



Internal Correspondence

To: Dr. John Butenhoff, Manager
Corporate Toxicology

From: Dr. Robert Roy
Corporate Toxicology

Subject: Draft Drinking Water Health Advisory (DWHA) - PFOS

Date: July 7, 1999

John --

The attached document presents the derivation of a draft lifetime DWHA for PFOS. The draft DWHA is based on a reference dose (RfD) which was derived using a conservative, composite uncertainty factor (UF).

A very similar process of RfD development (e.g. selection of appropriate UFs based on available data) has been used by EPA for Arochlor 1016; this is also included for your reference (Appendix).

If you have questions or would like to discuss, please let me know.

Rob

DRAFT –

Lifetime Drinking Water Health Advisory (DWHA) for PFOS

Background¹

The DWHA for PFOS was calculated using standard EPA methodology. Briefly, the following three equations were used:

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

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

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

Where:

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 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 exposure 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 = Total 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

DRAFT --

experimental animal to human; 3) extrapolation from subchronic to chronic exposure; 4) extrapolation from LOAEL to NOAEL; and 5) incomplete database to complete database.

A modifying factor (MF) may also be applied to account for areas of scientific uncertainty not accounted for in the five sub-UFs.

The standard EPA default factor for each of the five sub-UFs = 10; that for the MF = 1. 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.***

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 [is 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)

Lifetime Drinking Water Health Advisory (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.

References

Cicmanec, J.L. *et al.* (1996). Noncancer risk assessment: present and emerging issues. In: Fan, A.M. and Chang, L.W. (editors) *Toxicology and Risk Assessment: Principles, Methods, and Applications*. Marcel Dekker, New York, pp. 293-310. *(copy of paper attached)*

Dourson, M.L. *et al.* (1996). Evolution of science-based uncertainty factors in noncancer risk assessment. *Regulatory Toxicology and Pharmacology* 24: 108-120. *(copy of paper attached)*

Environmental Protection Agency (1999). Integrated Risk Information System (IRIS). WWW address: <http://www.epa.gov/ncea/iris.htm>

Environmental Protection Agency (1999). Office of Water. Drinking Water Regulations and Health Advisories. WWW address: <http://www.epa.gov/OST/Tools/dwstds0.html>

DRAFT –

I. Lifetime Drinking Water Health Advisory (DWHA) for PFOS

Step 1. RfD Calculation

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

NOAEL = 0.15 mg/kg-day [NOAEL from 6-month monkey oral capsule study]

UF = 900 (rounded up = 1000) [total UF = 900 (10x3x10x1x3). Individual sub-UFs were as follows [also refer to Appendix]:

Interhuman (person-to-person variability) = 10 [standard EPA default]

Extrapolation from experimental animal-to-human (Interspecies variability) = 3 [used non-human primate]

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); PFOS also appears to accumulate in the body on repeated exposure due to poor elimination]

LOAEL to NOAEL = 1 [standard default - NOAEL used]

Incomplete database = 3 [significant data accumulated on chemical; results of the 2-year bioassay are still pending]

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

DRAFT -

Therefore:

$$RfD = \frac{0.15 \text{ mg/kg-day}}{1000} = 0.00015 \text{ mg/kg-day} = (0.2 \text{ } \mu\text{g/kg-day})$$

Note: The precision associated with the RfD is usually one significant figure, therefore, RfD should be rounded to = 0.2 $\mu\text{g/kg-day}$

II. Lifetime Drinking Water Health Advisory (DWHA) for PFOS

Step 2. DWEL Calculation

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

$$DWEL = \frac{(0.2 \text{ } \mu\text{g/kg-day}) (70 \text{ kg})}{2 \text{ L day}} = 7 \text{ } \mu\text{g/L}$$

III. Lifetime Drinking Water Health Advisory (DWHA) for PFOS

Step 3. Lifetime DWHA Calculation

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

$$\text{Lifetime DWHA} = (7 \text{ } \mu\text{g/L})(0.2) = 1.0 \text{ } \mu\text{g/L (ppb)}$$

DRAFT –

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^{-6} 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