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October 30, 2009

Ms. Nickolette Roney
Division of Toxicology and Environmental Medicine
Agency for Toxic Substances and Disease Registry
Mailstop F–62
1600 Clifton Road, NE
Atlanta, Georgia 30333

Subject: Comments on draft Perfluoroalkyls Toxicological Profile, docket control number ATSDR–253

Dear Ms Roney:

As requested in the Federal Register notice of July 23, 2009, I would like to submit comments on the ATSDR Draft Toxicological Profile for Perfluoroalkyls.

The attached comments on the epidemiological studies reviewed in the draft Toxicological Profile for Perfluoroalkyls represent my analysis of human health effects, primarily focused on perfluorooctanoic acid (PFOA). They accompany comments focused primarily on laboratory animal studies, submitted separately by Dr. Gloria Post of the New Jersey Department of Environmental Protection

Dr. Post and I serve on the New Jersey Drinking Water Quality Institute and its Health Effects Committee and develop risk assessments on drinking water contaminants. (The Institute is a legislatively mandated advisory body that recommends drinking water standards to the New Jersey Department of Environmental Protection.) Currently, we are updating our current drinking water guidance on PFOA and developing a New Jersey Health-based Maximum Contaminant Level for New Jersey.

We have recently been informed about the imminent publication of another epidemiological study shortly after the due date for these comments and we plan to send a separate letter briefly discussing this study after its release.

If there is any question on the material discussed here, I can be reached by email at Perry.cohn@doh.state.nj.us or by phone at 609-588-3128. However, the phone number will be changing shortly because the office is being moved to another location.

Sincerely,

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C: Jerald Fagliano, NJDHSS
Gloria Post, NJDEP

Comments on the Draft ATSDR Toxicologic Profile on Perfluoroakyls: Assessment of Epidemiological Studies

Perry Cohn, PhD MPH
New Jersey Department of Health and Senior Services
Consumer Environmental and Occupational Health Service

October 30, 2009

Introductory Comments

These comments on the draft Toxicological Profile on Perfluoroalkyls are directed at the descriptions and conclusions about the epidemiological studies involving exposures to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), as requested in the Federal Register notice of July 23, 2009. These include separate sections on occupational and population-based studies. General comments in each section include relevant studies available by August, 2009. Specific comments on studies that were included in the draft ATSDR Toxicological Profile are noted in the page-by-page analysis following the general comments. Citation of new studies, including a synopsis and critique, are listed at the end in each section.

An important concern is that the epidemiological studies reviewed in this Toxicological Profile do not seem to have been critically analyzed beyond what each of the cited authors noted in their text. In addition, there was a general absence of reporting on marginally statistically significant findings and trends that tended to show concordance among the studies. Subdividing categories of mortality or morbidity often results in too few cases to achieve statistical significance and can obscure more generalized effects, such as the combination of metabolic disease, hypertension and atherosclerosis that can affect the overall system.

I also think that it important that the final draft include findings from both the C8 Health Project and the C8 Science Panel on the populations served by the perfluoroalkyl (largely PFOA) contaminated water systems around DuPont Washington Works in Parkersburg, West Virginia, even though it is a cross-sectional study. Since the focus of this document is health effects from environmental exposures, these data are even more relevant than the occupational studies.

The available epidemiological studies have numerous limitations, as discussed in this document, but the health effects reported in the epidemiological literature are more concordant, given those limitations, than reflected in the summary opinions expressed in the Toxicological Profile. In particular, there is insufficient rationale to the statement, "Thus, the lack of reported health effects at the reported body burdens precludes identifying the animal model that would be most appropriate for human risk assessment based on similar toxic effects." (Animal-to-Human Extrapolation. Lack of Reported Effects in Humans, p. 198). ATSDR should not use that rationale to avoid development of Maximum Risk Levels (MRLs). Especially for PFOA there is more than adequate data from experiments with laboratory animals to develop a quantitative risk assessment that can be used to develop a chronic oral MRL (further addressed in the comments on the Minimal Risk Levels portion of the Relevance to Public Health section), and there is sufficient evidence from the epidemiological literature, even with the limitations discussed in the draft document and below, to support the development of health-based guidelines and standards for the perfluoroalkyls.

