UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

OCT 2 8 2009

MEMORANDUM

SUBJECT: The Toxicity of Perfluorooctanic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

FROM: Janine Dinan, Environmental Health Scientist
Office of Emergency Management (OEM)
Office of Solid Waste and Emergency Response (OSWER)

Dave Crawford, Environmental Scientist
Office of Superfund Remediation and Technology Innovation (OSRTI)
Office of Solid Waste and Emergency Response (OSWER)

TO: Glenn Adams, Chief
Technical Services Section
Superfund Division
US EPA Region 4

Background

PFOA and PFOS have been found at sites in EPA Region 4 and in other regions. As a result, Region 4 has asked the Headquarter's Office of Superfund Remediation and Technology Innovation (OSRTI) and the Office of Emergency Management (OEM) to recommend toxicity values.

On December 5, 2003, OSRTI released guidance (OSWER Directive 9285.7-53) establishing a three-tiered hierarchy of human health toxicity values. Tier 1 is EPA's Integrated Risk Information System (IRIS). Tier 2 is the provisional peer reviewed toxicity values (PPRTVs) completed for the EPA Superfund Program by the EPA Superfund Health Risk Technical Health Risk Support Center. Tier 3 are toxicity values from other credible sources such as other federal or State agencies. Three sources of Tier 3 toxicity values were identified in

2003, but OSRTI also stated that additional Tier 3 sources may exist, and that additional Tier 3 sources may be identified in the future. As there are no toxicity values for PFOA or PFOS available in IRIS or as PPRTVs, this memorandum constitutes a Tier 3 consultation and recommends Tier 3 toxicity values for PFOA and PFOS.

Process

OSRTI and OEM consulted with several EPA program offices to discuss the use of the EPA Office of Water (OW) provisional health advisories as Tier 3 toxicity values. After weighing input from these offices, we make the following recommendations regarding the OW advisory and the interim oral non-cancer toxicity values for PFOA and PFOS.

Recommendations

On January 8, 2009 OW completed and released Provisional Health Advisories for PFOA and PFOS (See Attachment 1). Prior to the release of this assessment, OW invited, received and considered internal and external peer review comments on the then draft assessment. Although derived using methods that differ from the Superfund program's risk-based approaches, OSRTI and OEM find the OW provisional drinking water advisories of 0.4 µg/l for PFOA and 0.2 µg/l for PFOS credible as protective health-based concentrations for these contaminants in drinking water.

Because the OW provisional health advisories address only water consumption, oral reference dose values (RfDs), which can be used to address oral exposure to other media such as soil, were not developed. However, the methodology used by OW in deriving its provisional health advisories can also be used to derive subchronic RfD values for PFOA and PFOS, as shown below:

- **Perflurooctanoic Acid (PFOA)**

  For PFOA, the OW provisional health advisory relies on data from a sub-chronic study in mice (Lau, et al 2006) to derive a Benchmark Dose Level ($BMDL_{10}$) of 0.46 mg/kg-day[1]. When calculating toxicity values such as an RfD, a BMDL or a No Observed Adverse Effect Level (NOAEL) can be used to derive an RfD. In deriving an RfD for PFOA, certain numerical factors are applied to the BMDL to account for differences in the metabolism and sensitivity among test animals and humans to the effects of PFOA. Using the numerical factors presented in OW's provisional health advisory, a subchronic RfD can be developed, as follows:

[1] EPA toxicity assessments, including Integrated Risk Informaiton System (IRIS) assessments, using BML modeling in the derivation of an RfD typically use the 10% response level from the BML modeling ($BMDL_{10}$) to derive an RfD.

Subchronic RfD = $(BMDL_{10}) / UF_H * (UF_A = UF_{pharmacodynamic} * UF_{pharmacokinetic})$
= (0.46 mg/kg-day) / 10 * (3 * 81)
= **2E-4 mg/kg-day**

UF_H = a factor of 10 to account for variations in the dose-response (i.e., sensitivity) among humans to the effects of PFOS

UF_A= a factor to account for differences in the metabolism of PFOA in mice vs. humans
- $UF_{pharmacodynamic}$ = a factor of 3 to account for variations in the dose-response among mice to the effects of PFOA
- $UF_{pharmacokinetic}$ = a factor of 81[2] to account for differences in the rate of clearance of PFOA in mice vs. humans

