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October 30, 2009 (Corrected 11/2/09)

Ms. Nickolette Roney
Division of Toxicology and Environmental Medicine, ATSDR
Mailstop F-62, 1600 Clifton Road, NE
Atlanta, Georgia 30333

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

Dear Ms. Roney,

As requested in the Federal Register notice of July 23, 2009, I am submitting comments on the ATSDR Draft Toxicological Profile for Perfluoroalkyls. I am the toxicologist with the New Jersey Department of Environmental Protection (NJDEP) with responsibility for developing the human health basis for New Jersey drinking water standards and guidance. I was responsible for the development of the current NJ health-based drinking water guidance for PFOA (NJDEP, 2007); the basis for this guidance has recently been published in a peer-reviewed journal (Post et al., 2009, as referenced in the attached comments). Currently, the New Jersey Drinking Water Quality Institute (DWQI), an advisory body to the Commissioner of NJDEP, is developing a recommendation for a New Jersey drinking water standard (MCL) for PFOA. I am one of the scientists involved with updating the 2007 guidance based on review of recent studies in order to develop a recommended human health basis for this MCL.

My comments focus on PFOA since I am most familiar with the literature on that compound. Additional detailed comments focusing on the epidemiological studies of PFOA are being submitted by Dr. Perry Cohn of the New Jersey Department of Health and Senior Services. Like me, Dr. Cohn is part of the effort to develop a recommendation for the health basis for the New Jersey drinking water standard for PFOA.

Additionally, I am aware of an important new PFOA study which will be published next week. I will submit an addendum to my comments discussing this study after it becomes available.

Thank you for the opportunity to comment on the Draft Toxicological Profile for Perfluoroalkyls. Please feel free to contact me at gloria.post@dep.state.nj.us if you have any questions or need further information.

Sincerely,

Gloria B. Post, Ph.D., DABT
Research Scientist

cc: Judy Louis, NJDEP
Perry Cohn, NJ DHSS

General Comments
I have several overall comments about the material presented in the document.

First, there is often a lack of synthesis and critical analysis of the conclusions made by the authors of the studies described in the document. Instead, the conclusions are given as stated by the authors of the studies, even if they contradict the conclusions of other studies presented in the same section or in other sections, without an attempt to synthesize and draw conclusions from the whole body of information. Some specific examples of where this problem occurs are discussed below.

Second, some important literature, both recent and older, is not included in the document. In other cases, key studies that are listed in the Reference section, but are not discussed in the text, should be discussed in the text. Below, I discuss the studies which I consider most important and which I recommend including in the document, and I provide the citations for those studies which are not already cited. It should be noted that there are many additional recent studies on health effects in humans and animals, environmental occurrence, human exposure, and fate and transport of PFOA that I am not including in these comments.

Finally, and most importantly, I strongly disagree both with the conclusion that there is insufficient information and too much uncertainty to develop a chronic oral MRL for PFOA and with the reasons given in the draft document to support this conclusion. I believe that there is currently enough information to develop a chronic oral MRL for PFOA and that there is less uncertainty for the chronic risk assessment of PFOA than many of the other contaminants for which chronic MRLs have been developed by ATSDR. This is discussed in detail below.

My specific comments follow. The citations for all studies mentioned in the comments which are not already cited in the draft document are provided at the end of the comments.

Section 1 – Public Health Statement
Please note: Some of the information suggested for inclusion in the comments below may be too detailed for the Public Health Statement. This information could be summarized in this section and then discussed in more detail in the relevant sections later in the document.

p. 3 Section 1.3
Water and Soil
PFOA and PFOS have been detected in drinking water not impacted by known sources such as fluorochemical facilities (Post et al., 2009a, Ericson et al., 2009, Jin et al, 2009, Rumsby et al., 2009, Mak et al., 2009, Takagi et al., 2009). The contribution of exposure to the relatively low concentrations commonly detected in drinking water is substantial compared to the total exposure in the general population (Post et al., 2009).

An important source of perfluoroalkyls in surface water and drinking water is discharge from wastewater treatment plants (Kelly and Solem, 2008, Yu et al, 2009, Clara et al, 2008). Precursor compounds (fluorotelomer alcohols) found in wastewater are transformed to PFOA and other perfluoroalkyls through biodegradation which occur during wastewater treatment (Sinclair et al, 2006, Loganathan et al, 2007). The sludge from wastewater treatment plants has been applied to agricultural land. Perfluoroalkyls from the land-applied sludge can contaminate groundwater and soil. These chemicals may then potentially enter the food chain (milk, meat) through grazing of cattle or other animals (Renner, 2009, USEPA Region 4, 2009).

Perfluoralkyls have recently been shown to be taken up into crops from soil (Stahl et al., 2009).

Recent research (Washington et al., 2009) suggests that an acrylate-linked fluorotelomer polymer can degrade to PFOA in soil.

Consumer Products

Fluorotelomer alcohols and larger molecules containing fluorotelomer alcohols (e.g. mono- and diphosphates) are widely used in consumer products such as greaseproof food packaging. These have been shown to break down to PFOA and related compounds both through metabolic transformation in the body and through biodegradation and atmospheric reactions in the environment (D'eon et al., 2009, Martin et al., 2005, Sinclair et al., 2007, Ellis et al., 2004, Henderson and Smith, 2007, Kudo et al., 2005, D'eon and Mabury, 2007, Mahmoud et al., 2008). Exposure to these precursors in consumer products may be a major source of human exposure to PFCs, and should be mentioned here.

p. 4 Section 1.5

Workers

"Inhalation/dermal—Long-term exposure to perfluoroalkyls at work has not been associated with significant adverse health effects, but two studies in workers found changes in sex hormones and cholesterol associated with the levels of PFOA in blood."
Comment: I agree with the comment submitted by Dr. Perry Cohn: "This statement falls short of describing the published observations and those from the docket. There is reasonable evidence (see above and below), given that most of the investigations are based on death certificates, that exposed workers are indeed affected."

General Population

The C8 Health Study is an ongoing study of almost 70,000 people in Ohio and West Virginia who were exposed for one year or longer to PFOA in drinking water at concentrations ranging from approximately 0.05 ug/L to approximately 3 ug/L or higher. Data collected for each subject in this very large study includes serum PFOA levels, drinking water exposure history (e.g. PFOA concentration, current vs. former residence), levels of many parameters which can be measured in blood, and the subjects' medical histories. Additionally, there are other planned segments of this study which are described under Ongoing Studies on p. 224 of the document. It includes the community

studied by Emmett et al. (2006a, 2006b), referred to here, but includes many more people and many more parameters than did Emmett et al. (2006a, 2006b).

The currently available data and the data which will later become available from this major study provide crucial information on the relationship in humans between external dose (exposure through drinking water), internal dose (serum level), and biological endpoints and adverse health effects. The median serum levels in the first and second deciles, 6 and 9.8 μg/L are within the range prevalent in the U.S. general population, where, for the 2003-2004 National Health and Nutrition Evaluation Survey (NHANES), the 75th and 95th percentile levels were 5.8 and 9.8 μg/L (Calafat et al., 2007) while the highest serum levels in the C8 Health Study are in the 100s to 1000s of ug/L range. The median serum level in the study is about 28 ug/L. Such extensive data on the relationship between environmentally relevant exposures and effects in humans is rarely if ever available for environmental contaminants of concern.

In the draft document, the only mention of this study is on page 224 under Ongoing Studies, and even here, no background information on the design of the study is provided. Perhaps this is because the reports and publications which are now available were not available at the time when the draft document and peer review comments were written. There are currently several sources of information on this study which are essential for inclusion in the ATSDR Toxicological Profile. These include published papers on design and results of the study (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009), reports from the C8 Science Panel, including Fletcher et al. (2009) which reports associations with immune endpoints not yet published in a peer reviewed journal, and extensive data from the C8 Health Project which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009).