General Comments

Inhalational Exposure: Occupational Studies

Occupational exposures included primarily inhalation, but probably also dermal and oral routes. Occupational studies were conducted at the 3M Cottage Grove, MN, Decatur, AL, and Antwerp, Belgium facilities, the DuPont Washington Works plant in Parkersburg, WV, and the Miteni plant in Italy. These facilities included buildings where PFOA and/or PFOS were manufactured, as well as buildings using these chemicals in the manufacture of other chemicals and films. Workers at the 3M Decatur plant, which manufactured POSF, had elevated serum PFOA and PFOS (Olsen et al., 2003b).

Chronic Diseases

Several mortality studies, one incidence study and one health claims study of workers at the two companies, 3M and DuPont, with facilities in the U.S. constitute the literature on health effects from occupational exposures. (The incidence study and the health claims study were not included in the draft Toxicological Profile, but are highly relevant.) Unfortunately, in the DuPont studies did not include any analysis by exposure, except for ischemic heart disease. Some commonalities have been observed among the results of those studies, in contrast to the statements made in the Draft Toxicological Profile.

Bladder cancer incidence appeared to be elevated among the entire workforce (no exposure assessment) (Leonard, 2003), but not with mortality data at the DuPont Washington Works. It was also found to be elevated by job exposure assessment using mortality and health claims data at the 3M Decatur plant (Alexander et al., 2003; Alexander and Olsen, 2007).

Kidney cancer mortality was elevated among the exposed workforce at the 3M Decatur plant (Alexander et al., 2003), and kidney cancer incidence among the entire workforce (no exposure assessment) using incidence (Leonard, 2003).

Prostate cancer mortality was increased with exposure at the 3M Cottage Grove plant (Lundin and Alexander, 2007) and prostate cancer health claims were marginally elevated at the 3M Decatur plant (Olsen et al., 2004). (Prostate cancer incidence was elevated with marginal significance versus serum PFOS level in the Danish population-based study (Eriksen et al., 2009).) DuPont did not find an increase in prostate cancer mortality or incidence, but the DuPont studies were not based on exposure (Leonard, 2003; Leonard et al., 2008).

Multiple myeloma incidence and mortality were elevated with marginal statistical significance at the DuPont Washington Works (Leonard, 2003; Leonard et al., 2008), though at the 3M Cottage Grove plant there were fewer deaths. There was no analysis of leukemia and lymphoma health claims at the 3M Decatur plant.

Deaths from diabetes, ischemic heart disease (IHD), acute myocardial infarction, and the category, atherosclerosis and aneurysm, were elevated among workers at the Washington Works plant (Leonard et al., 2008). Death attributed to IHD was elevated among exposed workers in the top two quartiles of serum PFOA (Sakr et al., 2009). These findings are consistent with elevated total cholesterol and LDL (Sakr et al., 2007a,b). Diabetes and cerebrovascular disease (CVD) mortality was elevated among exposed workers at the 3M Cottage Grove plant (Lundin and Alexander, 2009), which parallels the association (though not in all analyses) of PFOA levels with elevated total cholesterol and TG and decreased HDL (Olsen et al., 2000; Olsen et al., 2007). Death from hypertension with and without heart disease was marginally elevated among those with known or probable exposures (Lundin and Alexander, 2007). In addition, there were increased health claims at the 3M Decatur plant for diabetes, as well as biliary tract disorders and combined acute and chronic cholecystitis (Olsen et al., 2004). It appears that the combination of all heart disease with the related category, cerebrovascular disease, suggests an overall connection between PFOA exposure and atherosclerosis across the various studies, which is also consistent with effects on serum lipid chemistry.

There were also notable increases of white cell neoplasms (Leonard, 2003; Leonard et al., 2008) and carcinoid (Morel-Symons et al., 2007) at the Washington Works.

There are general limitations among the available studies assessed in the draft Toxicologic Profile. These were only partially acknowledged for some studies. In addition, some associations that were reported in the literature were not acknowledged.

Many of the studies reported on mortality rates. Death certificates provide information that is frequently inaccurate because there can be multiple contributing causes. For example, prostate cancer is usually not the primary of death in men with prostate cancer. Another example is diabetes. In a study of known diabetic patients (N = 2766), only 10% had diabetes listed as the cause of death (Bild and Stevenson, 1992). In addition, incorrect diagnoses increase with age of the patient (Bain et al., 1998).

