LOAEL value for the derivation. The TLV documentation lists Prendergast *et al.* (1967) as its key study. The six-week study is deemed inadequate for RfC derivation.

The EPA's Integrated Risk Information System (IRIS; 2000) oral reference dose (RfD) of 0.2 mg/kg/day for CFC-12 was based on a two-year oral gavage study in rats. Charles River CF strain rats (50/sex/dose) received 15 or 150 mg/kg/day CFC-12. The rats received the compound seven days/wk for the first six weeks, then five days/week for the remainder of the study. Data were collected on reproductive and developmental indices, food consumption, clinical signs, mortality, hematology, urinalysis, biochemistry, bone fluoride, and pathology. No treatment effects were seen beyond a depression in body weight throughout the study in the high-dose group for both sexes, as much as 12% difference from controls. (Sherman and Barnes, 1974; Sherman *et al.*, 1974). A NOAEL (no-observable-adverse-effect-level) of

15 mg/kg/day was indicated for this study. The U.S. Environmental Protection Agency (EPA) applied a 10-fold uncertainty factor each for species extrapolation and sensitive individuals to attain an RfD of 0.2 mg/kg/day.

According to the AQD rules governing ITSL derivations, data derived from an EPA RfD takes precedence over data derived from an occupational exposure level. Additionally, Rule 232(1)(b) states that an ITSL shall be determined from an oral reference dose (RfD) from the best available information provided that none of the data showed that oral to inhalation route extrapolation is inappropriate. The oral exposure studies used in the IRIS RfD derivation indicated that the only adverse effect was a depression in body weight in the rats receiving 150 mg/kg/day CFC-12. The critical effects following inhalation were hepatonecrosis and potential pulmonary impacts in guinea pigs. Other effects observed in laboratory animals exposed to CFC-12 via inhalation were cardiovascular abnormalities as seen in ECGs (Taylor and Drew, 1975; Taylor *et al.*, 1976) and cardiac sensitization to epinephrine-induced arrhythmias (Reinhardt *et al.*, 1971; Lessard *et al.*, 1977, 1978). Because the effects caused by oral and inhalation exposures are dissimilar, it is inappropriate to use oral data for derivation of an RfC. Therefore, the ITSL will be derived from the TLV.

The ITSL was determined as follows:

ACGIH TLV = 4950 mg/m^3

4950 $mg/m^3 \div 100 = 49.5\ mg/m^3$

49.5 mg/m^3 X 1000 $\mu g/mg = 49{,}500\ \mu g/m^3$

The ITSL for dichlorodifluoromethane = 49,500 $\mu g/m^3$ based on an 8 hour averaging time.

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MLH:CB:DB
cc: Cathy Simon
Sheila Blais