Association of PFOA serum levels with biological endpoints, including some which may be considered to be adverse, have been observed down to the lowest exposure groups. Although causality has not been established, as is the case for most epidemiological studies for environmental contaminants, it is notable that elevated cholesterol and other lipids (Steenland et al., 2009a) and elevated uric acid (Steenland et al., 2009b), as well as changes in several indicators of inflammatory and immune response (Fletcher et al., 2009), were significantly associated with serum PFOA levels, after adjustment for age, gender, body mass index, and other factors. These associations are especially important, because the serum levels in the lower deciles in which the dose-response is seen for these endpoints coincide with the serum levels found in the general US population, as discussed by Steenland et al. (2009b).

In the cholesterol study (Steenland et al., 2009a), the median PFOA serum level was 27 μg/L, and the risk of high cholesterol increased in each quartile of exposure with a 40-50% increase in the top quartile compared to the lowest quartile.

In the uric acid study (Steenland et al., 2009b), the risk of hyperuricemia (greater than 6.0 mg/dl in women and 6.8 mg/dl in men) increased in a dose-related fashion with serum

PFOA. The increased risk plateaued in the higher exposure groups, with an odds ratio of 1.47 and 95% confidence interval of 1.37-1.58 in the two highest quintiles.

A separate analysis of uric acid within the lower exposure group, with serum PFOA of less than or equal to 20 ug/L, revealed a dose-response by quartile within this group. . The highest quartile with serum levels of 15-20 ug/L serum PFOA had an increase in uric acid of 0.24 mg/dl above the lowest quartile with serum PFOA of less than 5 ug/L.

Additionally, data from this study which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009) suggest associations between PFOA serum levels and multiple other clinical parameters measured in blood, including liver enzymes, hormones, and electrolytes. As for the other endpoints discussed above, the apparent exposure-response curve for many of these endpoints is steepest in the lowest deciles of exposure, and no threshold is apparent in the dose-response curves.

p.5 Laboratory Animals
Other effects besides liver should be mentioned here. At a minimum, immune system effects should be mentioned.

p. 6 Section 1.6
Effects in Children
RE: First paragraph.
The C8 Health Study includes 4915 subjects under 10 years old and 7561 subjects from 10 to 18 years old. The serum PFOA levels in these subjects spans a wide range and includes many subjects with serum levels in the range of the US general population. Preliminary data suggest associations of several parameters measured in blood with serum PFOA levels in children (West Virginia University School of Medicine, 2009).

RE: Second paragraph.
The studies referred to found associations with PFOA and/or PFOS and birth weight in the general population, not just with PFOA as stated. Apelberg et al. (2007) found associations with both PFOS and PFOA for birth weight and size, Fei et al. (2007, 2008a,b) found associations with PFOA but not PFOS for several measures of fetal growth, and Washino et al.(2009) found associations with PFOS but not PFOA for birth weight.

Also, Stein et al. (2009) identified modest associations of PFOA with preeclampsia and birth defects and of PFOS with preeclampsia, preterm births, and low birth weight in the C8 Health Study population.

Laboratory Animals
Exposure to low levels of PFOA during gestation in mice has been shown to cause metabolic effects which become apparent in adulthood, including increased weight and changes in insulin and leptin (Hines et al., 2009a). Such exposures have also been shown to cause a unique anatomical change at the junction between the cervix and the uterus in the female offspring (Hines et al, 2009b).

p. 7 Section 1.8
Detecting Exposure
RE: Third paragraph.
In addition to Little Hocking, elevated PFOA serum levels have been found in the other five communities which are part of the C8 Health Study. These other communities had drinking water concentrations and serum levels lower than those in Little Hocking (Anderson-Mahoney, et al., 2008). Also, elevated serum levels have been found in other communities with contaminated drinking water including in Germany (Holzer et al., 2008) and Minnesota (MDH, 2009).

RE: Last paragraph.
The sentence should be revised to say, "**For example,** mean serum PFOA levels ...in Decatur, Alabama, were..." Elevated serum levels have been found in workers at sites other than Decatur, Alabama, and, as written, it implies that this was the only site where this has been found.

p. 8 First full paragraph.
It is important to mention that the USEPA Provisional Health Advisories for PFOA and PFOS are intended to protect for short term exposure, not chronic exposure.

Relevance to Public Health
p. 9, second paragraph, last sentence. Perfluoroalkyls can be formed through degradation of precursor compounds found in consumer products (D'eon and Mabury, 2007, D'eon et al., 2009, Martin et al., 2008, Washington et al., 2009)

p. 9, third paragraph. It is very important to discuss the fact that contamination of groundwater with PFOA has been found to occur via release to air from an industrial facility followed by deposition from air onto the soil and migration through the soil to the groundwater (Paustenbach et al., 2007). Unlike other groundwater contaminants, significant groundwater contamination by PFOA does not occur solely through migration of the groundwater plume. Thus, significant contamination can occur at some distance from the industrial source, beyond the groundwater plume.

Also, fluorotelomer alchols are much more volatile than perfluoroalkyl acids, and are converted to the acids in the atmosphere by chemical reactions. Long range transport of these precursors is thought to be a major contributor to the occurrence of PFOA and related compounds in remote regions (Ellis et al., 2004)

p. 10, last paragraph.
As noted above, a major source of PFOA exposure may be exposure to the telomer alcohols and the molecules into which they are incorporated (e.g mono- and diphosphates) followed by metabolic conversion to PFOA in the body. These chemicals are present at much higher concentrations in some consumer products than PFOA itself.

p. 11. Summary of Health Effects
Last sentence of paragraph. Studies of reproductive and developmental effects should also be mentioned here.

p. 12. Partial paragraph beginning at top of page.
Available results of the C8 Health Study and discussion of additional results that will be available from it should be included here. This information is discussed in detail above. This is a much larger study in the same community where the study of 371 subjects discussed here was done.

p. 13. Partial paragraph beginning at top of page.
Several epidemiology studies show an increase in diabetes mellitus associated with PFOA exposure (Leonard et al., 2008; Lin et al., 2009). See comments of P. Cohn for more detail. Also, regarding animal models, Hines et al. (2009a) found that exposure of mice to low levels of PFOA during gestation significantly increased body weight, and serum insulin and leptin (0.01-0.1mg/kg) in mid-life, while exposure during young adulthood did not have these effects.

p. 14. Partial paragraph beginning at top of page.
In the study described here, serum PFOA levels were not available, complicating evaluation of the results. Also, Stein et al. (2009), discussed above, should be mentioned here.

Last sentence of the paragraph: The authors of the studies themselves never concluded that the associations were causal. Why is it necessary to make the statement in the last sentence? If a statement is included, it should say that it is not known if the associations seen are causal or non-causal.

p. 15 First paragraph.
I have major concerns with the statements made in this paragraph about the implications of the toxicokinetic differences between humans and animals and of issues related to the mode of action on the relevance of animal studies to human health. This paragraph represents a summary of the discussion of these topics in the MRL section starting on p. 21. My comments on these issues are given in the MRL section, below, but also apply to the shorter discussion in this paragraph.

Second paragraph.
The discussions of the effects of PFOA that occur through activation of PPAR alpha presented here and in many other places in this document are overly simplistic, do not consider all relevant information, and may convey to the reader the unwarranted implication that all effects of PFOA that occur through PPAR alpha are not relevant to humans.

Specific to the writeup on this page, the following sentence should be revised to add the words "IN PART" as follows, as it is incorrect and contradicted by the writeup on the next page (page 16): Liver toxicity in rodents results **IN PART** from the ability of these

compounds (with some structural restrictions) to activate the peroxisome proliferator-activated receptor-α (PPARα), a member of the nuclear receptor superfamily.

