

3M Lifetime Drinking Water Health Advisory for Perfluorooctanoate

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SUMMARY

A lifetime drinking water health advisory (DWHA) was developed for perfluorooctanoate based on a review of the animal and human health-effects information available for PFOA and its various salt forms, predominantly the ammonium salt (APFO). The method used involved calculating a reference dose (RfD), from which a drinking water exposure level (DWEL) was derived and modified using a relative source contribution factor (RSC). The RfD was calculated using established USEPA methodology and was based on the results of a six-month oral dosing study of APFO in cynomolgus monkeys. Using a total uncertainty factor of 1800, the RfD was established at 2 ug/kg - day. Using the default assumptions of two liters of water consumed per day and a 70 kg human, the DWEL was thus calculated to be 70 ug/L. Using the default assumption that drinking water constitutes 20 percent of daily exposure, the lifetime DWHA was calculated to be 14 ug/L (ppb).

This lifetime DWHA is meant as an advisory to be considered in cases where potential exposure to PFOA occurs through drinking water sources in communities. Certain modifying factors can alter the value of this advisory, such as information which would change the value of the default assumptions. As such, PFOA concentrations in water in excess of 14 ug/L should not be interpreted to represent excess risk without further consideration of exposure parameters.

METHODOLOGY

The DWHA for APFO was calculated using standard EPA methodology as described in documents cited in the references section and appendix to this document. Briefly, the following three equations were used:

$$RfD = \frac{(NOAEL) \text{ or } (LOAEL)}{(UF)} = mg/kg \text{ body weight / day}$$

$$DWEL = \frac{(RfD) (70 \text{ kg})}{2 \text{ L/day}} = mg/L \text{ or } ug/L$$

$$\text{Lifetime DWHA} = DWEL \times RSC = mg/L \text{ or } ug/L$$

Abbreviations:

- RfD** Chronic Reference Dose [the estimate (with uncertainty spanning an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime]
- NOAEL** No Observed Adverse Effect Level [the exposure/dose level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and the appropriate control; some effects may be produced at this level but they are not considered to be adverse, nor to be a precursor to specific adverse effects]
- LOAEL** Lowest Observed Adverse Effect Level [the lowest exposure/dose level at which there are statistically or biologically significant increases in the

frequency or severity of adverse effects between the exposed population and the appropriate control]

- UF** Uncertainty Factor (chosen using EPA guidance). The total UF is composed of five sub-factors that attempt to account for uncertainty with regard to: 1) interhuman variability; 2) extrapolation of results from experimental animal to human; 3) extrapolation from subchronic to chronic exposure; 4) extrapolation from LOAEL to NOAEL; and 5) incomplete database to complete database. The standard EPA default factor for each of the five sub-UFs = 10. Sub-UFs <10 may also be used when existing data reduce or eliminate the need to account for a particular area of uncertainty. The choice of appropriate sub-UFs and the MF is accomplished on a case-by-case basis using professional judgment by experienced risk assessors. A modifying factor (**MF**) may also be applied to account for areas of scientific uncertainty not accounted for in the five sub-UFs. The default value of the MF is 1.
- DWEL** Drinking Water Equivalent Level [the concentration of a substance in drinking water that is not expected to cause any non-carcinogenic health effects in humans over a lifetime of exposure]
- RSC** Relative Source Contribution [the proportion of exposure to a chemical from drinking water relative to other sources such as food and air](in the absence of any other data the EPA default value = 20% is used)
- DWHA** The concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects over a lifetime of exposure, with a margin of safety.

