DRAFT: DEVELOPMENT OF PROVISIONAL ORAL AND INHALATION REFERENCE DOSES AND PRELIMINARY SCREENING LEVELS FOR AMMONIUM PERFLUOROOCTANOATE

A Provisional Oral Reference Dose (PRfDo) of 3 x 10-5E or 0.00003 mg/kg/day for Ammonium Perfluorooctanoate (C8) and a Provisional Inhalation Reference Concentration (PRfCi) of 0.02 $\mu g/m^3$ have been developed by WVDEP. Subsequently, a Preliminary Screening Level (PSLw) for groundwater of 1 ppb was calculated based on this PRfDo and on the model for the water ingestion exposure pathway with default parameters commonly used by USEPA and WVDEP. The PRfCi of 0.02 $\mu g/m^3$ would serve as the Preliminary Screening Level (PSLi) for air. The scientific rationale used to develop the PRfCi and the PRfDo, and to calculate the PSLw is described below.

Development of the Provisional Oral Reference Dose:

Ammonium perfluorooctanoate (C8 or APFO) is a potent synthetic surfactant. In biologic media, the ammonium quickly dissociates. C8, as perfluorooctanoic acid (PFOA), comprises 93 – 98% of FC-143 FLUORAD Brand Fluorochemical Surfactant. Toxicity studies have been conducted on APFO, PFOA, and FC-143. The USEPA has conducted a literature search and review of toxicological data regarding PFOA; their findings are summarized in the Draft Hazard Assessment of PFOA (in preparation). This document, including supporting references, and information provided to WVDEP by DuPont, and the data contained on 7 compact discs as part of the TSCA submittal by 3M were the major sources of toxicological information utilized in the development of the reference doses.

The first step in the development of a reference dose is to identify appropriate exposure studies. Chronic studies utilizing the appropriate route of exposure and animal model are most highly desirable. However if such studies are not available, then subchronic studies utilizing other routes of exposure may be employed for reference dose development by including additional uncertainty factors. Ideally a NOAEL, No Observable Adverse Effect Level, was determined in the study; however, if a NOAEL was not determined, then a LOAEL, Lowest Observable Adverse Effect Level, may be employed in reference dose development by including an additional uncertaintly factor.

The only chronic oral exposure study available was conducted in male and female rats fed FC-143 over a two-year period (3M, 1987). A LOAEL of 300 ppm (14.2 mg/kg/day for male, and 16.1 mg/kg/day female) was determined in rats based on decreased body weight gains; increased liver and kidney weight; and toxicity in the hematological and hepatic systems. However, a LOAEL for female rates of 30 ppm (1.6 mg/kg/day) was determined based on incidence of ataxia and reversible ovarian tubular hyperplasia.

To date, four 90-day subchronic oral exposure animal studies have been conducted - two in monkeys and two in rats. A LOAEL of 30 ppm (1.72 mg/kg/day) was determined by Goldenthal (1978a) in male rats exposed to a diet including FC-143 based

on increased liver weight; increased blood glucose; and decreased red cell counts. Palazzolo (1993) found a NOAEL of 30 ppm (1.44 mg/kg/day) and a LOAEL of 100 ppm (4.97 mg/kd/day) based on decreased body weight and body weight gain, and on increased absolute and relative liver weights with hepatocellular hypertrophy in male rats exposed to PFOA in the diet for 13 weeks.

Goldenthal (1978b) determined an oral NOAEL of 3 mg/kg/day in rhesus monkeys. However, this dose group occasionally had soft stools or moderate to marked diarrhea, and frothy emesis. Also, there were trends toward increased glucose levels, and decreased alkaline phosphatase levels in this dose group.

Butenhoff, et al., (2001) found an oral LOEL of 3 mg/kg/day based on increased liver weight in cynomolgus monkeys, which occurred at serum concentrations that overlapped those observed in some workers with high exposure; therefore the liver enlargement was considered to be a significant effect by the authors. A NOEL was not determined in this study. Because the monkey is most physiologically similar to humans, as evidenced by the long half-life of C8 in humans (1 – 3.5 years) and monkeys. This LOEL was utilized to estimate an the PRfDo as decribed below:

Calculation of the Oral Provisional Reference Dose:

$$PRfDo = \frac{LOEL}{(UFH)\,(UFA)\,(UFS)\,(UFL)\,(MF)}$$

where:
PRfDo = Provisional Oral Reference Dose (mg/kg/day);
LOEL = Lowest Observable Effect Level (mg/kg/day) = 3;
UF = Uncertainty Factors (unitless);
H = intrahuman variability accounts for variation in sensitivity among the human population =10;
A = animal to human extrapolation = 10;
S = extrapolation from subchronic exposure to chronic exposure = 10;
L = extrapolation from a LOEL to a NOEL = 10;
D = insufficiency in the toxicological database = 3;
MF = Modifying Factor (unitless) = 3
A modifying factor of 3 was used because of the following characteristics of C8:

- Long half-life in humans (approximately 1 – 3.5 years);
- Potential for bioaccumulation;
- Potential for biopersistence;
- Unusual physical properties such as solubility and partition coefficient.