Additionally, the information on page 20 about the EPA Science Advisory Board's reservations about attributing the hepatocarcinogenicity of PFOA totally to PPAR alpha agonism should be synthesized with the discussions on p. 15 and 16. In the current draft, the issues related to PPAR alpha and liver effects are presented separately on pages 15, 16, and 20, and the discussions on these three pages are contradictory and confusing to the reader.

It has been concluded that humans are refractory to the PPAR alpha mediated peroxisome proliferating effects in liver which are thought to lead to liver cancer in rodents (Klaunig et al., 2003). However, PPAR alpha is known to mediate many effects other than peroxisome proliferation and carcinogenesis in humans, both in liver and in other organs. Thus, the conclusions about liver cancer should not necessarily be extended to other PPAR alpha-mediated effects. It should be noted that Klaunig et al (2003) also concluded that the data are insufficient to characterize the MOA for the Leydig cell tumors and the PACT tumors of PFOA.

Effects mediated by PPAR alpha in humans include stimulation of fatty acid metabolism and suppression of inflammation (Fruchart and Duriez, 2004, Lefebvre et al. 2006), and, in fact, this is the basis for the use of PPAR alpha activators such as fibrates as hypolipidemic drugs in humans. Also, the role of PPAR alpha in human and animal development is not well characterized, but, based on their physiological roles, PPARs are expected to have important roles in reproduction and development (Abbott et al. 2008). Thus, the potential for PPAR alpha mediated effects on human development cannot be dismissed.

Most PPAR alpha activators lower cholesterol and lipids in both rodents and humans. Similarly, PFOA lowers lipid levels in experimental animals (e.g. Loveless et al. 2006). However, statistically significant elevations of cholesterol, as well as of the risk of hypercholesterolemia defined as greater than or equal to 240 mg/dl, are associated with serum PFOA and PFOS in a dose-related fashion in humans exposed through drinking water (Steenland et al., 2009a) and are also seen in occupationally exposed individuals, as summarized in Steenland et al. 2009a, 2009b.. As discussed by Steenland et al. (2009a), the findings on human serum cholesterol indicate that PFOA does not have the same effects as other PPAR alpha activators on lipid metabolism in humans.

As noted on the following page of the document (page 16), some effects of PFOA on the liver are not mediated by PPAR alpha. Effects of PFOA seen in PPAR alpha null mice include increased liver weight (Yang et al.2002, Wolf et al., 2008) and histological changes and increased cell proliferation (Wolf et al., 2008), while the prototype PPAR alpha agonist Wyeth 14, 643 did not increase liver weight in PPAR alpha null mice in these studies. PFOA also activated genes not associated with PPAR alpha, including genes associated with other nuclear receptors such as CAR in livers of adult mice (Rosen

et al., 2008a, 2008b) and newborn mice (Rosen et al., 2007). Additionally, PFOA caused fatty liver in mice, an effect not associated with PPAR alpha (Kudo and Kawashima, 1997).

As discussed on page 20, the USEPA SAB (2006) review of the USEPA (2005) draft PFOA risk assessment states that available data do not warrant the conclusion PPAR alpha is the sole MOA for liver tumors or that the PPAR alpha MOA for liver carcinogenesis does not occur in children.

Finally, a recent paper by Guyton et al. (2009) raises issues about the role of PPAR alpha activation in the liver carcinogenesis even in compounds which are well characterized as rodent peroxisome proliferators and the conclusion that hepatic tumors in rodents caused by PPAR alpha activators are not relevant to human risk. Guyton et al. (2009) discusses the findings of Ito et al. (2007) and David et al. (1999) on the liver carcinogenicity of di(2-ethylhexyl)phthalate (DEHP). DEHP caused liver tumors in wild type B6C3F1 mice which have PPAR alpha (David et al., 1999). However, in another strain of inbred mice, Ito et al (2007) found increased liver tumors from DEHP in PPAR alpha null mice, but not in the analogous wild type mouse strain. They also discuss the potential interindividual variability in human response to liver effects related to PPAR alpha activation due to differences in amount, structure, and function of PPAR alpha among people and the limitations of epidemiological studies on people taking PPAR alpha drugs

p. 16, first full paragraph.
Reductions in serum cholesterol and triacylglycerols are commonly seen in animals, but, as discussed above, the opposite is seen in humans. This should be mentioned.

p. 17 Second paragraph
The study of Hines et al. (2009a) showing metabolic effects in adult mice after prenatal, but not adult, exposure should be mentioned. White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age. Also, anatomical changes in the uterus of mice exposed prenatally to very low doses has been reported in an abstract by Hines (2009b).

p. 18. First paragraph.
The discussion of whether developmental effects are mediated by PPAR alpha needs to be put into context by saying that the role of PPAR alpha in human development is currently unknown (Abbott et al., 2008). The discussion presented here, in the context of the PPAR alpha discussion on page 15, suggests to the reader that effects mediated through PPAR alpha are by definition not relevant to humans, which is not the case. White et al. (2007) discusses the fact that "PPAR alpha is not a critical element of mammary gland differentiation in the neonate," so that "effects of gestational PFOA exposure on neonatal mammary tissue must not be mediated through this pathway."

The cross-fostering studies of Wolf et al (2007), as well as the more recent study of White et al. (2009) which is not cited in the document, showed that decreased body weight, increased liver to body weight ratios, and delayed mammary gland developmental changes occur in mice exposed in utero to PFOA who are nursed by unexposed animals. This finding contradicts the earlier suggestion that these effects are due to poor nutrition resulting from changes in the quantity or quality of milk produced by PFOA exposed mice.

p. 19 First full paragraph. Again, the significance of the discussions of whether or not the effects on the immune system are due to activation of PPAR alpha is not clear, particularly in this introductory section intended more for the non-scientist. As above, it has not been established that PPAR alpha mediated effects on the immune system are not relevant to humans.

p. 20 As mentioned above, this discussion of the role of PPAR alpha and the SAB's conclusion needs to be synthesized with the earlier discussions on pages 15 and 16. It is important that the fact that about three-quarters of the SAB concluded that "PFOA cancer data are consistent with the EPA guidelines descriptor 'likely to be carcinogenic to humans' " be added to this discussion.

Minimum Risk Levels

I strongly disagree that there is not enough information and too much uncertainty to develop a chronic MRL for PFOA. In general, the issues and uncertainties discussed in this section can be addressed by using 1) available information on the relationship between external dose (intake) and internal dose (serum levels) in humans, and 2) by using serum levels from animal studies, rather than administered dose, as the Point of Departure for the risk assessment. It is important to realize that this approach actually has less uncertainty than the standard approach for extrapolating from humans to animals Detailed comments are provided below:

Human Data

A general comment is that, as is the case for the vast majority of risk assessments for environmental contaminants, the available human data are not appropriate to serve as the quantitative basis for an MRL. However, the human data do provide important information which can support a risk assessment based on animal data.

Bottom of p. 21. As discussed, a median ratio of approximately 100:1 between serum level and drinking water concentration was found in Little Hocking, Ohio, which had a high level of PFOA, about 3.5 ug/L (Emmett et al., 2006a). This approximate 100:1 ratio has been confirmed in communities with lower PFOA concentrations in their water supplies (about 0.05 ug/L or greater) by Post et al. (2009a) and is supported by the models of Harada et al. (2005). Tardiff et al. (2009) predicts similar, but slightly higher, ratios, as discussed by Post et al. (2009a, 2009b). It is also supported by the unpublished work of Hinderliter and Jepson (2001) and Gray (2005).