The issue of the "healthy worker effect" is partly addressed by internal workplace rate comparisons, but the general failure of available studies to include short-term workers who may have had very high exposures (e.g., those cleaning batch-processing equipment) could have missed important associations. There is a history of many chemical companies using short-term workers to clean the most contaminated equipment. The rationale is that the longer the duration of exposure, the better the chances of detecting an effect if it is true, but that is not necessarily the reality. One interesting observation (Olsen et al., 2003b) is that the highest serum PFOA levels among 3M Cottage Grove plant employees who worked 5 years or less. Of the 11 male employees with serum PFOA above 10 ppm, 5 worked 5 years or less, and, likewise, above 20 ppm 4 of the 7 worked 5 years or less. It appears that longer-term employees (up to 40 years) had job duties with much less exposure. Therefore, exclusion of short-term workers with < 1 yr employment, as done in the 3M studies reported above, may undercount exposed cases.

Another issue is that the small proportion of female employees limits the ability of the occupational epidemiology to adequately address specific effects among women.

A final issue is that differences in the exposure to other chemicals between the different manufacturing facilities may also influence outcomes by effect modification.

Blood Chemistry (Hepatic Effects and Endocrine Effects)

Regarding serum liver chemistry observations, both the studies at 3M (Olsen and Zobel, 2007), at DuPont (Sakr et al., 2007a,b) and at Miteni (Costa et al., 2009) showed elevated levels of either aspartate aminotransferase (AST), alanine aminotransferase (ALT) or gamma glutamyl transpeptidase (GGT).

One of the potential problems with the blood chemistry studies is the failure to account for sample times relative to biorhythms, i.e., shift, time within shift, and time relative to meals, which can affect the parameters studied

Not mentioned in the Toxicological Profile is the finding by Sakr et al. (2007a) that serum calcium, iron, potassium, and the enzyme lactate dehydrogenase were significantly associated with serum PFOA, though the direction of those associations was not given. No mention was made of those parameters in any other occupational study, but the C8 Health Project descriptive statistics revealed similar phenomena with calcium iron, magnesium, and, among women, potassium. The point is that there are data in the literature that were not addressed, and that there may be a significant number of parameters that had also been measured to which study author paid inadequate attention.

A more subtle issue is that dose-response may be stronger at lower, environmentally relevant, levels (see Oral Exposure section, below). Therefore, a comparison of blood chemistry results in the occupational setting, where even the least exposed had levels that were high compared to the highest levels seen in environmental studies, might not always show associations with exposures that are observed within the lower range of exposures in the general population.

Oral Exposure: Community and Population-Based Health Studies

Community health studies include those conducted and in progress in the area around the DuPont Washington Works facility located in Parkersburg, WV (C8 Health Project and C8 Science Panel). These were largely due to a court settlement. In particular, the Little Hocking, OH, water system had the highest water contamination ($\geq$3 ug/L) and its residents had the highest serum PFOA level. Five other communities around Little Hocking had lower levels ($\geq$0.05 ug/L) of PFOA in the drinking water. People with at least one year of residence, work or school in one of those communities were eligible for inclusion in the studies. There are various studies in progress and completed. Serum PFC and clinical data were collected for most of the 67,000 subjects. Participation was estimated to be approximately 80% (MacNeil et al., 2009). The richness and size of the

collected data is unusual for situations of environmental contamination, but was relegated to brief mention in the Ongoing Studies section in the draft Toxicological Profile.

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, as shown in the 2003-2004 National Health and Nutrition Evaluation Survey (NHANES), where the 75th and 95th percentile levels were 5.8 and 9.8 µg/L (Calafat et al., 2007). The highest serum levels in the Little Hocking area were in the 100s to 1000s of ug/L range. The median serum level was approximately 29 ug/L.

Serum levels of total cholesterol, LDL cholesterol and uric were significantly elevated with increased PFOA among adults and appeared to plateau at higher levels (Steenland et al., 2009a; Steenland et al., 2009b). Similar results were seen for the relationships between PFOA and lipids (C8 Science Panel, 2009b). The liver enzymes, ALT and AST, also showed a strong dose-response with serum levels of PFOA using with univariate analysis (C8 Health Project, 2009), but the dose-response curve appears to plateau within the concentration bounds of the study. Anti-nuclear antibody and the self-reported incidence of Sjögren's disease and scleroderma, which both primarily affect women, were associated with serum PFOA levels in 30-50 year old females (C8 Health Project, 2009a).