- **Perfluorooctane Sulfonate (PFOS)**

For PFOS, the OW provisional health advisory relies on data from a sub-chronic study in monkeys (Seacat, et al. 2002) to derive a NOAEL of 0.03 mg/kg-day. As with PFOA, certain numerical factors are applied to the NOAEL to account for differences in the metabolism and sensitivity among test animals and humans to the effects of PFOS. Using the numerical factors presented in OW's provisional health advisory, a subchronic RfD can be developed, as follows:

Subchronic RfD = $(NOAEL) / UF_H * (UF_A = UF_{pharmacodynamic} * UF_{pharmacokinetic})$

= 0.03 mg/kg-day / 10 * (3 * 13)
= **8E-5 mg/kg-day**

UF_H = a factor of 10 to account for variations in the dose-response (i.e., sensitivity) among humans to the effects of PFOS
UF_A= a factor to account for differences in the metabolism of PFOS in monkeys vs. humans
- $UF_{pharmacodynamic}$ = a factor of 3 to account for variations in the dose-response among monkeys to the effects of PFOS
- $UF_{pharmacokinetic}$ = a factor of 13[3] to account for differences in the rate of clearance of PFOS in monkeys vs. humans

Currently, OEM has not established removal action levels for PFOA or PFOS as the basis for considering alternate water supplies, nor have these contaminants been addressed in the Regional Screening Levels for Chemical Contaminants at Superfund Sites. However, the Tier 3 sub-chronic RfDs presented in this memorandum may be used in the Superfund program's risk-based equations to derive Removal Action Levels and/or Screening Levels for water and other media, as appropriate.

---

[2] See Attachment 1, page 4 for additional details about this UF.
[3] See Attachment 1, pages 4 and 5 for additional details about this UF.

Please be aware that the recommendations made in this memorandum may be modified by OSRTI and OEM as the state of the science evolves with respect to deriving toxicity values and determining protective concentrations of PFOA and PFOS. Such changes may include the availability of an IRIS or a PPRTV assessment and/or the promulgation of a Safe Drinking Water Act Maximum Contaminant Level by OW.

Questions related to the use of this memorandum and its recommendations may be directed to Dave Crawford (703-603-8891) and to Janine Dinan (202-564-8737) in OEM.

Attachment 1

January 8, 2009

Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

1. Introduction

EPA recently concluded limited testing of agricultural sites in Alabama where sewage sludge was applied from a local wastewater treatment plant that receives wastewater from numerous industrial sources, including facilities that manufacture and use perfluorooctanoic acid (PFOA) and other perfluorinated chemicals (PFCs). The results from this limited testing indicated elevated levels of PFCs in the sludge and the soil that received the sludge. As a result, EPA has conducted sampling of public drinking water. The levels of PFOA and perfluorooctane sulfonate (PFOS) recently analyzed in community water systems in Lawrence and Morgan Counties are all lower than 0.04 ppb. Based on its current understanding, EPA believes these levels are not of concern and residents may rely upon public water systems. EPA will soon begin groundwater and surface water sampling to determine if PFOA or PFOS has migrated into any private drinking water supplies and ponds in the affected area.

The Office of Water (OW) has developed Provisional Health Advisory values[1] for PFOA and PFOS to assess potential risk from exposure to these chemicals through drinking water. Other PFCs have been found at this site. However, information on the toxicity of PFCs other than PFOS and PFOA is limited and therefore no attempt is made at the present time to develop Provisional Health Advisory values for these other PFCs.

2. Summary of Data for PFOA

Epidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present.

Several animal toxicological studies have been conducted using PFOA. These include subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. An evaluation of these studies was conducted by the European Food Safety Authority (EFSA) and no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), and critical endpoints identified (EFSA, 2008).

Among these studies, a recent and well conducted developmental toxicity study in mice was selected by the Office of Water (OW) as the critical study for the derivation of the

[1] Provisional Health Advisory values are developed to provide information in response to an urgent or rapidly developing situation. They reflect reasonable, health-based hazard concentrations above which action should be taken to reduce exposure to unregulated contaminants in drinking water. They will be updated as additional information becomes available and can be evaluated.