Top of p. 22. Increased risk of levels of serum cholesterol (Steenland, 2009a) and uric acid (Steenland, 2009b) considered clinically elevated have been associated in a dose-related fashion with specific serum levels of PFOA. As discussed above, these findings are especially notable because dose-related increases are seen in the lower exposure groups which coincide with the exposures of the general United States population.

p. 22 Main paragraph. As discussed above, the population study of Emmett et al. (2006b) is greatly expanded upon by the C8 Health Study. Some results of this study are available and other portions of this study are ongoing.

"Furthermore, even if a wide range of end points had been examined in the studies available and points of departure could have been defined, there is currently not enough information regarding the pharmacokinetics of this group of compounds in humans to facilitate estimations of exposure levels resulting in measurable body burdens of perfluoroalkyls."
Comment: Clewell (2006) predicts the relationship between exposure and serum level in humans, as discussed in Tardiff et al. (2009). Clewell's model predicts factors of 0.1 and 0.127 relating intake (µg/kg/day) to serum concentration (µg/mL). Based on mean water ingestion of 17 mL/kg/day (USEPA, 2004), the 100:1 ratio between serum and drinking water levels (Post et al., 2009a) gives a factor of 0.167 ug/kg/day intake per ug/ml in serum (Post et al., 2009b).

Animal Data
The issues discussed here relating to differences in serum concentrations resulting from the same administered dose in humans and animals, as a result of differences in elimination rates, can be addressed by using serum levels instead of administered doses as the starting point for the risk assessment. This approach also addresses differences in elimination rates between male and female animals of the same species (e.g. rats). Measured or modeled serum levels are available for many of the key studies of PFOA in animals. This approach was used by USEPA (2005) in its draft risk assessment, as well as by Post et al. (2009a) and Tardiff et al. (2009) in their drinking water risk assessments.

The serum level at the NOAEL, LOAEL, or Benchmark Dose in animal data can be identified or predicted by modeling and used as the Point of Departure. Uncertainty factors are applied to the serum level at the Point of Departure in the same way that uncertainty factors are applied to administered doses in other risk assessments in order to develop target human serum levels.

It is important to realize that there are differences in body burden resulting from a given administered dose between species and sexes for all or most chemicals for which MRLs are developed. In most cases, this is addressed through the application of a default uncertainty factor. The approach suggested here for PFOA, which is based on internal dose and uses data specific to this chemical thus actually has less uncertainty in this regard than the approach used for most other chemicals.

The fact that humans take longer to achieve steady state than animals should not preclude the use of animal studies as the basis for a chronic MRL, if the serum levels in animals are used as the basis for the risk assessment. Even though chronic MRLs are defined as applying to exposures of one year are longer, in practice, they are used to address chronic exposures, such as residential exposure to contaminated soil or drinking water. Humans who are exposed through environmental media (e.g. water, soil) at the level of the chronic MRL for a duration somewhat shorter than the duration required to reach steady state will have somewhat lower serum levels than they will have at steady state. Thus, application of a chronic MRL for exposures through environmental media (e.g. water, soil) for durations longer than those considered to be "Intermediate" but which are not long enough for steady state to be reached will be protective for potential health effects

Additionally, the half life of PFOA may be shorter than 1000 days, and/or four half-lives may not be required for PFOA to reach steady state in humans. Emmett et al. (2006a) found that duration of exposure to PFOA in drinking water did not impact serum levels in a group of individuals exposed for two years or longer, suggesting that the time needed to achieve steady state is much shorter than 12 years. Monkeys reached steady state in about two weeks (Butenhoff et al., 2002), much shorter than the predicted 90 days.

Recent studies relevant to human half life are Holzer et al. (2009) and Bartell et al. (2009).

In summary, based on the above considerations, kinetic extrapolations from animals to humans are likely to be less uncertain than for risk assessments of most chemicals, for which these issues are not considered quantitatively.

Maternal-fetal transfer

Information on maternal-fetal transfer and levels of the chemical under study in the fetuses of animals and humans is not available for most chemicals for which MRLs are developed. The default approach is to use the maternal dose in the animal study as the starting point and to assume that maternal-fetal transfer occurs similarly in humans and animals. For PFOA, uncertainty factors can be applied to the animal maternal serum level at the Point of Departure (NOAEL, LOAEL, or Benchmark Dose) to develop the target human maternal serum level which is the basis for the MRL. Fenton et al. (2009) showed that mouse pups exposed to a single dose of PFOA on gestation day 17 have significantly higher PFOA concentrations than their dams, and that their body burden increases after birth until at least day 8. Monroy et al. (2008) provides data on the concentrations of PFOA, PFOS, and other perfluorinated chemicals in maternal serum and umbilical cord serum in humans at delivery.

PBPK Models

A human PBPK model developed by Clewell (2006) is discussed by Tardiff et al. (2009). Harada et al. (2005) also developed a kinetic model for PFOA in humans.

p. 28 PFOA – Oral Exposure
Throughout this section, there are discussions of whether or not the effects being mentioned have been found to occur through PPAR alpha. The significance of this information as presented in the draft document is likely to be unclear to the reader. If this information is included, it should also be stated that PPAR alpha mediated effects may also occur in humans, with the possible exception of peroxisome proliferation and tumors resulting from peroxisome proliferation in the liver.

Several additional studies which provide NOAELs or LOAELs more sensitive than the studies mentioned in the draft document should be included. PFOA serum levels are available or could be modeled for these studies:

Significantly increased body weight, leptin, and insulin in mid-life were found in mice exposed to doses of PFOA as low as 0.01 mg/kg/day for 17 days of gestation, but not in mice exposed as young adults (Hines et al., 2009a).

In an abstract, Hines et al. (2009b) also reported that mouse pups exposed to doses as low as 0.01 mg/kg/day during gestation had increased uterine weight and a unique anatomical change at the utero-cervical junction.

White et al. (2009) reported changes in mammary gland development and differentiation in cross-fostering studies in which mouse pups were exposed during gestation, lactation, or both. Delayed development was seen for exposure periods as short as one day or less in mice exposed only through lactation. Effects were seen at serum levels as low as about 2000 ug/L.

The NOAEL for reduced mouse pup survival of 0.3 mg/kg/day for 17 days of gestation (Abbott et al., 2007) is mentioned in the draft document. However, a LOAEL of 0.1 mg/kg/day (the lowest dose tested) for increased pup liver/body weight ratio was also seen in this study, and data on serum levels are presented.

Loveless et al. (2006) reported a LOAEL of 0.3 mg/kg/day (the lowest dose tested) for increased liver to body weight ratio in mice given PFOA for 14 days. Serum levels are reported.

It should be noted that mortality occurred in 1 of 4 monkeys (25%) in the lowest dose group (3 mg/kg/day) in the study of Butenhoff et al. (2002).

Health Effects
Inhalation Exposures
Detailed comments on occupational epidemiology studies are being submitted by Dr. Perry Cohn of New Jersey Dept. of Health and Senior Services. Concise and relevant summaries of some of the findings of the occupational studies are provided in Steenland et al. (2009a, 2009b). They discuss associations of elevated uric acid in two occupational studies, increased cholesterol in six occupational studies, increased liver enzymes in three occupational studies, and diabetes mortality in one occupational study.

Oral Exposures

p. 56. In the cynomolgus monkey study of Butenhoff (2002), 1 of 4 monkeys in the 3 mg/kg/day group and 1 of 6 monkeys in the high dose group (30 mg/kg/day lowered to 20 mg/kg/day) were sacrificed *in extremis* during the study. Thus, mortality should be considered an effect in this study.

p. 116 Hepatic Effects

The C8 Health Study will provide additional data on liver effects in humans exposed to PFOA through drinking water. Preliminary data associations of increased serum liver enzymes with serum PFOA levels (West Virginia School of Medicine, 2009). No threshold for increase in some liver enzymes is apparent in these preliminary data. These associations have also been observed in occupational studies, as discussed by Steenland et al. (2009a).

