

**COMMENTS OF 3M COMPANY
TO THE EPA SCIENCE ADVISORY BOARD
PFOA REVIEW PANEL**

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February 10, 2005

3M appreciates the opportunity to provide comments to the members of the U.S. EPA Science Advisory Board (SAB) Perfluorooctanoic Acid Risk Assessment review panel. 3M, in collaboration with Drs. David Gaylor, Jack Moore and Joseph Rodricks, has addressed many of the issues pending before the SAB in its published risk assessment by Butenhoff et al., “Characterization of Risk for General Population Exposure to Perfluorooctanoate,” in *Regulatory Toxicology and Pharmacology* 39:363-380 (2004). We have asked Drs. Moore and Rodricks to comment on various charge questions to the SAB, and we understand Dr. Jim Popp will be addressing other charge questions. These comments focus on issue 4c (human biomonitoring data) and address question #9 of the charge to the panel regarding the adequacy of the human exposure data for use in calculating a MOE.

COMMENTS REGARDING BIOMONITORING DATA

3M has summarized the PFOA biomonitoring data from North America that have been published in the scientific literature and/or submitted to the EPA AR-226 public docket. The human biomonitoring data, while not a representative sample of the United States general population, provide a reasonable estimate of the mean and 90th percentiles because the study results are relatively consistent across geography, sex, age, time and across multiple studies. Aggregating these study results offers support for the conclusion that the PFOA serum concentration in the general population is likely indicative of a near steady state condition. This near steady state assumption is sufficiently accurate for the purpose of calculating margins-of-exposure (MOE) as performed in the US EPA draft risk assessment for perfluorooctanoic acid and its salts, by multiplying the human mean PFOA concentration (or 90th percentile) by 24 hours to obtain an area under the curve (AUC) for the denominator of the MOE ratio.

1. Tabulation of Biomonitoring Data

Table 1 provides a summary of the serum PFOA concentrations reported in several published studies from individual blood samples collected in North America. Altogether, 2,153 samples from general population sources have been analyzed and, for the most part, provide very comparable results.

**Table 1. PFOA Concentrations (µg/mL) Reported
in North America Studies of General Populations**

Study	N	LLOQ	(n)	Mean	Range
American Red Cross (serum) 645 (Olsen et al. 2002a; 2003a)		≤0.0021	(50)	0.0055	LLOQ – 0.0523
<u>Six locations</u>					
1) Boston, MA	109	0.0021	(1)	0.0053	LLOQ – 0.0139
2) Charlotte, NC	96	0.0021	(2)	0.0050	LLOQ – 0.0029
3) Hagerstown, MD	108	0.0021	(11)	0.0045	LLOQ – 0.0523
4) Los Angeles, CA	125	0.0021	(20)	0.0046	LLOQ – 0.0341
5) Mpls-St. Paul, MN	100	≤0.0021	(4)	0.0045	LLOQ – 0.0020
6) Portland, OR	107	0.0021	(12)	0.0043	LLOQ – 0.0167
Children (serum) (Olsen et al. 2002b [#] ;2004a)	598	≤0.0029	(25)	0.0056	LLOQ – 0.0561
<u>States w/ ≥10 samples</u>					
1) Alabama	22	0.0029	(3)	0.0046	LLOQ – 0.0079
2) Arizona	18	-		0.0085	0.0047 – 0.0175
3) California	47	0.0019	(1)	0.0061	LLOQ – 0.0342
4) Colorado	39	-		0.0052	0.0021 – 0.0161
5) District of Columbia	25	-		0.0043	0.0024 – 0.0069
6) Florida	42	0.0029	(1)	0.0057	LLOQ – 0.0098
7) Idaho	16	0.0029	(3)	0.0041	LLOQ – 0.0086
8) Kentucky	18	-		0.0058	0.0020 – 0.0087
9) Massachusetts	45	<0.0019	(7)	0.0048	LLOQ – 0.0140
10) Missouri	10	0.0029	(1)	0.0041	LLOQ – 0.0070
11) New Jersey	38	0.0029	(1)	0.0054	LLOQ – 0.0151
12) New Mexico	28	-		0.0046	0.0025 – 0.0089
13) New York	30	-		0.0054	0.0025 – 0.0090
14) North Carolina	33	-		0.0058	0.0025 – 0.0116
15) Ohio	33	0.0029	(3)	0.0046	LLOQ – 0.0094
16) Oklahoma	28	0.0029	(2)	0.0053	LLOQ – 0.0094
17) Texas	47	0.0029	(2)	0.0079	LLOQ – 0.0561
18) Utah	26	-		0.0068	0.0021 – 0.0146
19) Virginia	13	-		0.0061	0.0039 – 0.0077
Elderly (serum) (Olsen et al. 2004b)	238	0.0014	(5)	0.0048	LLOQ – 0.0167
Kannan et al. (2004)					
1) Kentucky (blood)	30	-		0.0348	0.011 – 0.088
2) Michigan (serum)	75	0.003	(34)	0.0051	LLOQ – 0.0147
3) New York City (plasma)	70	-		0.0275	0.014 – 0.056

