MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Trichlorofluoromethane (CAS # 75-69-4)

FROM: Keisha Williams, Air Quality Division

DATE: February 22, 2019

SUBJECT: Screening Level Update for Trichlorofluoromethane

The initial threshold screening level (ITSL) for acute exposure to trichlorofluoromethane is 56,200 µg/m^3 (1-hour averaging time) (MDEQ, 1996). An ITSL for chronic exposure to trichlorofluoromethane is being adopted at this time. The chronic ITSL is 130 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). Trichlorofluoromethane (CFC-11) 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-11 has been used as a refrigerant, aerosol propellant, and solvent (HSDB, 2013). Figure 1 shows the chemical structure for CFC-11, and Table 1 shows some of its chemical properties.

Figure 1. Chemical structure of CFC-11

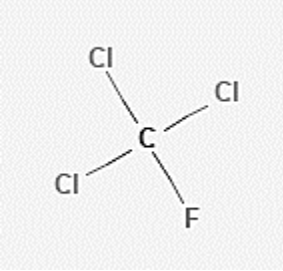

Table 1. Chemical and physical properties of CFC-11

Molecular weight (grams/mole)	137.359
Boiling point	24°C
Vapor pressure	5803 mm Hg at 25 °C
Physical state at room temperature	liquid

Reference: NCBI

There have been oral and subcutaneous studies conducted on rodents to investigate the carcinogenicity of CFC-11 (ACGIH, 2001). Based on these and a lack of information, CFC-11 has not been classified 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) in an animal inhalation study (MDEQ, 1996). 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 screening level (MDEQ, 2015).

The USEPA's PPRTV for the provisional inhalation reference concentration (p-RfC) for subchronic exposure is based on a controlled human study where healthy male volunteers (n=8) were exposed to only one concentration, 1000 ppm (5620 mg/m^3), for 8 hours/day, 5 days/week for 2 - 4 weeks (EPA, 2009). Accounting for the intermittent exposures, the time-weighted acreage exposure is thus 1338 mg/m^3. The exposure concentration was observed to be the lowest observable adverse effect level (LOAEL), where "statistically significant decrements were observed in cognitive performance tests." In the PPRTV documentation, it was further noted that the "confidence in the key study…is medium-to-low." The PPRTV was determined as shown in Equation 1.

Equation 1.

$$Subchronic\ p-RfC = \frac{LOAEL}{UF} = \frac{1338\frac{mg}{m^3}}{1000} = 1\frac{mg}{m^3}$$

Where uncertainty factors are 10 for intraspecies extrapolation, 10 for LOAEL to NOAEL extrapolation, and 10 for database limitations, because the database lacks reproductive, developmental and comprehensive neurobehavioral 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 lacks reproductive, developmental, and comprehensive neurobehavioral toxicity studies." Given that neurological effects are the critical effect observed, the rationale presented does support chemical-specific evidence for use of the database uncertainty factor. Therefore, the uncertainty factor of 10 applied for database deficiencies will 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, "…due to the brevity of available studies and insufficient justifications for considering long-term effects…" However, it has been AQD policy to extrapolate from subacute exposures to chronic exposures to determine health-protective chronic screening levels, and a chronic screening level will be adopted by AQD by applying an uncertainty factor of 10 for subchronic to chronic extrapolation as shown in Equation 2.

Equation 2.

$$chronic\ ITSL = \frac{subchronic\ p-RfC}{UF_{duration}} = \frac{1338\frac{mg}{m^3}}{10{,}000} = 0.1338\ x\ \frac{10^3 \mu g}{mg}$$
$$\approx 130\ \frac{\mu g}{m^3}, annual\ averaging\ time$$

Therefore, the ITSL for CFC-11 is 130 µg/m^3, annual averaging time.

References

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MDEQ. 2015. Chemical update Worksheet. August 19, 2015. RRD Toxicology Unit.

NCBI: National Center for Biotechnology Information. PubChem Compound Database; CID=6389, https://pubchem.ncbi.nlm.nih.gov/compound/6389 (accessed Jan. 15, 2019).

