MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

April 1, 2016

TO: File for 1,1,1,2-tetrafluoroethane (811-97-2)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for 1,1,1,2-tetrafluoroethane (Synonym: HFC-134a) is 80,000 µg/m³ based on an annual averaging time.

The U.S. Environmental Protection Agency (EPA, 1995) derived a reference concentration for 1,1,1,2-tetrafluoroethane of 80,000 µg/m³. This forms the basis of the ITSL, pursuant to Rule 232(1)(a). Based on the duration of the key study and the derivation of the screening level it was determined that an annual averaging time is appropriate, pursuant to Rule 229(2(b).

Critical Effect: Leydig cell hyperplasia
Type of Study: Rat Chronic Inhalation Study
Reference: Collins et al., 1995
Total Uncertainty factor: 100 (3 interspecies, 10 intraspecies, 3 database deficiency)

The Benchmark Concentration (BMC) associated with a 10% extra risk in the critical effect was determined to be 11,030 ppm = BCM10. The molecular weight (MW) of 1,1,1,2-tetrafluoroethane is 102 g/mol. Assuming 25 C and 760 mmHg,

BMC10 (mg/m³) = BMC10 (ppm) x MW/24.45 = 46,000 mg/m³.
BMC10(duration adjusted) = 46,000 x 6 hours/24 hours x 5 days/7 days = 8200 mg/m³.

The BMC10(human equivalent concentration or HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 is used for this ratio. BMC10(HEC) = 8200 x [b:a lambda(a)/b:a lambda(h)] = 8200 mg/m³.

A 2-year inhalation exposure study with 1,1,1,2-tetrafluoroethane (HFC- 134a) was conducted by Collins et al., 1995. In this study, groups of 85 Wistar-derived rats/sex were whole-body exposed to 0, 2500, 10,000, or 50,000 ppm (0, 10,400, 41,700, and 208,600 mg/m³) HFC-134a (99.8% pure) for 6 hours/day, 5 days/week (duration-adjusted concentrations = 1860, 7450, or 37,250 mg/m³, respectively). The only treatment-related

effects after 104 weeks of exposure were found in the testes. A statistically significant increase in absolute and relative testes weight was found at the terminal sacrifice (n = 75, relative weights were 0.6, 0.59, 0.61, and 0.66 in the 0-, 2500, 10,000-, and 50,000-ppm groups, respectively). In addition, there was a significant increase in the incidence of Leydig cell hyperplasia (incidence of 27, 25, 31, and 40 in the 0-, 2500-, 10,000-, and 50,000-ppm groups, respectively). The testicular effects were considered adverse. This study establishes a lowest-observed-adverse-effect-level (LOAEL) of 50,000 ppm [LOAEL(HEC) = 37,250 mg/m^3] and a no-observed-adverse-effect-level (NOAEL) of 10,000 ppm [NOAEL(HEC) = 7450 mg/m^3]. Because of the high background, a substantial difference in the estimates of benchmark concentration occurs for extra vs. additional risk models (65,000 vs. 46,000 mg/m^3). An extra risk model was selected as most appropriate, based on the conservative assumption of independence of mechanisms causing the background and treatment-related responses. Dose-response models for dichotomous data using a polynomial (multistage) and a Weibull form and either including a model parameter for a background intercept or not (sometimes referred to as a threshold parameter) were applied. Using any of these four model forms, an excellent model fit was obtained, and the BMC estimates were the same after rounding to two significant figures. The BMC for a 10% extra increase in Leydig cell hyperplasia is 46,000 mg/m^3 [BMC10(HEC) = 8200 mg/m^3].

The uncertainty factor of 100 reflects a factor of 10 to protect sensitive individuals, 3 for interspecies extrapolation, and 3 for database deficiencies, including the lack of a chronic study in a second species and a two-generation reproductive study. A full factor of 10 was not considered necessary for database deficiencies because rats and mice have been shown to respond similarly to several hydrofluorocarbons and in vitro studies show similar metabolism of HFC-134a in human and rodent liver tissue; therefore, a chronic study in a second species is considered unlikely to result in substantial changes of the database.

References:

EPA. 2003. 1,1,1,2-Tetrafluoroethane; CASRN 811-97-2. Chemical Assessment Summary Integrated Risk Information System (IRIS). National Center for Environmental Assessment. U.S. Environmental Protection Agency. Updated RfC. First on-line Updated: 08/01/1995. https://www.epa.gov/iris Accessed: 4/1/2016: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0656_summary.pdf

Collins, M.A., G.M. Rusch, F. Sato, P.M. Hext and R.J. Millischer. 1995. 1,1,1,2-Tetrafluoroethane repeat exposure inhalation toxicity in the rat, developmental toxicity in the rabbit, and genotoxicity in vitro and in vivo. Fund. Appl. Toxicol. 25: 271-280.