Therefore, the PRfDo equals 3 x 10E-5.

Calculation of the Preliminary Screening Level for C8 in Water:

The PSL of 1 µg/L or ppb was calculated using a Hazard Quotient of 1 and the following equation and default parameters:

$$GW = \frac{(PRfDo)\,(BWa)\,(CF)}{(IRWa)}$$

where:

GW = concentration in Groundwater (µg/L);
PRfDo = Provisional Oral Reference Dose (mg/kg/day) = 3 x 10E-5;
BWa = adult body weight (kg) = 70;
CF = conversion factor (from mg to µg) = 1000;
IRWa = Ingestion Rate of Water for an adult (L/day) =2.

Development of Provision Inhalation Reference Concentration:

No monkey inhalation exposure studies have been conducted for PFOA. However, two two-week (6 hr/day; five days/week) inhalation exposure studies were conducted in rats by DuPont (1994). In the first study, a LOAEL of 11 mg/m^3 was found based on decreased body weight and hepatic injury. In the second study, a NOAEL of 1 mg/m^3 was determined. This NOAEL agreed with a NOAEL of 1 mg/m3 found by Staples et al. (1984) in female rats during a developmental toxicity study of PFOA. Inhalation reference doses were calculated for the NOAEL and the LOAEL as described below.

Based on the LOAEL:

Conversion from intermittent exposure to continuous exposure:

LOAEL = E x D (h/24h) x W (days/7 days)

Where:
LOAEL = 11 mg/m^3;
E = exposure level in mg/m^3;
D = hours of exposure (6);
W = days of exposure (5);

Thus the continuous exposure LOAELc = 1.95 mg/m^3;

$$PRfCi = \frac{LOAELc}{(UFH)\,(UFA)\,(UFS)\,(UFL)\,(MF)}$$

where:
PRfCi = Provisional Inhalation Reference Concentration (mg/m^3);
LOAELc = Lowest Observable Effect Level (mg/m^3) = 11;
UF = Uncertainty Factors (unitless);
H = intrahuman variability accounts for variation in sensitivity among the human population =10;
A = animal to human extrapolation = 10;
S = extrapolation from subchronic exposure to chronic exposure = 10;
L = extrapolation from a LOEL to a NOEL = 10;
D = insufficiency in the toxicological database = 3;
MF = Modifying Factor (unitless) = 3
A modifying factor of 3 was used because of the following characteristics of C8:

- Long half-life in humans (approximately 1 – 3.5 years);
- Potential for bioaccumulation;
- Potential for biopersistence;
- Unusual physical properties such as solubility and partition coefficient.

Therefore, the PRfCi equals 0.022µg/m^3 based on the LOAEL of 11 mg/m^3.

Based on the NOAEL:

Conversion from intermittent exposure to continuous exposure:

NOAEL = E x D (h/24h) x W (days/7 days)

Where:
NOAEL = 1 mg/m^3;
E = exposure level in mg/m^3;
D = hours of exposure (6);
W = days of exposure (5);

Thus the continuous exposure NOAELc = 0.18 mg/m^3;

$$PRfCi = \frac{NOAELc}{(UFH)\,(UFA)\,(UFS)\,(UFL)\,(MF)}$$

where:
PRfCi = Provisional Inhalation Reference Concentration (mg/m^3);
NOAELc = No Observable Effect Level (mg/m^3) = 1;
UF = Uncertainty Factors (unitless);
H = intrahuman variability accounts for variation in sensitivity among the human population =10;
A = animal to human extrapolation = 10;
S = extrapolation from subchronic exposure to chronic exposure = 10;
D = insufficiency in the toxicological database = 3;

MF = Modifying Factor (unitless) = 3

A modifying factor of 3 was used because of the following characteristics of C8:

- Long half-life in humans (approximately 1 – 3.5 years);
- Potential for bioaccumulation;
- Potential for biopersistence;
- Unusual physical properties such as solubility and partition coefficient.

Therefore, the PRfCi equals 0.02µg/m^3 based on the NOAEL of 1 mg/m^3. The PRfCi estimated using the NOAEL and the LOAEL are approximately equal.

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