RATIONALE FOR RfD

The health-effects information available for PFOA was thoroughly reviewed in order to establish the most appropriate and sensitive endpoint for derivation of the RfD. Liver enlargement, as measured by increases in absolute and relative liver weight, was identified as the most sensitive endpoint based on the fact that liver enlargement is an early and consistent finding in multiple repeat-dose studies. The six-month oral capsule-dosing study in male cynomolgus monkeys (Butenhoff *et al.*, submitted 2002) was chosen as the most sensitive and appropriate study for deriving the RfD based on the endpoint of liver weight increase. In the cynomolgus monkey study, liver weight increases were present in all APFO treated groups after six months of oral capsule dosing with APFO. In the two lower dose groups (3 and 10 mg APFO/kg/day) the liver weight increases were the only treatment-related finding in the study and are believed to be reversible, based on the fact that two monkeys assigned to "recovery" for 90 days post-treatment did not have increased absolute or relative liver weight. Normally, liver weight increases would not be considered an adverse finding in the absence of evidence for hepatocellular hyperplasia or degenerative effects on liver tissue. In the case of the cynomolgus monkey study, mitochondrial proliferation is believed to explain some, if not all, of the liver weight increases. The reasons for the proliferation of liver mitochondria in the study are not understood; however, factors which lead to reduced oxidative phosphorylation may stimulate the proliferation of mitochondria (Fosslien, 2001). It could be argued that 10 mg/kg/day represents a NOAEL for the cynomolgus monkey study. The fact that sub-populations of exposed workers may have body burdens in the range of those of monkeys in the two lower treatment levels in the cynomolgus monkey study suggests a conservative view of the study findings. Therefore, for purposes of establishing an RfD, a LOEL/NOAEL of 3 mg/kg/day was used.

Two chronic dietary oncogenicity studies in SD rats were reviewed in relation to the entire database of toxicology and human-health information (Biegel *et al.*, 2001 and 3M Riker Laboratories, 1987). It was concluded that it was appropriate to use a reference-

dose approach based on a non-tumorigenic endpoint. The basis for this conclusion stems from the facts that APFO has not been demonstrated to have direct genotoxic properties in multiple assay systems, that the tumor response in these studies was weak, and that available evidence from mechanistic studies suggests that the hepatocellular adenomas and Leydig cell adenomas observed in rats arise from mechanisms that have questionable relevance to humans (Biegel *et al.*, 2001; Butenhoff *et al.*, submitted 2002). The hepatocellular adenoma observed in rats is believed to be a result of increased proliferation of peroxisomes via a PPAR-alpha-mediated process. Leydig cell adenomas in the rat are believed to be related to the induction of aromatase leading to sustained increases in estradiol, thus causing a proliferative effect in the testes (Biegel, *et al.*, 1995; Biegel *et al.*, 2001; Cook *et al.*, 1992; Liu *et al.*, 1996(a); Liu *et al.*, 1996(b)). Increases in peroxisome proliferation and estradiol did not occur in the cynomolgus monkey study, even at the highest treatment level of 30/20 mg/kg/day, which caused significant toxicity. Both two-year dietary studies demonstrated qualitatively similar results with respect to the occurrence of hepatocellular adenoma and Leydig cell adenoma at a dietary concentration of 300 ppm; however, they differed in that the 3M study did not produce an excess of pancreatic acinar cell adenomas at either the 30 or 300 ppm dose level. Sustained increases in cholecystokinin or changes in bile acid composition have been proposed as mechanisms for the production of pancreatic acinar cell tumors (Obourn *et al.*, 1997). In the cynomolgus monkey study, there were no observed increases in cholecystokinin or changes in bile acid composition. Furthermore, epidemiological studies and medical monitoring of the exposed 3M workforce have revealed no associations of PFOA with adverse effects, including excess cancer risk, effects on liver function, changes in sex hormones, and changes in cholecystokinin (Olsen *et al.*, 1998; Olsen *et al.*, 2000; Alexander *et al.*, 2001). The conclusion that the tumors seen in the rat studies have questionable relevance to humans is consistent with the conclusion of the American Conference of Governmental Industrial Hygienists (ACGIH) as expressed in the *Documentation of the Threshold Limit Value*, (ACGIH, 1999) for APFO.

CALCULATION

Step 1. RfD Calculation

$$RfD = \frac{(NOAEL) \text{ or } (LOAEL)}{(UF)} = mg/kg \text{ body weight} - day$$

Establishment of Uncertainty Sub-Factors:

LOEL/NOAEL = 3.0 mg/kg-day [From 6-month cynomolgus monkey oral capsule-dosing study]

UF = 1800 [total UF = 1800 (10x3x10x6x1X1)]

Individual sub-UFs were as follows:

Interhuman (person-to-person variability) = 10 [Standard EPA default considered appropriate in this case due to known non-occupational exposure of the population]

Extrapolation from experimental animal to human = 3 [Used male non-human primate data to establish the RfD. The lack of metabolism of APFO after dissociation to PFOA (Kuslikis *et al.*, 1992; Vanden Heuval *et al.*, 1991) removes uncertainty in the interspecies extrapolation (monkey-to-human), and the cynomolgus monkey is believed to be a close surrogate species to represent possible human response to toxic levels of PFOA.]

