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Subject: Comments on ATSDR Draft Toxicological Profile on Perfluoroalkyls

To: ATSDR Division of Toxicology and Environmental Medicine
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Draft Writers and Reviewers:

I have read your draft on the perflouroalkyls and wanted to take this opportunity to make some constructive comments on both the content and the interpretation of what is presented. Since my expertise in the general area of health effects, that is where I will focus my comments. I was actually quite impressed with your peer review panel and believe that they were able to give you some good guidance, and will continue to do the same following the next round of edits to the document.

In general, this document is outdated. That is no fault of yours, but the science on this family of chemicals has moved forward so quickly this calendar year that this document is no longer current and many statements are incorrect. A review and inclusion of the many documents in the May 2009 *Reproductive Toxicology* issue 27(3-4) is needed. This is needed to update the toxicokinetic and health effects information available on compounds other than PFOA and PFOS, to provide important information on the disposition of PFOA in the pregnant and lactating mouse and her offspring over the nursing period, compare and contrast PFOS and PFOA in their ability to induce PPAR-α and the requirement for this signaling pathway for more than liver effects, and update some of the information on human exposure and early life end points in humans. Other epidemiological studies should also be added (these are just some examples) – Hamm et al., *JESEE* advance online publication, 28 October 2009, doi:10.1038/jes.2009.57; Lundin et al., Epidemiology. 2009 Nov;20(6):921-8; MacNeil et al., Environ Res. 2009 Nov, 109(8):997-1003; Stein et al., Am J Epidemiol. 2009 Oct 1;170(7):837-46; Joensen et al.,

Environ Health Perspect. 2009 Jun;117(6):923-7; an update of exposure levels in the USA by Steenland et al., Environ Health Perspect. 2009 Jul;117(7):1083-8; and comparisons of these data with 2009 data that is accumulating from other areas of the globe, such as Japan, China, Australia, and Denmark should be made.

Many of the interpretations of the data presented in the Public Health Statements are too basic – the large majority of the human data to date had not considered early life exposure to this family of compounds and that should be stated. Just because these epidemiological studies had no significant associations of current serum levels or even those 10 yr ago (in an adult) does not mean that if early life exposure accumulation was taken into consideration, that the results would be the same. The current animal studies agree that developmental exposure to these compounds is important in manifestation of effects. An example of this is the paper by Hines et al, Mol Cell Endocrinol. 2009 May 25;304(1-2):97-105. In this paper, the investigators demonstrate that the increased weight gain effects in adult mice exposed prenatally to PFOA do not occur when adult mice are exposed to the compound for similar lengths of time and dose. This paper specifically shows a low dose effect of PFOA on end points that are of importance to human health and are not likely related to PPAR-α signaling.

There are also discussions in Tardiff et al., Food Chem Toxicol. 2009 Oct;47(10):2557-89; Post et al., Environ Sci Technol. 2009 Jun 15;43(12):4547-54; and the Repro Toxicol issue mentioned above that need to be included in this document for your discussion of MRLs. Furthermore, there is now more information on human milk as a source of exposure to PFAAs, not that it would change your presentation of the data much. This area should be updated, however. I also think it is important to point out that the human data that you refer to for comparison of PFAA in serum:milk is from very limited information (1 study) with no comparison over time or parity and based on our work in mice (Fenton et al., 2009 Reprod Toxicol) the time of lactation that the sample is collected can have a fair influence on the ratio of PFOA in serum and milk.

Although there are many updates needed in the document, there are also a few places where care must be taken to present the actual state of the science. Most of the epidemiological studies that have been published to date have been careful to state that they found associations of PFAA levels with a certain health outcome, but in your document in several places phrases like "..perflouroalkyl compounds produce cancer.." and "causality" discussions should be carefully considered and possibly rewritten to reflect the interpretations of the authors of that work. Causality is hard to prove, but significant associations are easy to cite.

Finally, I would like to add that the mammary gland tumors that were found in female rats in the 2 yr study (work by Beigel et al., and cited in the PFOA SAB report) should not be brushed under the rug. Because female rats do excrete PFOA nearly as fast as they take it in, the very low circulating levels that may have been in those rats did cause an increased incidence of mammary tumors. Work by my lab, in addition to independent work by Sandra Haslam (in 2009 Reprod Toxicol) has indicated altered mammary gland development in at least two mouse strains and our current work will determine the NOAEL and LOAEL for those end points. The effects of this perturbation of early life development is not fully understood, but other endocrine disrupting compounds demonstrating similar shifts in timing of mammary gland maturity have

demonstrated increased risk for mammary hyperplasia, spontaneous adenocarcinoma, and carcinogen-induced tumor development (i.e, dioxin and bisphenol A). With this in mind, expansion of the primary health discussion on liver effects is recommended. Diabetes (and altered growth patterns, leptin, insulin in animal models) is another area to consider when defining the health effects of interest for PFOA and/or a mixture of exposures in this family of compounds.

I hope you find these comments helpful and if I can clarify any of my statements or provide further assistance, please feel free to contact me at the address given.