(The Emmett et al. (2006) study of the C8 exposed population, which was the first analysis of health effects in these communities to be published, was small and suffered from low participation.)

In addition, there have been a series of population-based reproductive outcome studies in a variety of locations around the world. A general comment about those studies is that analysis with more data on potential confounders, such as the Apelberg et al. (2007) study in Baltimore, the Danish (Fei et al. (2007, 2008a,b) study, and a Japanese (Washino et al., 2009) study found associations between reproductive effects and perfluoroalkyls, while those with the less data on confounders (Grice et al., 2007; Monroy et al., 2007) did not find associations. This trend of being able to detect associations when there is better adjustment for confounding was also noted by Olsen et al. (2009). Stein et al. (2009) did not find associations between low birth weight or preterm birth with PFOA in the Little Hocking area, but the incidence of preeclampsia was moderately associated. They di d find that PFOS was associated with preterm births and low birth weight, as well as preeclampsia. However, 60% of the women included in the PFOS analysis were excluded from the PFOA analysis due to missing data on residency in a water system of interest, even though the analysis method used only serum PFOA or PFOS levels.

Two population-based studies on adult-onset diabetes (i.e., Type 2) are also available, including one by the C8 Science Panel (MacNeil et al., 2009), which was negative. In that study ≥20 years of residence in the contaminated water systems was required for eligibility, which excluded many cases. Furthermore, ascertainment depended initially on self-reporting, which probably excluded a large number of adults who were unaware that they were insulin-resistant. However, the Lin et al. (2009) study of 2003-2004 data

from the CDC National Health and Nutrition Evaluation Survey (NHANES) found an association with PFOA and PFOS and was analyzed with much more biochemical detail relevant to the insulin-resistant form of adult onset diabetes.

A matter is that is not addressed by any study at this point is whether there are effects in adulthood resulting from exposures during development (prenatal or infancy), such as the effects seen in the study by Hines et al. (2009) on metabolic endpoints and White et al. (2008) on mammary gland development in mice.

Specific Comments

Page 4. Public Health Statement, HOW CAN PERFLUOROALKYLS AFFECT MY HEALTH?

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.

This statement falls short of describing the published observations and those from the unpublished reports available through the USEPA docket AR-226 which contains a tremendous amount of published and unpublished information on these chemicals. 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	Little research has been done on the general population to answer the question of whether perfluoroalkyls may be associated with adverse health effects. Ingestion—A single study of people whose drinking water contained perfluoroalkyls did not find problems in a number of clinical measures tested. The study did not, however, examine developmental risks for children or cancer. The 326-person study was too small to address these issues.

At this time there are unpublished data as well as peer-reviewed studies stemming from the C8 Health Study of 67,000 subject in Ohio and West Virginia exposed to drinking water contaminated with $\geq$0.05 ug/L to over 3 ug/L of PFOA. These studies are using data collected on serum perfluoroalkyls, liver enzymes, lipoproteins, hormones, and other blood constituents, as well as self-reported diseases. The lowest decile of serum PFOA, which has a median of 6 ug/L of serum, approximates the 75th percentile level, 5.8 µg/L, found in the 2003-2004 National Health and Nutrition Evaluation Survey (Calafat et al., 2007). The highest levels are in the 100s – 1000s ug/L range. More studies are underway. The size of this effort dwarfs the small studies by Emmett et al. (2006a,b) that were cited in the draft Toxicological Profile.

Two of these studies (Steenland et al., 2009a,b) show an increased percentage of subjects with clinically elevated cholesterol and uric acid, starting with PFOA concentrations just above the lowest category.

Preliminary descriptive statistics from the C8 Health Project suggest that there are other clinical parameters, including serum levels of liver enzymes, hormones and electrolytes that are associated with serum PFOA. The slope of some of these appears to be steepest at the lowest deciles of exposure.

Page 6. Public Health Statement, HOW CAN PERFLUOROALKYLS AFFECT CHILDREN?

The C8 Health Study includes almost 5000 children under 10 years old and approximately 7500 children from 10-18 years old. Preliminary evidence suggests associations of several parameters and serum PFOA levels.

The developmental studies noted in the Statement also found associations with PFOS. For example, 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. 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.

Page 7 Public Health Statement. IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PERFLUOROALKYLS?