Table 1, continued

Study	N	LLOQ	(n)	Mean	Range
Kuklenyik et al. (2004) Atlanta, GA (serum)	20	-		0.0049	0.0002 – 0.0104
Kubwabo et al. (2004) Ottawa & Gatineau (serum) 56 (Quebec and Ontario)		0.0012	(15)	0.0034	LLOQ – 0.0072
Hansen et al. (2001) Biological supply company samples located in U.S. (serum)	65	<0.0049	(33)	0.0064	LLOQ – 0.0352
Serum/liver study (Olsen et al. 2003b) Sera & liver donor tissue obtained through Institute for Advancement of Medicine	23 pairs	< 0.0359 (3) liver $\leq$ 0.0187 (18) liver < 0.0054 (1) liver < 0.006 (1) serum < 0.0031 (12) serum		-	LLOQ – 0.047
Longitudinal study Hagerstown, MD regional area (Olsen et al. 2005)					
1) Year 1974 (serum)	178	0.0010	(51)	0.0023*	LLOQ – 0.0080
2) Year 1989 (plasma)	178	0.0019	(1)	0.0056*	LLOQ – 0.0717

See Figure 1 of Olsen et al. 2002b for geometric means

- All values measured above study LLOQ

* Median value reported.

It needs to be acknowledged that none of these studies are statistically representative samples of the U.S population. However, such a biomonitoring effort is periodically conducted by the Centers for Disease Control and Prevention National Center for Environmental Health (NCEH). The NCEH is scheduled in 2007 to provide its first analysis of PFOA concentrations in representative samples of the United States general population. (Federal Register 2003.)

The EPA draft risk assessment cites the two largest studies, which represent 58 percent of all samples presented in Table 1. These two studies were the American Red Cross adult blood donors in 2000-2001 (n = 645) and an analysis of 598 children serum samples that were collected in 1994-95 who were enrolled in a Group A Streptococcal infection clinical trial multi-center study (Olsen et al. 2003a; 2004a). Both of these

studies reported similar mean PFOA concentrations and 90th percentiles across different geographical locations.

It does not appear that measurements below detection limits have skewed the reported data sets for either adults or children:

- The midpoint value between zero and the LLOQ was assumed for those values reported below the LLOQ. This approach can be biased if the percentage of measurements below detection limits is above 5 to 10 percent (Lubin et al. 2004). Neither of these studies had more than 8 percent of its measurements below LLOQ values.
- In addition to the midpoint value, different estimates for those values less than the LLOQ were also used to estimate the mean PFOA concentration, but these resulted in minimal differences from the midpoint value (Olsen et al. 2002a; 2004a).

The majority of PFOA concentrations reported in Table 1 are similar to each other, including an analysis of 20 samples from Atlanta, Georgia by researchers from the NCEH (Kuklennyik et al. 2004).