Provisional Health Advisory for PFOA (Lau et al., 2006). In this study, CD-1 mice were given the ammonium salt of PFOA by oral gavage from gestational day (GD) 1 to 17 at doses of 0, 1, 3, 5, 10, 20 or 40 mg/kg/day. Significant increase in the incidence of full-litter resorption occurred at 5 mg/kg/day and higher doses. Weight gain in dams that carried pregnancy to term was significantly lower in the 20-mg/kg/day group. At GD 18, some dams were sacrificed for maternal and fetal examinations (group A), and the rest were treated once more with PFOA and allowed to give birth (group B). Postnatal survival, growth, and development of the offspring were monitored. PFOA induced enlarged liver in group A dams at all dosages, but did not alter the number of implantations. The percent of live fetuses was lower only in the 20-mg/kg/day group (74 vs. 94% in controls), and fetal weight was also significantly lower in this group. However, no significant increase in malformations was noted in any treatment group. The incidence of live birth in group B mice was significantly lowered by PFOA: ca. 70% for the 10- and 20-mg/kg/day groups compared to 96% for controls. Postnatal survival was severely compromised at 10 or 20 mg/kg/day, and moderately so at 5 mg/kg/day. Dose-dependent growth deficits were detected in all PFOA-treated litters except the 1-mg/kg/day group. Significant delays in eye-opening (up to 2–3 days) were noted at 5 mg/kg/day and higher dosages. Accelerated sexual maturation was observed in male offspring, but not in females. These data indicate maternal and developmental toxicity of PFOA in the mouse, leading to early pregnancy loss, compromised postnatal survival, delays in general growth and development, and sex-specific alterations in pubertal maturation (Lau et al., 2006).

Toxicity endpoints identified in the Lau et al. (2006) study included a number of developmental landmarks: neonatal eye opening, neonatal survival and body weight at weaning, reduced phalangeal ossification at term, live fetus weight at term, maternal liver weight at term, and maternal weight gains during pregnancy. The most sensitive endpoint was for increased maternal liver weight at term. This endpoint for liver effects was identified in a number of other studies described in EFSA (2008).

Benchmark dose (BMD_{10}) and the 95% lower bound on the BMD ($BMDL_{10}$) were calculated for these toxicity endpoints by the EFSA on the basis of raw data provided by the principal author (Lau, personal communication, November 18, 2008). The lowest $BMDL_{10}$ in the Lau et al. (2006) study was 0.46 mg/kg/day for increase in maternal liver weight at term. This value was used as the point of departure for the derivation of the Provisional Health Advisory value for PFOA. It should be noted that liver effects were also reported in studies in rats and monkeys. $BMDL_{10}$ values for increased liver weight in studies in mice and rats ranged from 0.29 to 0.74 mg/kg/day (EFSA, 2008). The $BMDL_{10}$ for Lau et al. (2006) was in the middle of this range.

3. Summary of Data for PFOS

Epidemiological studies of exposure to PFOS and adverse health outcomes in humans are inconclusive at present.

Several animal toxicological studies have been conducted with PFOS. These include subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. An evaluation of these studies was conducted by the EFSA (2008) and NOAEL, LOAEL and critical endpoints identified.

The subchronic toxicity study in Cynomolgus monkeys (Seacat et al., 2002) was selected by the OW as the critical study for the derivation of the Provisional Health Advisory value for PFOS. In the study by Seacat et al. (2002), groups of male and female monkeys received orally potassium PFOS at doses of 0, 0.03, 0.15 or 0.75 mg/kg/day for 183 days. Compound-related mortality in 2 of 6 male monkeys, decreased body weights, increased liver weights, lowered serum total cholesterol, lowered triiodothyronine (T_3) concentration, and lowered estradiol levels were seen at the highest dose tested. At 0.15 mg/kg/day, increased levels of thyroid-stimulating hormone (TSH) in males, reduced total T_3 levels in males and females, and reduced levels of high-density lipoproteins (HDL) in females were seen. A NOAEL of 0.03 mg/kg/day was identified in this study.

4. Calculation of Provisional Health Advisories for PFOA and PFOS

The general equation for the derivation of a Provisional Health Advisory is:

$$\frac{(\text{NOAEL or BMDL}_{10}) \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{Extrapolation Factor} \times \text{Water intake}}$$

Where BW = body weight; RSC = relative source contribution; UF = uncertainty factors

The OW is using the exposure scenario of a 10-kg child consuming 1 L/day of drinking water to calculate the Provisional Health Advisories for PFOA and PFOS. This population subgroup was used because children, who consume more drinking water on a body weight basis than adults, have a higher exposure on a body weight basis than adults. The selection of children's exposure parameters will help to ensure that this Provisional Health Advisory is protective of sensitive populations potentially exposed. A default relative source contribution (RSC) of 20% was used to allow for exposure from other sources such as food, dust and soil. The relevant period of exposure for the Health Advisory is a short-term exposure. This time period is consistent with the toxicity data used for PFOA and PFOS, both of which rely upon subchronic data. The value should be protective of all population subgroup and lifestages.