In the Detecting Exposure section, elevated perfluoroalkyl serum levels in residents exposed to contaminated drinking water have also been found in Germany (Holzer et al., 2009) and in Minnesota (Minnesota Department of Health, 2009). Also, elevated serum PFOA among workers has also been found at other facilities, so the last sentence in this section should start with, "For example,".

Pages 7-8 Public Health Statement. WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

It should be noted that the USEPA Provisional Health Advisories for PFOA and PFOS are intended to protect for short-term exposure, not chronic exposure.

Pages 11-14 Relevance to Public Health. Summary of Health Effects

This section is densely packed with summary statements. The General Comments (above) and the Specific Comments (below) show some disagreements with those statements. Certainly, the occupational studies, which are the primary source of the statements, have numerous limitations, e.g., use of death certificates, inclusion of few females, and insufficient person-years for less frequent diseases. The DuPont study that was summarized on Page 14 was based on the whole plant and did not include an analysis by exposure, with the exception of one disease category.

Nevertheless, there are concordant findings across a larger body of studies, including new studies and older studies not included in the draft document. The concordant morbidity and/or mortality findings, as noted in General Comments, include diabetes, a combination of cardio- and cerebrovascular end points, bladder cancer and prostate cancer. Blood chemistry results from cross-sectional studies indicate that liver enzymes and lipid chemistry results can be seen as concordant across studies at 3M, DuPont, and Miteni (Italy).

The developmental studies are not concordant, but the ones that had better adjustment for confounding found significant outcome associations with serum PFOA levels.

Pages 21-22 Relevance to Public Health. Minimal Risk Levels. Human Data.

As noted in my General Comments, the draft Toxicological Profile does not present sufficient justification for the decision not to develop a chronic oral MRL based on the animal studies supported by the results of the epidemiology. This was more or less acknowledged in the statement, summarized on Page 25 of the draft,

"Although MRL derivation is not recommended for perfluoroalkyls at this time based on the information [on humans] summarized above, relevant information from animal studies that could have been considered for MRL derivation (i.e., studies with the LOAELs) for perfluoroalkyls with at least a minimal size database is summarized below."

There are similar epidemiological issues for most chemicals for which MRLs have been developed.

By comparing across species by using internal dose and using the relationship between external dose in ug/kg./day and serum concentration (ug/L) discussed by Post et al. (2009a,b) and Tardiff et al. (2009), one can develop a chronic MRL in mg/kg/day from the extensive scientific literature on health effects of PFOA in laboratory animals. 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).The USEPA (2005) draft risk assessment also made comparisons between species (e.g. experimental animals and humans) by serum PFOA level. Through the use of uncertainty factors established by ATSDR, USEPA, and other regulatory agencies, one can address the interests of public health before fully resolving the issues in the epidemiology. However, as noted in these comments, there is sufficient support from the results of epidemiological studies, as discussed in these comments to warrant moving ahead with an MRL.

The comments provided by Dr. Gloria Post elaborate further on this subject.

"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."

Page 35. Inhalation: Death.

Subjects in the Gilliland and Mandel (1993) at the 3-M Cottage Grove APFO plant were assembled from workers with >6 months of employment, which may have excluded short-term highly exposed workers.

3M also conducted a major mortality study of workers at the Cottage Grove plant (Lundin and Alexander, 2007; now published as Lundin et al., 2009). This was in the USEPA docket but was missed.

The cohort was assembled from workers who spent one year or more employed between January, 1943 and December, 1997. Follow-up continued until December, 2002. Jobs were categorized by a panel of "veteran" workers and industrial hygienists (Alexander, 2001) as having had jobs with definite exposure, probable exposure and no exposure to PFOA (in the absence of air data or serum levels). There were 68, 368 and 371 death certificates available for workers with definite exposure, probable exposure and no exposure to PFOA. Only 25 deaths were ascertained for those with > 1 year of working in a job with definite exposure. Exposure-stratified SMRs were calculated by life table analysis using data for Minnesota, and internally compared hazard ratios (HR) were calculated using Cox time-dependent modeling. HRs were adjusted for gender, age at entry to the study, birth year, and wage type (hourly versus salary). In addition, HRs were generated using actual and imputed smoking data, though there was a problem with the degree of missing data.