Second paragraph. The hepatic response of rodents to PFOA is partially independent of PPAR alpha, as shown by studies in PPAR alpha null mice by Yang et al. (2001), which is cited in the document, and Wolf et al. (2008) which is not cited in the document. Wolf et al. (2008) showed increased liver weight and increased labeling index caused by PFOA in PPAR alpha null mice. Additionally, Kudo and Kawashima (1997) showed that PFOA caused fatty liver in mice, an effect not seen with typical PPAR alpha activators such as fibrates.

p. 117 As mentioned above, Loveless et al. (2006) reported a LOAEL of 0.3 mg/kg/day (the lowest dose tested) for increased liver to body weight ratio in mice given PFOA for 14 days.

As above, the studies in PPAR alpha null mice of Wolf et al. (2008) should be cited along with Yang et al. (2001).

p. 118. Full paragraph beginning with "Treatment..." Abbott et al. (2007) is a mouse study, not a rat study as stated here.

Also, in this study, liver weight was increased in wild type pups at 0.1 mg/kg/day and higher.

p. 119 First paragraph. Regarding the Butenhoff et al. (2002) study, it should be mentioned in this section or elsewhere than 1 of 4 monkeys in the 3 mg/kg/day group and 1 of 6 monkeys in the high dose (30/20 mg/kg/day) group were sacrificed in moribund condition during the study. Three additional monkeys in the high dose group were removed from the study because they could not tolerate the dosing.

p. 124 and 125. Renal Effects, Endocrine Effects

Steenland et al. (2009b) reported no interactions between PFOA and creatinine, an indicator of kidney disease in ~55,000 adults who were part of the C8 Health Study. The

C8 Health Study will provide additional data on whether there is an association between serum PFOA and these effects.

Immune
Fletcher et al. (2009) reported that changes in several indicators of inflammatory and immune response were significantly associated with serum PFOA levels, after adjustment for age, gender, body mass index, and other factors. These include IgA, IgE, antinuclear antibodies, and C-reactive protein.

p. 132 DeWitt et al. (2009) showed that the suppression of humoral immunity by PFOA in mice is independent of increased corticosterone levels and thus is not secondary to liver toxicity or stress.

Son et al. (2008) showed effects of PFOA on T lymphocyte phenotypes and cytokine expression in mice.

Loveless et al. (2008) studied immune effects of PFOA in rats and mice.

p. 133 Neurobehavioral Effects
Johansson et al. (2008) which showed permanent behavioral changes in mice after a single dose of PFOA or PFOS at age 10 days should be mentioned here.

Also, Johansson et al. (2009) showed that a single dose of PFOA or PFOS given to neonatal mice altered the levels of proteins important for brain development.

p. 135 Reproductive Effects
Two recent studies in the general population should be mentioned in this section. Joensen et al. (2009) studied associations between semen quality and reproductive hormone levels with serum levels of perfluoroalkyl acids in young Danish men. They reported a significant association of high levels of PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters.

Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

p. 136 Butenhoff et al. (2002) reported that estradiol levels in the high dose monkeys appeared to be decreased.

p. 136 Last paragraph. White et al. (2009) is not mentioned in the document. It is a followup study to White et al. (2007). This study had a cross-fostering design, so that pups were exposed in utero, through lactation, or both. Exposure only in utero only during the final days of pregnancy or only through lactation caused adverse mammary development as early as post-natal day 1 that persisted beyond post-natal day 63. The findings that these effects occurred in pups exposed only late in gestation, with no exposure through lactation because they were nursed by unexposed mice, contradicts the

earlier suggestion that the effects on mammary gland development are due to alterations in the quality of the milk which the pups consumed.

p. 141 The studies of developmental endpoints in human populations of Monroy (2008) and Stein et al. (2009) should be discussed.

p. 142 The rat multigeneration study of Butenhoff et al. (2004) which is mentioned on page 136 should be discussed here. The fact that female rats excrete PFOA very quickly so that exposure to pups is lower than in other species given the same dose should be mentioned. Effects seen included reduced body weight during lactation in the F1 generation given 30 mg/kg/day, increased deaths of F1 males given 30 mg/kg/day at 2-4 days post-weaning, delays in sexual maturation in F1 males and females,

p. 143 It should be mentioned that lactational exposure alone caused decreased body weight and increased relative liver weight in the cross fostering studies of Wolf et al. (2007).

p. 144 The findings of the following recent mouse developmental studies should be added: White et al. (2009), Yang et al. (2009), Hines et al. (2009a), Hines et al. (2009b). These studies show developmental effects at lower doses and/or shorter exposures than previous studies. Furthermore, White et al. (2009) showed that mammary gland changes caused by short exposures during development persist into adulthood, Hines et al. (2009a) showed metabolic changes not evident in adulthood as a result of developmental exposures, and Hines et al. (2009b) showed a unique anatomical change in the uterus after exposure to a very low dose for only 3 days of gestation. These effects may be more significant than the developmental delays reported in earlier studies.

p. 148 Cancer
I suggest removing the following sentence regarding 3M (1983): "The investigators did not consider PFOA carcinogenic in the rat under the conditions of the study." If it is not removed, it should also be stated that the USEPA SAB (2006) judged PFOA to be a "likely carcinogen" based on data from this study and the study of Beigel et al. (2001).

Toxicokinetics
p. 162 Oral Exposure
Post et al. (2009a) discussed exposures through drinking water with PFOA at lower concentrations than those in Little Hocking studied by Emmett et al. (2006a). The recent Minnesota Dept of Health Biomonitoring Project (2009, http://www.health.state.mn.us/divs/eh/tracking/finalpfcrpt.pdf) studied exposure to 7 PFCs from drinking water. Data currently being analyzed from this study will provide further information on the relationship between drinking water concentrations and serum levels in residents with contaminated private wells.

p. 172 Metabolism
It should be stated that PFOA is a stable compound that does not undergo chemical reactions in the body (or in the environment, under normal circumstances). This is one of

the most notable features of PFOA as compared to most other organic chemicals which are found in the environment (Lau et al., 2007).

p. 190 Risk Assessment
As discussed above, I do not agree that the pharmacokinetic differences between humans and animal species preclude development of MRLs, since extrapolations can be done on the basis of serum levels. A pharmacokinetic model developed for monkeys has been adapted to humans and used in risk assessment, as discussed in Tardiff et al. (2009).

p. 195. 3.5.2 Mechanisms of Toxicity
The same general comments provided on page 6 above about discussions of PPAR alpha mediated effects apply to this section.

This sentence should be changed as follows: Liver toxicity in rodents results IN PART from the ability of these compounds (with some structural restrictions) to activate the peroxisome proliferator activated receptor-α (PPARα),...." As discussed above, PFOA caused increased liver weight, fatty liver, and histological changes in PPAR alpha null mice, and has been shown to activate genes associated with pathways other than PPAR alpha in liver.

"Although humans are refractory to the many effects induced by peroxisome proliferators in rodents, humans have a functional PPARα as suggested by the pharmacological reductions
in serum triglycerides and cholesterol in patients treated with the peroxisome proliferator clofibrate, a response known to be mediated by the PPARα in mice." As discussed above, PPAR alpha is known to mediate many effects in humans in liver and in other organs, and its role in human development and in young children has not been characterized. Furthermore, PFOA has been shown to be associated with increased cholesterol in humans both in occupational studies and in a very large population exposed through drinking water with much lower serum PFOA levels (Steenland et al., 2009a). In this way, it differs from the fibrate drugs which lower cholesterol in humans.

p. 197 In discussing Tilton et al. (2008), it should be mentioned that PFOA acted as a promoter for liver tumors in rainbow trout exposed to an initiator. Rainbow trout have been used for many years as a model for human liver cancer, since they are also insensitive to peroxisome proliferation in the liver. The authors concluded that the liver tumors in trout occurred through an estrogenic mechanism that may be relevant to humans.

p. 197, Second paragraph
Discussion of non-PPAR alpha mechanisms needs to be mentioned at the beginning of this section on page 195, not just at the end where it is not connected with the earlier discussion.