Analyses on 30 whole blood samples from Kentucky and 70 plasma samples from New York City (Kannan et al. 2004) were approximately 50 percent higher than the other general population mean results reported in Table 1. The Kannan et al. New York City results are inconsistent with several other regional general population analyses cited in Table 1 including serum samples from New York, Boston, Washington, D.C., New Jersey and Massachusetts. Although not noted in the publication, Dr. Kannan has informed 3M that the New York samples were occupational samples taken from workers engaged in post-9/11 cleanup at the World Trade Center (personal communication to Dr. William Reagen of 3M). The Kannan et al. mean PFOA concentration for their 30 Kentucky whole blood samples are inconsistent with the findings reported from 18 children serum samples that originated from Kentucky as reported by Olsen et al. (2004a).

Reasons for these differences are not fully understood. It should be noted, however, that Kannan et al. incorporated higher LLOQs (0.003 – 0.020 µg/mL) in their laboratory methods for PFOA analysis than what other investigators have reported, although all the samples were reported above the LLOQ. In particular, the ion pairing extraction method was applied without the usage of extracted matrix calibration curves. This could lead to significant bias in the analytical results that can be both analyte (e.g., PFOA) and matrix dependent. Kannan et al. acknowledged that the whole blood from the Kentucky population might account for differences from previously reported sera or plasma data. In addition, Kannan et al. acknowledged that the more recently published solid phase extraction (SPE) sample preparation methodology would be a valuable contribution to confirm their published results, and we understand that Kannan et al.

intend to reanalyze their samples using current state-of-the-art SPE methodology in the near future (personal communication to Dr. William Reagen of 3M).

2. Longitudinal Study

3M and Johns Hopkins University researchers have recently published an analysis of temporal changes in the human blood concentration of several fluorochemicals, including PFOA (Olsen et al. 2005). We raise this newly published data in accordance with EPA's direction that new data relevant to methodology may be considered by the SAB. The study results provide support for EPA's use of the general population biomonitoring data, because they show the lack of any increase in general population blood levels between 1989 and 2001.

1974 and 1989 Data

Blood samples were obtained from two large community-based cohorts established in Washington County, Maryland in 1974 and 1989 for studying clues to the development of heart disease and cancer (CLUE I and CLUE II studies). The volunteer participants were asked to donate a blood sample and respond to a brief health questionnaire. Among the donors in 1974 and 1989, residents outside a 30-mile radius of the study center were not used in the CLUE studies, and thus these samples were eligible to be used for an analysis of temporal trends in fluorochemical concentrations.

A total of 356 adult samples (178 from each time period, equally distributed by sex) were included in the fluorochemical study. Fifty-eight were paired samples, meaning those 58 individuals donated blood samples in both years. Samples had been stored since 1974 or 1989 at -70°C until thawed for this analysis. Liquid chromatography mass spectrometry methods were used for the analysis of PFOA.

Results

The 1974 (serum) and 1989 (plasma) median PFOA concentrations for the 58 paired samples were 0.0023 µg/mL (parts per million) and 0.0056 µg/mL, respectively. This is equivalent to 2.3 ng/mL (parts per billion) and 5.6 ng/mL, respectively.

Comparison of the nonpaired samples (120 per each year) resulted in similar findings. The 1974 median PFOA concentration was 0.0024 µg/mL compared to 0.0057 µg/mL for samples collected in 1989.

The percentage of samples reported at the lower limit of quantitation (LLOQ = 0.0019 µg/mL) decreased from 29 percent in 1974 to 1 percent in 1989.

Comparison to 2001 Data

The data were then compared with blood samples (serum) collected in 2001 from 108 American Red Cross adult blood donors from the same region (Hagerstown,

Maryland) (Olsen et al. 2003a). This comparison did not suggest a continued increase in PFOA concentrations between 1989 and 2001. The median PFOA concentration in 2001 was 0.0047 µg/mL, compared to 0.0057 µg/mL reported in 1989.

The authors concluded that PFOA concentrations appeared to have increased a few ng/mL between 1974 and 1989, which resulted in a two-fold increase in median concentrations. Comparison with the data collected in 2001 from the same region did not suggest a continued increase in PFOA median concentrations since 1989.