The SMR for **diabetes** mortality (N = 18) was elevated among workers with probable (2.0, 95% CI 1.2, 3.2) PFOA exposure. In contrast, those never exposed had an SMR of 0.5. The known exposed group had zero deaths from diabetes, but that group was too small and had too little follow-up time to have meaningful numbers. The adjusted HR comparing those with probable exposure to those with no exposure was 3.7 (95% CI 1.4, 10).

Death from hypertension with and without heart disease was somewhat elevated among those with known or probable exposures, SMR = 1.7 (95% CI 0.3, 5) and 1.8 (95% CI 0.4, 5), respectively, stemming from 3 cases in each disease category. The weighted SMR for death from hypertension overall would be 1.75 with an approximate 95% CI of 0.6 to 4 (using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987). Data on all hourly workers includes 5 deaths from heart disease with hypertension and 4 from hypertension only. The respective SMRs are 2.1 and 1.8 and the combined weighted SMR would be 1.95 with an estimated 95% CI of 0.9 – 3.7. This is marginally significant and is consistent with elevated deaths from diabetes and an increase in total cholesterol in most occupational- and community-based studies of PFOA. *No internal HR comparisons were reported for these categories.*

Cerebrovascular disease (CVD) exhibited statistically significant adjusted HRs in the range of 5 to 7, based on 3 deaths among those definitely exposed for ≥6 months, and HRs of approximately 2 among those moderately exposed, based on 19 deaths, depending on whether and which smoking data was included (Lundin and Alexander, 2007). (Adjustment included gender, age at study eligibility, birth year and wage type.) In Lundin and Alexander (2009) the HRs for CVD among workers with high or moderate exposure jobs were 4.6 (95% CI 1.3, 17) adjusted for gender and birth year. The HR of workers with ≥5 years of cumulative time in a job with definite exposure was 2.1 (95% CI 1.0, 4.6) compared with those with <1 year. Stratifying on latency period reduced the HR to 4.4 in the analysis with a 10-year exposure lag. (It is notable that the risk dropped with extended follow-up: the SMR was 1.6 (95% CI 0.5, 3.7) based on 5 deaths among workers with definite exposures, but in an earlier analysis (Alexander, 2001) the SMR was notably higher, 2.6 (95% CI 0.84, 6.0), based on the same 5 deaths, and 3.1 (95% CI 0.89, 8.5) when analyzed by cumulative exposure. In that study workers with ≥5 years of exposure to PFOA had 3 observed deaths from CVD while 0.42 deaths were expected, yielding an SMR of 7.1 with an estimated 95% CI of 1.5 to 21.) This observation would be consistent with decreasing risk after exposure was diminished, e.g., by changing jobs or retirement, but that analysis was not presented.

The SMR for death from prostate cancer among workers with known exposure for any amount of time was 2.1 (95% CI 0.4, 6.1), based on 3 cases, while workers with probable exposure had an SMR of 0.9 and office-based employees had an SMR of 0.5. Workers with at least one year of known exposure had an SMR of 2.7 (95% CI 0.3 – 10), based on 2 cases. The HR for the high exposure group was statistically significant 6.6 (95% CI 1.1, 38), based on 2 deaths, while those in the moderately exposed group exhibited an HR of 3.0 (95% CI 0.9, 9.7), based on 10 deaths. The HR in the combined moderate and high exposure category was 3.2 (95% CI 1.0, 10). The HR of workers with ≥5 years of cumulative time in a job with definite exposure was 3.7 compared with those with <1 year. Adding a 10-year latency period (Lundin and Alexander, 2007)) increased the respective adjusted HRs to 8 (95% CI 1.5, 45) and 3.4 (95% CI 1.1, 11), based on 2 and 8 deaths, respectively. Inclusion of data on smoking had only a small effect on the observed HRs. Since most prostate cancer is a disease from which men usually die of other causes before it becomes fatal, these numbers may represent death from more aggressive forms of the cancer.

Limitations of this study included the reliance on mortality data, the relatively small number of definitely exposed workers and their ascertained deaths, and the exclusion of workers with less than one year of employment. This latter approach may miss very high exposures among short-term workers who have been found in other occupational studies to be used to conduct cleanings of highly contaminated equipment, such as batch reactors. In addition, for the HR analysis those employed for less than 6 months in high exposure job were added to the probable exposure group, which may have removed some employees who should have remained a purely high exposure group analysis. Another limitation was that smoking data, an important risk factor for bladder cancer, was available for only 36% of the cohort, though there was a much greater percentage (65%) from those with definite exposures compared with the unexposed (20%). Among those

with data, workers definitely exposed to PFOA had a higher prevalence of those who ever smoked, 65%, compared to unexposed workers, 47%, but there may be substantial bias due to the minimal data available. Lung cancer was not increased among any exposure group.

