October 27, 2009

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE Mail Stop F-62
Atlanta, Georgia 30333

RE: Comments on Draft Toxicological Profile for Perfluoroalkyls
Docket Control Number ATSDR-253

To Whom It May Concern:

I appreciate the opportunity to comment on the Draft Toxicological Profile for Perfluoroalkyls (Profile) dated May 2009. I have served and am currently serving as a toxicology consultant to plaintiffs in litigation involving perfluoroalkyl chemical issues. I have the following comments on the profile.

On page 21 the Profile states the following.

> In the cohort studied by Emmett et al. (2006b), the average concentration of PFOA in water that the subjects may have consumed over a period of 3 years before the health assessment was conducted was 3.5 ug/L. Median serum PFOA levels in residents were 105 times the level in their residential drinking water. Blood levels of perfluoroalkyl compounds have been measured both in workers and in members of the general population. As indicated in the preceding section, no significant health effects have been associated with specific serum levels of perfluoroalkyl compounds, although minor alterations in serum lipids and in serum estradiol levels in male workers have been reported (Costa 2004; Olsen et al. 1998; Sakr et al. 2007b).

There are a number of problems with these statements. First, the elevations in liver enzymes associated with PFOA serum concentration in studies of worker populations are not included (Olsen et al. 2003; Sakr et al. 2007). Second, the elevations of serum lipids and serum estradiol (and presumably liver enzymes had they been included) are described as "minor alterations." These alterations are likely not minor for the subset of individuals experiencing them. While the mean, median, or geometric mean serum levels are not pushed into a clinically unacceptable range by the association with PFOA in these studies, the alterations in central tendencies for these parameters are very likely the result of a larger impact on a small subset of susceptible individuals whose elevations may well be clinically adverse. While the characterization of these elevations as "minor alterations" may be somewhat consistent with those of the industry authors of these studies, the Profile description should represent an independent critique of study data. Accepting the assessment of the industry study authors without an independent assessment of study data is a criticism voiced by Dr. Lynn Goldman who peer reviewed an earlier draft of the Profile. The problem remains.

An illustration of the subset effect is the association of PFOA or PFOS with liver enzyme elevations for the Olsen et al. (2003) study of workers in two facilities producing PFOA and PFOS containing products.

The liver enzyme alanine aminotransferase (ALT) is significantly elevated in the fourth serum PFOS/PFOA quartile versus the first quartile. The magnitude of the elevation is 7 IU/L (33 versus 26, respectively). The upper bound of the reference range for ALT is 40 IU/L so the elevated value of 33 IU/L for the fourth quartile is within the reference range and an individual with such a level would not be considered to be exhibiting signs of liver toxicity. If, however, one considers the small portion of workers that were actually pushed into the clinically excessive ALT range by the association of ALT with PFOS/PFOA, it is apparent that adverse effects likely occurred. The number of individuals exceeding the reference range for the fourth quartile was 13 of 105 while the number for the first quartile was 4 of 105. The difference between first and fourth quartiles is an indicator of the impact of PFOA on ALT. Nine workers (8.6 percent) may have experience elevated liver enzyme levels beyond the reference range as a result of their exposure to PFOA. ALT values for quartile three are also elevated (7 IU/L) but less so than for the fourth quartile.

The analysis shown above for liver enzymes cannot be done for lipids or estradiol because the individual serum data for workers were not included in the reported studies. It is likely that the modestly elevated mean values for these parameters would also be the result of more extreme alterations in a subset of workers.

The other problem with the Profile statement shown above is that declares the Emmett et al. (2006b) study to have resulted in "no significant health effects" and then goes on to suggest that a no-observed-adverse-effect-level (NOAEL) could possibly be established based on the PFOA human body burden observed in this study. This statement is troubling as the Emmett 2006b study has a serious weakness that would limit its ability to detect a positive association between serum PFOA and any outcome assessed. The major limitation of the Emmett et al. (2006b) study is the participation rate which is only 37 percent. This very low participation rate results in likely self-selection bias. The process normally used to address a low participation rate is a follow up on a sample of nonparticipants to determine if their outcome response would be different from that of participants. No such follow up was done by Emmett (2006b). There is a large literature on self-selection bias, sometimes referred to as volunteer bias, that indicates that individuals with conditions that make them more susceptible to adverse effects tend to participate in health surveillance studies to a lesser extent than do healthy individuals and that the absence of these less healthy study subjects will bias the study results toward the null. Such a bias in the relationship between exposure and health outcomes may underestimate or fail to detect an adverse effect when one exists. Cross sectional volunteer studies have been reported to average 74 percent participation (Morton et al. 2005. Amer J Epidem 163:197-203). Self-selection bias has been detected with participation rates as high as 93 percent (Lyngbye et al. 1988. Scand J Soc Med 16:209-215). The 37 percent participation rate of the Emmett et al. (2006b) study is very low and likely biased the results of that study toward the null. Emmett et al. (2006b) should not be considered for use as a NOAEL and should not be considered convincing evidence of the absence of an association between PFOA body burden and adverse effects in the general population.

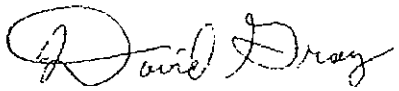
The participation rate limitation of the Emmett et al. (2006b) study is also present in most of the occupational studies although to a lesser extent. Many of the occupational studies have participation rates of 55 percent or less.

Finally, the Profile does not include a number of important recent reports relating to PFCs and human health. Studies by Lundin et al. (2009)[1] and Steenland et al. (2009)[2] need to be included. Steenland et al. (2009) was conducted in 46, 294 members of the general population with an estimated 81 percent participation rate. The Steenland et al. (2009) findings conflict with those of the much smaller Emmett et al. (2006b) study. Steenland et al. (2009) state the following.

> A cross-sectional study of lipids and PFOA and PFOS was conducted among 46,294 community residents aged 18 years or above, who drank water contaminated with PFOA from a chemical plant in West Virginia. The mean levels of serum PFOA and PFOS in 2005-2006 were 80 ng/mL (median, 27 ng/mL) and 22 ng/mL (median, 20 ng/mL), respectively. All lipid outcomes except high density lipoprotein cholesterol showed significant increasing trends by increasing decile of either compound; high density lipoprotein cholesterol showed no association. The predicted increase in cholesterol from lowest to highest decile for either compound was 11-12 mg/dL. The odds ratios for high cholesterol (≥240 mg/dL), by increasing quartile of PFOA were 1.00, 1.21 (95% confidence interval (CI): 1.21, 1.31), 1.33 (95% CI: 1.23, 1.43), and 1.40 (95% CI: 1.29, 1.51) and were similar for PFOS quartiles. Because these data are cross-sectional, causal inference is limited. Nonetheless, the associations between these compounds and lipids raise concerns, given their common presence in the general population.

The negative findings of the Emmett et al. (2006b) study are cited in many locations in the Profile. The Profile concludes that there is an absence of observed health effects in PFOA community studies. This conclusion should be modified given the more recent human studies.

Sincerely,



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[1] Lundin J.I. et al. 2009. Ammonium perfluorooctanoate production and occupational mortality. Epidemiol. 20:921-28.

[2] Steenland K. et al. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. Am J Edpidemiol. DOI: 10.1093/aje/kwp279.