3. Human Half-Life of Elimination

The draft EPA risk assessment for PFOA cites a 3M interim report that estimated the half-life of serum elimination for PFOA was 4.4 years (Burris et al. 2002). This was a research study designed to determine the serum elimination half-life of PFOA and other fluorochemicals over a 5-year time period in a group of retired fluorochemical production workers. This research effort has been recently completed (Ehresman et al. 2005, abstract published, manuscript in preparation). The final results of the study are generally similar to the interim results, and support EPA's one-compartment modeling for PFOA. The mean half-life of elimination was 3.8 years (95% CI 3.1 – 4.4).

A total of 27 3M retirees from the Decatur (n = 24) and Cottage Grove (n = 3) fluorochemical production facilities were included in the study. Two participants were females. Retirees were the study population of choice because they no longer had potential occupational exposure to PFOA and its salts but had serum PFOA concentrations higher than the general population that would minimize any influence nonoccupational sources of exposure might have had on the determination of the elimination rate.

Blood collections occurred periodically between November 1998 and March 2004. All serum samples were analyzed concurrently using liquid chromatography mass spectrometry for the analysis of PFOA. Version 4.1 of WinNonlin[®] software (Pharsight Corporation, Mountain View, CA) was used to calculate the half-life of elimination. A one compartment model fit the data quite well.

One male subject was excluded from the data analysis due to his repeated potential for occupational exposure to fluorochemicals from his consultant work.

Characteristics of 26 Subjects in Half-Life of Elimination Study

	Mean	Range
Age at 1998 initial blood collection	61 years	55-75 years
Years since retired at 1998 initial blood collection	2.6 years	0.4 – 11.5 years
Initial serum PFOA concentration	0.691 µg/mL	0.072 µg/mL to 5.1 µg/mL
End-of-study serum PFOA concentration	0.262 µg/mL	0.017 µg/mL to 2.435 µg/mL

The mean half-life of elimination was 3.8 years (95% CI 3.1 – 4.4) with a range of 1.5 to 9.1 years (median 3.5 years). The two female retirees had comparable half-life of elimination data (i.e., each 3.3 years). These study results support the previously reported serum half-life of elimination observed in these participants by Burris et al. (2002).

It was not readily apparent why two male subjects had markedly lower serum half-lives (approximately 1.5 years) and three male subjects had higher serum half-lives (above 6 years) than the other 21 retirees. The half-life of elimination was not associated with initial or end-of study serum PFOA concentrations, age of subject, years worked or years since retirement.

Using the Burris et al. (2002) estimate of the half-life of serum elimination of PFOA, Harada and colleagues (2004) from Japan have recently published an analysis of the renal clearance of PFOA in humans based on their study subjects' serum and urine biomonitoring data. Regardless of sex, the renal clearance was 0.001% that of the glomerular filtration rate in humans. This indicates the absence of active excretion of PFOA in human kidneys. Harada et al. also reported lower mean PFOA concentrations among pre- than post-menopausal women although the sample size per group was 5 subjects. Age-dependent differences among adult women were not observed by Olsen et al. (2003a). Because of the substantial differences in renal excretion of PFOA among species, Harada et al. suggested an internal dose approach should therefore be considered when animal data are extrapolated to humans.

Conclusion

The human biomonitoring data, while not a representative sample of the United States general population, provide a reasonable estimate of the mean and 90th percentiles (approximately 0.005 µg/mL and 0.009 µg/mL, respectively). The study results are relatively consistent across geography, sex, age, time and across multiple studies. Aggregating these study results offers support for the conclusion that the PFOA serum concentration in the general population is likely indicative of a near steady state condition. This near steady state assumption is sufficiently accurate for the purpose of

calculating margins-of-exposure (MOE) as performed in the US EPA draft risk assessment for perfluorooctanoic acid and its salts, by multiplying the human mean PFOA concentration (or 90th percentile) by 24 hours to obtain an area under the curve (AUC) for the denominator of the MOE ratio.

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