Page 36. Inhalation: Death.

The Alexander et al. (2003) study at the 3-M Decatur plant required at least one year of employment to be included in this analysis, which similarly may have excluded short-term highly exposed workers.

Notably, the 1998 biomonitoring at the Decatur POSF plant conducted by Olsen et al. (2003b) showed serum PFOA levels as high as PFOS levels, which indicates that PFOA levels were elevated even before initiation of PFOA manufacture in 1999, and that the epidemiology conducted at that plant is relevant to the discussion. There was little relationship between individual PFOS and PFOA levels.

Deaths from cerebrovascular disease and heart disease were not elevated, but there were too few cases of the former to support any conclusion. Diabetes mortality was not reported.

Page 36 Inhalation: Death.

As noted in the Toxicological Profile, follow-up of bladder cancer occurrence (incidence and mortality) among the 2083 3-M Decatur workers through 2002 was more thorough, using a series of outreach efforts with questionnaires to obtain information (Alexander and Olsen, 2007). A total of 11 bladder cancer cases were ascertained, compared with 3 cases in the earlier effort (see above), though 4 more self-reported cases were not included since they did not consent to validation. Thus, the exposures of those 4 cases were not characterized and the effect of their exclusion was not tested in a sensitivity analysis.

Bladder cancer was elevated for the whole group of participants, 11 observed versus 8.6 expected, SIR = 1.3 (95% CI 0.64, 2.3), though if the 4 excluded cases were also counted, the SIR would be 1.7 (0.98, 2.9; using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987).

Although there are various study limitations, these findings are consistent with the observation of elevated bladder cancer incidence among DuPont workers (Leonard, 2003; see below).

A minor note is that the text in the Toxicological Profile states that this follow-up of bladder cancer at the Decatur plant included "all current, retired, and former employees", as well as information about 188 deceased workers. The writers probably did not intend to confuse the reader by implying that even short-term employees were included in this

analysis. In fact, this is exactly the same cohort as in Alexander et al. (2003), but with more through follow-up that also added 5 additional years.

Epidemiological investigations at the Decatur plant also included a health claims study (Olsen et al., 2004), which is discussed in more detail below (Inhalation: Cancer and Inhalation: Endocrine Effects).

Pages 37-38 Inhalation: Death.

The Leonard (2006) study of mortality at the DuPont Washington Works from 1948 through 2002 has been published (Leonard et al., 2008 and Sakr et al., 2009).

The text in the Toxicological Profile should make clear that all SMRs were based on the entire plant, without additional analyses by exposure or job category. Only the Cox proportional hazards modeling of IHD (Sakr et al., 2009) employed exposure categories and cumulative exposure.

Regarding diabetes, the Toxicological Profile states that the "investigator noted that the lack of agreement with other studies of PFOA workers". This is in sharp contrast to results at the 3-M Cottage Grove plant (Lundin and Alexander, 2007) where the SMR for diabetes mortality (N = 18) was elevated among workers with probable (2.0, 95% CI 1.2, 3.2) PFOA exposure. In contrast, those never exposed had an SMR of 0.5. At the 3-M Decatur plant health claims for diabetes among those with 10+ years of employment in the chemical plant was 30% elevated above expected with marginal significance. Of course, as note above, death certificate ascertainment of and treatment for adult-onset diabetes are likely incomplete.

In addition to the elevated internal SMRs for kidney cancer and diabetes mentioned in the Toxicological Profile, death from hypertension without heart disease was elevated compared to other DuPont workers in the region, though not to statistical significance (SMR = 2.0; 95% CI 0.7, 4.8; based on 5 deaths). The impact on deaths attributed to hypertension and diabetes is consistent with observations at 3-M plants.