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

USEPA. 2009. Provisional Peer-Reviewed Toxicity Values for Trichlorofluoromethane. U.S. Environmental Protection Agency, Washington, DC, EPA/690/R-09/066F.

KW:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

December 11, 1996

TO: File for Trichlorofluromethane (75-69-4)

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The final Initial Threshold Screening Level (ITSL) for trichlorofluromethane is 56,200 ug/m^3 based on an 1 hr. averaging time. This compound was initially evaluated by AQD staff in 1993, using interim ITSL procedures to derive an impact of 1050 ug/m^3 (24 hr), and 56,000 ug/m^3 (1 hr) averaging times. In an effort to finalize all interim chemical screening levels, this chemical was re-reviewed to set a final ITSL/(IRSL). The following references or databases were searched to identify data to determine the ITSL/IRSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, and ACGIH Guide.

Pulmonary uptake of inhaled CFC-11 by rabbits and dogs is prompt. Peak circulating concentrations after exposure at 4500 to 5000 ppm were achieved in 15 seconds with steady-state reached at 20 minutes. Elimination of CFC-11 is relatively rapid. Dogs exhaled within 1 hour essentially all the CFC-11 inhaled during a 6- to 20-minute exposure at 5000 ppm. In male and female volunteers, most (79-100%) of the inhaled ^{14C}CFC-11 was exhaled within the first hour after a 7- or 17-minute inhalation at 1000 ppm. Only 0.12% of the inspired compound was recovered as $^{14}CO_2$ and only 0.08% appeared in urine.

Acute studies have shown that CFC-11 has a low order of toxicity by all routes of administration (oral, inhalation, and dermal). Application of CFC-11 to the skin and eyes of rabbits and rats caused minor reversible irritation but no serious injury; while inhalation exposure causes weak narcotic-like effects. An LC_{50} value of 130,000 ppm for a 15-minute exposure with rats has been reported, whereas a 100,000 ppm exposure to rats caused death within 20 to 120 minutes. When dogs and rabbits inhaled CFC-11 for 20 minutes at 50,000 ppm, the only metabolic modifications were slight increases in blood glucose and lactic acid.

A number of subchronic studies have also shown CFC-11 to have a low order of toxicity. In a German study (Leuschner, 1983), dogs and rats were exposed to 5,000 and 10,000 ppm by volume, respectively to CFC-11; 6 hrs/day for 90 consecutive days. No adverse effects were noted in any of the test animals. Likewise, in a 4-week series of 3.5 hr exposures at 12,500 or 25,000 ppm, a 6-week study with 7-hr exposures at 4,000 ppm, and another 6-week study with 8-hr exposures at 10,250 ppm showed no adverse effects attributable to inhaled CDC-11 in various species.

Jenkins et al., exposed various species (squirrel monkeys, dogs, guinea pigs and rats) to 58,000 mg/m^3 CFC-11, 8 hrs/day, 5 days/wk, for 6 weeks. Compared with controls, effects noted in treated animals were elevated serum urea nitrogen in dogs, mild liver discoloration in some rats and guinea pigs, and a

liver lesion in one exposed monkey. Additionally, nonspecific inflammatory changes in hematological or biochemical data or body weight was observed for all species. Jenkins et al., also exposed squirrel monkeys, beagles, guinea pigs and rats to 5600 mg/m^3 CFC-11 continuously for 90 days. The results were nonspecific inflammatory changes in the lungs of all species, elevated serum nitrogen levels in dogs, and mild liver discoloration in some rats and guinea pigs.