Section 3.5.3 Animal-to-Human Extrapolations
I strongly disagree with the statements made in the first paragraph of this section. Details are given below.

Toxicokinetic Differences
This issue is also discussed in detail under Animal Studies in the MRL Development section above. As stated above, the issues discussed here relating to differences in serum concentrations resulting from the same administered dose in humans and animals, as a result in differences in elimination rates, can be addressed by using serum levels instead of administered doses as the starting point for the risk assessment. This approach also addresses differences in elimination rates between male and female animals of the same species (e.g. rats). Measured or modeled serum levels are available for many of the key studies of PFOA in animals. This approach was used by USEPA (2005) in its draft risk assessment, as well as by Post et al. (2009a) and Tardiff et al. (2009) in their drinking water risk assessments.

As discussed above. The serum level at the NOAEL, LOAEL, or Benchmark Dose can be identified and used as the Point of Departure/ Uncertainty factors are applied, in the same way that uncertainty factors are applied to administered dose in other risk assessments, to develop target human serum levels. It is important to realize that there are differences in body burden resulting from a given administered dose between species and sexes for all or most chemicals for which MRLs are developed. In most cases, this is addressed through the application of a default uncertainty factor. The approach suggested here for PFOA, which uses data specific to this chemical thus actually has less uncertainty in this regard than the approach used for most other chemicals.

The fact that humans take longer to achieve steady state than animals does not preclude the use of animal studies if serum levels are used as the basis for the risk assessment. The half-life of PFOA in humans exposed through drinking water has recently been estimated to be 2.3 years (Bartell et al, 2009). Additionally, PFOA may not take four half lives to reach steady state in humans. Emmett et al. (2006a) found that duration of exposure to PFOA in drinking water did not impact serum levels in a group of individuals exposed for two years or longer, suggesting that the time needed to achieve steady state is much shorter than 12 years. Monkeys reached steady state in about two weeks (Butenhoff et al., 2002), much shorter than the predicted 90 days.

p. 198 "As a result of these large differences in kinetics, internal doses (i.e., serum concentrations of PFOA) achieved during intermediate-duration exposures in rats or monkeys would not represent steady-state internal doses that might be achieved in humans over longer exposure durations." The logic and intent of this sentence is unclear. Animals reach steady-state more quickly than humans, so any comparison based on serum levels in which humans have not yet reached steady state might be slightly overprotective, rather than underprotective, and thus the use of animal serum levels as the basis for human risk assessment should not be precluded. Also, as discussed above, humans may reach steady state more quickly than the 12 years mentioned in the draft document. As above, because of the availability of date on the relationship between

administered dose and serum levels in both humans and animals, the uncertainties in this area are less than for the risk assessments for most other chemicals for which a default uncertainty factor is used for interspecies extrapolation.

Lack of Reported Effects in Humans

This paragraph should be rewritten to better convey a balanced summary of the data on associations seen in occupational and general population studies. Concise summaries of some of these data are provided in the introductory sections of Steenland et al. (2009a) and Steenland et al. (2009b),

As mentioned above, Steenland et al. (2009a) report a dose-related increased risk of hypercholesteremia in a large population exposed through drinking water, with an odds ratio of 1.51 in the highest quartile compared to the lowest quartile. The data of Steenland et al. (2009a) are especially significant because the associations exhibited no threshold down to the lowest deciles of exposure, and the serum levels in the lower deciles in the C8 study population are within the range of exposures of the general US population (Calafat et al., 2007).

In the uric acid study (Steenland et al., 2009b), the risk of hyperuricemia (greater than 6.0 mg/dl in women and 6.8 mg/dl in men) increased in a dose-related fashion with serum PFOA. The increased risk plateaued in the higher exposure groups, with an odds ratio of 1.47 and 95% confidence interval of 1.37-1.58 in the two highest quintiles.

A separate analysis of uric acid within the lower exposure group (within the range of the US general population), with serum PFOA of less than or equal to 20 ug/L, revealed a dose-response by quartile within this group. . The highest quartile with serum levels of 15-20 ug/L serum PFOA had an increase in uric acid of 0.24 mg/dl above the lowest quartile with serum PFOA of less than 5 ug/L.

Steenland et al. (2009a) summarize some of the literature on associations in humans as follows: "It (PFOA) .... has been shown to be weakly associated with lower birth weight in humans (5, 6). It has been shown to be associated with increased liver enzymes in 3 occupational studies of workers (7–9) but not in 1 study of community residents exposed via contaminated drinking water (10). It has also been found to be positively correlated with cholesterol in 5 occupational studies (7–9, 11, 12) and 1 community study (10), although in several of these the relation was not statistically significant at the 0.05 level."

Steenland et al. (2009b) summarizes as follows: "PFOA has been found to be significantly associated with elevated uric acid in two cross-sectional studies of workers (n=160 and n=1024) (Sakr et al. 2007a; Costa et al. 2009). There is also evidence in the literature for an association of PFOA with cholesterol and diabetes in humans. A positive correlation of PFOA with cholesterol was observed in six occupational studies (Sakr et al. 2007a; Costa et al. 2009; Sakr et al. 2007b; Olsen et al. 2000; Olsen and Zobel 2007b; Olsen et al. 2003), and two community studies (Emmett et al. 2006; Steenland et al. 2009), although in one community study and two occupational studies, the relationship was not statistically significant. PFOA exposure was observed to be associated with a

two-fold increase in diabetes mortality in one cohort study of highly-exposed workers when the exposed workers were compared to non-exposed workers, although no association was seen in another cross-sectional study of diabetes prevalence (Leonard et al. 2008; McNeil et al. 2009)."

Additionally, among other studies showing associations of PFOA exposure with health endpoints, Lundin et al. (2009) recently reported associations of occupational exposure with prostate cancer, cerebrovascular disease, and diabetes. Costa et al. (2009) reported associations with increased uric acid, as well as cholesterol.

As mentioned above, Dr. P. Cohn of the NJ Dept. of Health and Senior Services will provide extensive comments on human studies.

Mode(s) of Action
As discussed in detail above, the following sentence is an oversimplification and should be modified to add the words in capitals as follows: "As previously mentioned, many PFOA-or PFOS-induced effects in rats and mice are mediated through the PPARα and it is generally agreed that humans and nonhuman primates are refractory, or at least less responsive than rodents, to PPARα-mediated effects IN THE LIVER THAT LEAD TO TUMOR FORMATION."

"Therefore, further studies in PPARα-null mice are needed to expand the knowledge regarding PPARα-dependent and independent effects that would allow selection of an appropriate animal model for perfluoroalkyls toxicity." Comment: This sentence should be rewritten to emphasize that PPAR alpha does mediate effects in humans other than liver cancer. As written, it implies that only effects seen in PPAR alpha null animals are relevant to humans, which is not the case.

p. 198 Section 3.6 Toxicities Mediated Through the Neuroendocrine Axis
The following studies which have been discussed above relate to endocrine effects and should be considered for inclusion in this section:

Joensen et al. (2009) studied associations between semen quality and reproductive hormone levels with serum levels of perfluoroalkyl acids in young Danish men. They reported a significant association of high levels of PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters.

Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age.