Extrapolation to chronic exposure (chronicity) = 10 [Based on exposure duration longer than subchronic but significantly less than chronic (6 months in a non-human primate); PFOA has been shown to accumulate in the body on repeated exposure due to poor elimination; the cynomolgus monkey appears to have a much shorter whole-body elimination half-life as compared to humans.]

LOAEL to NOAEL = 6 [RfD is based on increased liver weight with no apparent clinical effect in male cynomolgus monkeys given 3 mg APFO/kg/day for six months. While this may normally be considered a NOAEL, the study sponsor, member companies of the Association of Plastic Manufacturer's in Europe (APME), took a cautious approach to the data and considered 3 mg/kg/day as a lowest observable effect level (LOEL) for the male cynomolgus monkey. Female cynomolgus monkeys have a terminal-phase elimination half-life which appears to be longer than male cynomolgus monkeys with a mean of approximately 30 days in the female as opposed to approximately 20 days in the male; although, the number per sex in the elimination study was small (3), this observation may indicate a potential for females to respond to effects of compound at lesser doses than the male.]

Incomplete database = 1 [Significant data have been accumulated on APFO/PFOA, covering all traditional endpoints and dosing methods as well as extensive mechanistic investigation; two chronic dietary studies of APFO in rats are available.]

Modifying Factor = 1 [human data available; significant data accumulated on APFO/PFOA; sensitive endpoint established in studies; uncertainties accounted for in other sub-factors.]

Therefore:

$$RfD = 0.002 \text{ mg/kg-day or } 2 \text{ ug/kg-day}$$

$$RfD = \frac{3.0 \text{ mg / kg - day}}{1800} = 0.0017 \text{ mg / kg - day (rounded to 0.002)}$$

Step 2. DWEL Calculation

$$DWEL = \frac{(RfD) (70 \text{ kg})}{2 \text{ L/day}} = \text{mg/L or ug/L}$$

$$DWEL = \frac{(2 \text{ ug / kg - day}) (70 \text{ kg})}{2 \text{ L/day}} = 70 \text{ ug / L}$$

Step 3. Lifetime DWHA Calculation

$$\text{Lifetime DWHA} = DWEL \times RSC = \text{mg/L or ug/L}$$

$$\text{Lifetime DWHA} = (70 \text{ ug / L})(0.2) = 14 \text{ ug / L (ppb)}$$

The value established for lifetime exposure to drinking water is 14 ug / L (ppb).

This value assumes that twenty percent of an individual's exposure to APFO is from drinking water and may be adjusted if the relative source contribution can be shown to be lesser or greater than twenty percent.

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APPENDIX

Precedent exists (see Arochlor example, below) for a reduction in sub-UFs (*i.e.* versus using standard defaults = 10 for each sub-UF) when the experimental data warrant. Based on the significant amount of available toxicological data for PFOS (including data from studies on other FCs in which PFOS is hypothesized to be the “toxic” metabolite) it is very relevant to use both professional risk assessment and toxicological judgment to “adjust” the sub-UFs based on available data.

The EPA-derived RfD for Arochlor 1016 is 7×10^{-5} mg/kg-day. The total uncertainty factor used by EPA was 100; an MF of 1 was also used. Reductions in sub-UFs (from a default value of 10) were made based on the available data and professional judgment (similar to the case for RfD derivation for PFOS). The following is excerpted from the IRIS file for Arochlor 1016:

Arochlor 1016: UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- A 3-fold factor is applied to account for sensitive individuals. The results of these studies, as well as data for human exposure to PCBs, indicate that infants exposed transplacentally represent a sensitive subpopulation. A factor of 3 is applied for extrapolation from rhesus monkeys to human. A full 10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and metabolism of PCBs between monkeys and humans and the general physiologic similarity between these species. In addition, the rhesus monkey data are predictive of other changes noted in human studies such as chloracne, hepatic changes, and effects on reproductive function. A factor of 3 is applied because of limitations in the

data base. Despite the extensive amount of animal laboratory data and human epidemiologic information regarding PCBs, the issue of male reproductive effects is not directly addressed and two-generation reproductive studies are not available. As the study duration was considered as somewhat greater than subchronic, but less than chronic, a partial factor of 3 is used to account for extrapolation from a subchronic exposure to a chronic RfD.

MF – None