Both chronic and carcinogenic endpoints were studied in a rat and mouse NCI gavage bioassay conducted in 1978. In this study, 50 male and 50 female Osborne-Mendel rats and equivalent numbers of male and female B6C3F1 mice were administered CFC-11 by gavage 5 days/wk for 78 weeks. Adjusted doses equaled 500 or 1000 mg/kg and 2000 or 3900 mg/kg for rats and mice, respectively. No decreases in body weight was reported in rats. In male and female rats, dose-related early mortality was observed, but was associated with murine pneumonia. Low incidences (<20%) of pericarditis and pleuritis were observed in all treated groups of rats but not in controls. In mice, no statistically significant compound related effect on body weight gain or clinical signs was observed. Based on the Tarone test, a significant (p=.009) dose-related acceleration of mortality was observed in female but not male mice.

From this same study, carcinogenic results showed that there was no significant positive association between tumor incidence in rats surviving >52 weeks. These results were inconclusive, however, because of high early mortality in male and female rats; an inadequate number of rats survived long enough to be at risk for late-developing tumors. The results in mice showed no statistically significant increase in tumor incidence and no unusual tumors were found.

In human subchronic inhalation studies, Stewart et al., (1978) studied health effects in humans following repeated exposures to CFC-11. Eight male volunteers were exposed to 1000 ppm (5600 mg/m3) of CFC-11, 8 hrs/day, 5 days/wk for 4-weeks. These exposures did not produce any untoward physiological effects as determined by a number of biological endpoints, including clinical hematology, and chemistry, electrocardiogram, electroencephalogram, neurological parameters, pulmonary function, and cognitive tests.

The EPA has an established RfD of 0.3 mg/kg/day for CFC-11 based on the NCI bioassay mentioned above. The RfD was derived from a LOAEL of 488 mg/kg/day with critical effects of survival and histopathology. According to EPA, a statistically significant positive association between increased dosage and accelerated mortality by the Tarone test in male and female rats and female mice were observed. However, the quality of this study is questionable due to the fact that accelerated mortality was caused by murine pneumonia. The EPA reasoned that "the preferential acceleration of mortality among treated groups may have been a result of CFC-11 lowering the resistance to pneumonia". It is unknown, why EPA based a chemical specific outcome from a study on a confounder such as a bacterial infection. A bacterial infection in an animal study is indicative of an infectious precondition, or that *Good Laboratory Practice* was not followed. In addition to this, it was also unclear from the study whether or not the control animals were also affected. One part of the study mentioned a significant increase in dose-related mortality when compared to controls using the Tarone test, while another section of the study mentioned that murine pneumonia observed in 88-100% of rats in all groups, appeared to be a factor in early mortality. Because of these uncertainties, the RfD will not be used to derive an ITSL.

The final ITSL of 56,200 ug/m^3 (1 hr. averaging) based on the TLV-Ceiling of 5620 mg/m^3 will be the sole screening level for this compound. The ACGIH bases this ceiling limit on a no-observed-adverse-effect concentration in animals inhaling CFC-11 24 hours/day for 90 days at 1000 ppm. They state that this value should provide a substantial margin of safety to minimize the potential for systemic toxicity (including fluorosis) and incorporate a wide margin of safety to preclude acute cardiac sensitization. Both NIOSH and OSHA concur with this recommendation.

References:

1. Documentation of Threshold Limit Values and Biological Exposure Indices. 1991. Trichlorofluoromethane. American Conference of Governmental Industrial Hygienists (ACGIH), 6th Edition.

2. US EPA, Office of Health and Environmental Assessment and Office of Research and Development. 1987. Health Effects Assessment for Fully Halogenated Methanes. EPA/600/8-88/041.

3. Stewart R. D. et al., 1978. *Physiological Response to Aerosol Propellants.* Environmental Health Perspectives Vol. 26; 275-285.

4. Jenkins L. J. et al., 1970. *Repeated and Continuous Exposures of Laboratory Animals to Trichlorofluoromethane.* Toxicology and Applied Pharmacology. Vol. 16; 133-142.

5. Leuschner B. W. et al., 1983. *Report on Subacute Toxicological Studies with Several Fluorocarbons in Rats and Dogs by Inhalation.* Arzneim.-Forsch./Drug Res. Vol. 33(II), Nr. 10; 1475-1476.

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