Exposure to low levels of PFOA during gestation in mice has been shown to cause metabolic effects which become apparent in adulthood, including increased weight and changes in insulin and leptin (Hines et al., 2009a). Such exposures have also been shown to cause a unique anatomical change at the junction between the cervix and the uterus in the female offspring (Hines et al, 2009b).

p. 203 Children's Susceptibility
The ongoing C8 Health Project will provide information on associations of many endpoints with PFOA exposure in children as well as in adults.

Hoffman et al. (2009) recently reported an association with serum levels of PFOA and several other perfluorinated chemicals and attention deficit hyperactivity disorder in U.S. children age 12-15.

It should be mentioned that children exposed to PFOA in drinking water have higher serum PFOA levels than adults (Emmett et al., 2006a, Steenland et al., 2009c). This could be due to a greater volume of water consumed per kilogram body and/or differences in the toxicokinetics of PFOA in children and adults.

p. 204 Last paragraph
Hines et al. (2009a, 2009b) which showed metabolic effects in adulthood and anatomical changes in the uterus after fetal exposure should be mentioned here.

p. 205 Partial paragraph at top of page
In discussing the developmental effects of PFOA in wild type and PPAR alpha null mice (Abbott et al., 2007), it should be mentioned that full litter resorptions were independent of PPAR alpha. Also, if this topic is discussed, it should be mentioned that the role of PPAR alpha in human development is uncharacterized, and that it cannot be concluded that developmental effects mediated through PPAR alpha are not relevant to humans.

p. 207 Biomarkers used to characterize effects by perfluoroalkyls
It is agreed that there are no biomarkers of effects specific to perfluoralkyls. However, the following sentence is misleading and is also contradicted by the recent publications of Steenland et al. (2009a, 2009b) mentioned above. It is not necessary to include this statement in order to make the point that there are no biomarkers SPECIFIC to perfluoralkyls, and I suggest that it be deleted.
"Health evaluations of workers exposed to perfluoroalkyl compounds or of subjects environmentally exposed via their drinking water have not provided evidence of adverse health effects in the groups studied (Emmett et al. 2006a; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b)."

p. 207 3.10 Populations that are unusually susceptible
Steenland et al. (2009a) as well as the occupational studies cited by Steenland et al. (2009a, 2009b) show that PFOA has effects opposite to the hypolipidemic drugs on serum lipid levels. As mentioned in Steenland et al. (2009a), several studies have shown associations with increased liver enzymes, so it is agreed that people with compromised

liver function may be particularly susceptible. Similarly, Steenland et al. (2009b) has found associations of PFOA exposure with clinically elevated uric acid and Fletcher et al. (2009) has reported changes in immune function, so that people who already have elevated uric acid or immune system abnormalities may be particularly susceptible. There are also two occupational studies showing increased uric acid, as discussed in Steenland et al. (2009b)

p. 208 3.11.12 Reducing Body Burden
Bartell et al. (2009) recently reported on the rate of decline in serum PFOA concentrations after granular activated carbon filtration in the C8 Health Study population in Ohio and West Virginia.

p. 209 3.11.3 Interfering with the Mechanism of Action for Toxic Effects
It is agreed that there is no known method for interfering with the mechanism of toxicity of PFOA. However, the statements about no associations being found with adverse health effects should be removed, as they are not needed to make this point. If the statements are not removed, they should be modified as discussed under Section 3.10 above.

p. 212 First full paragraph
The data from the C8 Health Study on general population exposure, should be mentioned here. These include published papers on design and results of the study (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009), reports from the C8 Science Panel, including Fletcher et al. (2009) which reports associations with immune endpoints not yet published in a peer reviewed journal, and extensive data from the C8 Health Project which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009). These data are quite extensive, so it should be stated that data from both occupational and general population (environmental) exposures are available, without saying that the environmental data is limited.

p. 213 3.12.2 Identification of Data Needs
As discussed in detail above, I do not agree that there is insufficient information or too much uncertainty to develop a chronic oral MRL for PFOA.

p. 214. Chronic Duration and Cancer
I disagree with the statement that "for the most part, no significant adverse effects have been identified",

The DuPont incidence study (Leonard, 2003) and the more recent occupational studies of Lundin et al., (2009), Costa et al. (2009), and others should be discussed.

p. 215-216.
"In a 2-year bioassay, PFOA induced a "tumor triad" in rats, that is, liver tumors, Leydig cell tumors, and tumors in pancreatic acinar cells, characteristic of PPARα-agonist activation in rats (3M 1983; Biegel et al. 2001). The relevance of these findings to

humans has been questioned by some since humans are considered refractory to most, but not all PPARα-activation effects (Klaunig et al. 2003)." Comment: The focus of Klaunig et al. (2003) was on rodent tumors, not "all PPAR alpha activation effects", which include effects on lipid metabolism and many other biological endpoints in the liver and other organs, as well as on development. The statement as written is misleading.

"PFOA also increased the incidence of mammary gland fibroadenomas (3M 1983) and of mammary gland adenocarcinomas (mid-dose only)." Since PPAR alpha is discussed so extensively in this draft document, it should be mentioned that PPAR alpha is not known to be involved with mammary gland tumor formation.

p. 216. Reproductive Toxicity
As above, it should be mentioned that Joensen et al. (2009) found a significant association of high levels of serum PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters, in young Danish men.

Also, it should be mentioned that Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

p. 218 Developmental Toxicity
As above, the study of Hines et al. (2009a) showing metabolic effects in adult mice after prenatal, but not adult, exposure should be mentioned. White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age. Also, anatomical changes in the uterus of mice exposed prenatally to very low doses has been reported in an abstract by Hines (2009b).

p. 219. Immunotoxicity
The findings of associations with changes in immune parameters in the C8 Health Study population (Fletcher et al., 2009) should be mentioned here.

p. 220 Epidemiological and Human Dosimetry Studies
The findings of the C8 Health Study should be mentioned here, including the publications of the C8 Science Panel (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009) as well as the data of Fletcher et al., 2009 and the West Virginia University School of Medicine (2009). Since the focus of this document is health effects from environmental exposures, these data are even more relevant than the occupational studies.

p. 222 Second full paragraph
It should be mentioned that mice do not show the marked sex difference in elimination rate seen in rats. It is important to mention this because of the many studies showing developmental effects in mice which were not seen in rat developmental studies.

Bartell et al. (2009) recently reported that there is not a gender difference in elimination of PFOA in humans exposed through drinking water.

The relevance of the discussion of possible gender differences in humans with dose or plasma concentration is not clear, as the data from humans involve serum levels relevant to human exposure.

p. 223 Children's Susceptibility
As discussed above, the ongoing C8 Health Project will provide information on associations of many endpoints with PFOA exposure in children as well as in adults. It should be mentioned that children exposed to PFOA in drinking water have higher serum PFOA levels than adults (Emmett et al., 2006a, Steenland et al., 2009c). This could be due to a greater volume of water consumer per kilogram body and/or differences in the toxicokinetics of PFOA in children and adults.

p. 224 3.12.3 Ongoing Studies
As mentioned above, the C8 Health Study should be discussed in much more detail than in the draft document. In the draft document, the ongoing studies by the C8 Science Panel are simply mentioned with no context provided.

This ongoing study is unprecedented in size and scope among studies of exposure and effects of humans exposed to an environmental contaminant. It will provide extensive data on the relationships between human exposure, internal dose, and health effects. The design, scope, and currently available data from this study should be discussed. The design of the study is discussed in Frisbee et al. (2009). Information on predictors of serum levels is discussed in Steenland et al. (2009b) and on half-life in Bartell et al. (2009). Data on associations with health endpoints are found at (WVU School of Medicine C8 Health Project website and C8 Science Panel website), as well as in the following peer-reviewed publications: Stein et al. (2009),. MacNeil et al. (2009), and Steenland et al. (2009a, 2009b).