Data derived extrapolation factors for toxicokinetics were developed to better approximate internal doses for PFOA and PFOS. This step was deemed important because of the marked differences in retention time among humans and the test species in which toxicological data were collected. Available data for PFOA from female mice indicate a half-life of 17 days and from humans, a half-life of 3.8 years (1387 days). Critically, measures of internal exposure should be used as the basis for interspecies extrapolation; the assessment is somewhat complicated by the lack of area under the curve (AUC) or clearance (CL) data. However, the one-compartment model foundation

is useful to convert half-life data to clearance data, assuming steady-state has been reached (Equation 1).

$$\text{Half-life} = (\ln 2 \text{ or } 0.693) \times \text{Volume of Distribution} / \text{CL} \quad (1)$$

The volume of distribution of 198 $\pm$ 69 ml/kg has been estimated in female monkeys (Butenhoff et al., 2004). Olsen et al. (2007) summarized other findings on PFOS and PFOA as indicating primarily an extracellular distribution volume. Olsen et al. (2007) also cited other reports that these agents were highly bound to plasma proteins in rats, monkeys and humans. Together, these data support using the same volume of distribution for rodents and humans, based on the findings (198 ml/kg) in monkeys.

The mouse half-life of 17 days converts:
CL = (0.693 x 198 ml/kg) / 17 days = 8.07 ml/kg/day

The human half-life of 1387 days converts:
CL = (0.693 x 198 ml/kg) / 1387 days = 0.10 ml/kg/day

Calculating the toxicokinetic portion of the interspecies on the basis of plasma CL would be:

CL animal / CL human = 8.07 ml/kg/day / 0.10 ml/kg/day = 80.7

The total interspecies correction derived from using a 3X for toxicodynamics and 81X for toxicokinetics is 243X.

To calculate the Provisional Health Advisory for PFOA, a default intraspecies uncertainty factor of 10 was applied to the $BMDL_{10}$ of 0.46 mg/kg/day to account for variation in susceptibility within the human population. A default uncertainty factor of 3 was used for toxicodynamic differences between animals and humans.

The following Provisional Health Advisory is obtained:

$$\text{PFOA Provisional Health Advisory} = \frac{0.46 \times 1000 \times 10 \times 0.2}{10 \times 3 \times 81 \times 1} = 0.4\ \mu g/L$$

Similarly, a data-derived extrapolation factor was developed for PFOS. The half-lives of PFOS in humans and in male and female monkeys were estimated by Lau et al., (2007) to be 5.4 years and 150 days, respectively.

The monkey half-life of 150 days converts:
CL = (0.693 x 198 ml/kg) / 150 days = 0.915 ml/kg/day

The human half-life of 1971 days converts:
CL = (0.693 x 198 ml/kg) / 1971 days = 0.07 ml/kg/day

Calculating the toxicokinetic portion of the interspecies on the basis of plasma clearance would be:

CL animal / CL human = 0.915 ml/kg/day / 0.07 ml/kg/day = 13.1

The total interspecies correction derived from using a 3X for toxicodynamics and 13X for toxicokinetics is 39X.

To calculate the Provisional Health Advisory for PFOS, a default intraspecies uncertainty factor of 10 was applied to the NOAEL of 0.03 mg/kg/day to account for variation in susceptibility within the human population. A default uncertainty factor of 3 was used for toxicodynamic differences between animals and humans.

The following value is obtained:

$$\text{PFOS Provisional Health Advisory} = \frac{0.03 \times 1000 \times 10 \times 0.2}{10 \times 3 \times 13 \times 1} = 0.2\ \mu g/L$$

REFERENCES

Butenhoff JL, Kennedy GL Jr, Hinderliter PM et al. (2004). Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. Toxicol Sci. 82:394-406.

EFSA (2008) European Food Safety Authority. Opinion of the Scientific Panel on Contaminants in the Food Chain on Perfluorooctane sulfonate (PFOS) and Perfluorooctanoic acid (PFOA) and their Salts. EFSA Journal, 2008, Journal number 653, 1-131; available at http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902012410.htm).

Lau C, Thibodeaux JR, Hanson RG et al. (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol. Sci. 90 (2) 510-518.

Lau C, Anitole K, Hodes C et al. (2007). Perfluoroalkyl acids: A review of monitoring and toxicological findings. Toxicol. Sci. 99 (2) 366-394.

Olsen GW, Burris JM, Ehresman DJ et al. (2007). Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect. 115: 1298–1305.

Seacat AM, Thomford PJ, Hansen KJ et al. (2002). Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in Cynomolgus monkeys. Toxicol. Sci. 68, 249-264.