Potential for Human Exposure
The following studies should be discussed under this section:

Fromme et al. (2009) summarizes perfluorinated chemical concentrations in indoor and ambient air, house dust, drinking water and food, as well as biomonitoring data in blood, breast milk, and human tissues. These data are used to estimate overall human exposures.

Vestergren and Cousins (2009) conclude that dietary exposure is a major pathway of PFOA exposure in the general population.

Post et al. (2009a) show the exposure contribution of low concentrations of PFOA in drinking water (e.g. 0.01 ug/L) can be substantial relative to the total exposure of the general population.

Washburn et al. (2005) evaluate exposure from trace levels of PFOA in consumer products.

Tittlemier et al. (2007) report on dietary exposure of Canadians to perfluorocarboxylates and PFOS.

Tao et al. (2008) report on perfluorinated compounds in human breast milk in Asia, and in infant formula and dairy milk in the U.S.

Jogsten et al. (2009) report on dietary exposures to perfluorinated compounds in Spain.

Fromme et al. (2007) report on dietary exposures in Germany.

Guo et al. (2009) report perfluorocarboxylic acid content in 116 articles of commerce.

p. 249 Second full paragraph beginning with "Mean PFOA, PFOS,..."
It should be mentioned that telomer alcohols from food packaging can be metabolized in the body to PFOA and that this is may to be a greater source of expsosure to PFOA from food packaging than residual PFOA in these products (D'eon and Mabury, 2007, D'eon et al., 2009). Vestergren et al. (2008) evaluated the contribution of precursor compounds in consumer exposure to PFOS and PFOA.

6.2 Releases to the Environment
6.21 Air
Gewurtz et al. (2009) recently reported on studies of pefluoralkyl compounds on indoor and outdoor window films. These data were used to evaluate potential sources by sampling window films before and after new carpet installation and floor wax application, as well as in carpet stores. The results suggested that carpets may be a source of exposure indoors.

6.22 Water
The following studies are relevant to wastewater discharges of perfluorinated chemicals:

Kelly and Solem (2008) identified discharge from a chrome plating operation as the major source of PFOA at a wastewater treatment tlant in Brainerd, Minnesota.

In Alabama, perfluoroalkyls from the land-applied sludge from a wastewater treatment plant were found to contaminate groundwater and soil. These chemicals may potentially enter the food chain (milk, meat) through grazing of cattle or other animals (Renner, 2009, USEPA Region 4, 2009).

Sinclair and Kannan (2006) studied perfluorinated chemicals in sewage treatment plant influent and effluent. Increased concentrations of some chemicals in effluent was attributed to biodegradation of precursors present in the inflent.

A similar study was reported by Loganathan et al. (2007).

Clara et al. (2008) studied perfluorianted chemicals in industrial wastewaters and wastewater treatment plant effluents.

Yu et al. (2009) reported on perfluorinated chemicals in sewage treatment plants.

D'eon et al. (2009) Reported on the occurrence of di-PAPS, the compound containing fluorotelomer alcohols in paper products, in wastewater and sludge. This compound can biodegrade to fluorotelomer alochol which can further biogegrade to PFOA.

6.3 Environmental Fate
6.3.1 Transport and Partitioning
In addition to long range atmospheric transport, it is very important to discuss that contamination of groundwater near industrial facilities occurs through air emissions followed by deposition on the soil and migration to groundwater, as well as through migration in a groundwater plum from the facility (Paustenbach et al., 2007).

Issues related to environmental fate and transport and pathways of human exposure to PFOA released from an industrial facility are evaluated in Small et al. (2009).

6.4.2 Water
The following studies are relevant to occurrence of perfluorinated chemicals in surface water and ground water:
Murakami et al. (2009) reports on groundwater pollution by perfluorinated chemicals in Tokyo.

Loos et al. (2008) reports on PFOS and PFOA in European river waters.

Konwick et al. (2008) reports on concentrations and patterns of perfluoroalkyl acids in surface waters in Georgia near and distant to a major use source.

Orata et al. (2008) reported on PFOA and PFOS in Lake Victoria Gulf in East Africa.

Murakami et al. (2008a) reported on perfluorinated chemicals in rivers in Japan.

Murakami et al. (2008b) reported on wastewater and street runoff as sources of perfluorinated chemicals in water.

p. 281. Several studies have reported on occurrence of PFOA and other perfluorinated chemicals in drinking water supplies not located near an industrial facility known to discharge these chemicals.

Post et al. (2009a) reported on occurrence of PFOA in New Jersey public drinking water supplies. Data on PFOS from this study is found in NJDEP (200?). NJDEP is currently conducting an occurrence study of 30 additional public water supplies for 10

perfluorinated chemicals, and we will submit these data when available (anticipated to be within the next few months).

Ericson et al. (2009) reported on levels of perfluorinated chemicals in municipal drinking water from Catalonia, Spain.

Jin et al. (2009) reported on drinking water levels of PFOA and PFOS in China.

Loos et al. (2007) reported on PFOA and PFOS in surface and tap waters around Lake Maggiore in Northern Italy.

Rumsby et al. (2009) reviews PFOA and PFOS in drinking and environmental waters worldwide.

Mak et al. (2009) presents data on perfluorinated compounds in tap water in China, Japan, India, the U.S., and Canada.

Takagi et al. (2008) reported on PFOA and PFOS in raw and treated tap water in Osaka, Japan.

6.4.3 Sediment and Soils
As mentioned above, perfluorinated chemicals in land applied sludge from a local wastewater treatment plant has contaminated grazing land in Alabama. This could potentially be a route of contamination of the food supply. Currently, tissue levels of perfluorinated chemicals in cattle that grazed on this land are being studied.

p. 284 Paragraph beginning with "Limited monitoring data..."
As mentioned above, Paustenbach (2007) discussed soil deposition of PFOA emitted into the air from the Washington Works facility. This is a pathway for groundwater contamination in this vicinity.

House Dust
Kato et al. (2009) measured perfluoroalkyl chemicals in house dust.

Bjorklund et al. (2009) measured PFOA and PFOS in indoor dust in houses, apartments, day care centers, offices, and cars.

Section 6.5 General Population and Occupational Exposure
The studies listed under Potential for Human Exposure above are relevant to this section (e.g the discussions on p. 291-292).

p. 295. Emmett et al. (2006a) and Steenland et al. (2009c) reported higher serum levels for children than for young adults in a population exposed to PFOA in drinking water.

Section 6.7 Populations with Potentially High Exposure
Minnesota Department of Health (2009) reported on biomonitoring of populations exposed to perfluorinated chemicals through private wells or public water supplies.

Data from the C8 Science Panel about exposure in their study area should be discussed here: Steenland et al. (2009c), Bartell et al. (2009), West Virginia University School of Medicine (2009).

Section 6.8.1
Small et al. (2009) discusses data needs related to environmental fate and transport.

p. 315. 8. Regulations, Guidelines, and Advisories
PFOA and PFOS are included in USEPA's Contaminant Candidate List 3 for consideration for MCL development (USEPA, 2009. http://www.epa.gov/ogwdw000/ccl/ccl3.html) and USEPA is currently developing Lifetime Health Advisories for drinking water for PFOA and PFOS.

p. 316. Table 8.1. It is important to note that the provisional USEPA Health Advisories for PFOA and PFOS in drinking water are intended to protect for short term exposure and are not intended to protect for chronic exposure.

Citations
The citations listed below are not included in the draft document. Additionally, some citations mentioned in the comments above are listed in the citation list of the draft document, but are not currently cited in the text. It is recommended that those citations should be discussed in the text.

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