Page 46 Inhalation: Cardiovascular Effects. : DuPont Washington Works

In contrast to the statement made in the Toxicological Profile that there is "no convincing evidence of increased mortality due to heart disease in general or IHD specifically" in Leonard et al. (2006, now published as Leonard et al. (2008) and Sakr et al. (2009)), death from all heart disease (N = 314) was elevated with marginal statistical significance: the internally-based SMR for all heart disease was 1.10 (95% CI 0.98, 1.23) and the internally-based SMR for IHD (N = 239) was (1.09, 95% CI 0.96, 1.24). In heart disease studies even small elevations are regarded as important because of the frequency of occurrence. The SMRs for females were higher, but based only upon a handful of deaths. In addition, death from hypertension without heart disease was elevated compared to other DuPont workers in the region, though not to statistical significance (SMR = 2.0; 95% CI 0.7, 4.8; based on 5 deaths).

Only IHD was examined by exposure category and was found to be 40-60% elevated with marginal statistical significance among those in the third and fourth quartiles of serum PFOA. Sakr et al. (2009) concluded that there was "no convincing evidence" to link PFOA exposure to IHD mortality, but there was a general trend and the inability to adjust for known confounders could easily obscure an actual association.

The Toxicological Profile did not include Lundin and Alexander (2007, published in 2009), which is described below. Discussion of this study should be added. It provided strong evidence of an association between job exposure to PFOA and cerebrovascular disease as well as the suggestion that deaths attributable to hypertension were also associated with job exposure.

In addition, in Leonard (2003, see "new" studies, below) the SMR for acute myocardial infarction was 1.4 (95% CI 1.2, 1.6), based on 126 cases and the SMR for atherosclerosis and aneurysm was 2.0 (95% CI 1.2, 3.1), based on 18 cases, respectively from the 1957-2000 period. There was no analysis by exposure measures (job, serum PFOA, or duration) or personal lifestyle, BMI or SES.

Page 47 Inhalation: Hepatic Effects.

The study at the 3M Cottage Grove conducted by Gilliland and Mandel (1996) was small, as noted, composed of all directly exposed workers employed between 1985 and 1989 (N=50) and 65 randomly picked "low" exposure workers (without direct exposure for at least 5 years) workers. Total serum organic fluorine, representing all polyfluorinated chemicals, was used as a surrogate for PFOA exposure. Having "low" exposure workers was meant to provide a range of exposures, but this group had high total serum fluorine levels as well.

Page 48 Inhalation: Hepatic Effects.

This longitudinal study (Olsen et al., 1999) of blood sampling at the 3-M plants in Decatur and Antwerp in 1995 and 1997 was small and depended on volunteers. Missing from the description of the study in the draft Toxicological Profile are observations that are consistent with those in other studies. Total cholesterol exhibited a marginal statistically significant increase with serum PFOS in the 1997 sampling at each locations. Alkaline phosphatase displayed a non-significant trend of increase with serum PFOS in both 1995 and 1997 with combined data from both plants, while GGT showed a similar trend of increase in the 1997 data. Those with the highest serum PFOS exhibited a notably higher mean and median AST (33 IU/L) than the lowest category (25 IU/L) in the 1995 testing, while median ALT was notably elevated in the highest serum PFOS category (49 and 45 IU/L) versus the lowest PFOS category (43 and 30 IU/L) during both years. Unfortunately, there were no statistical tests to compare PFOS categories with the lowest category. As noted in the draft, there were only a handful of volunteers in the highest category.

Page 48 Inhalation: Hepatic Effects.

In addition to what is noted in the draft Toxicological Profile, multivariate analysis of combined data from all 3M plants showed statistically significant associations between PFOA and increased ALT and GGT (Olsen and Zobel, 2007). Analysis of the separate plants found a significant association of PFOA with increased AP, ALT, GGT, and marginally significantly increased cholesterol and TG among the workers at the Decatur plant. Serum AST was associated with PFOA among workers at the Cottage Grove plant. Exceedances of clinical reference range at the combined group of workers were greater in the 7th, 8th and 9th PFOA deciles for ALT and TG and the 9th and 10th PFOA deciles for GGT.

Page 49 Inhalation: Hepatic Effects.

In addition to what is noted in the draft Toxicological Profile about the Sakr et al. (2007a) study at the DuPont Washington Works, slopes for TG, LDL and ALT were positive. Statistical significance may have been difficult to achieve for ALT and GGT since there were only 233 tests available for analysis. Because of differences in longitudinal participation and because there were more than one test per individual, some individuals carried greater weight in the analyses.

Page 49 Inhalation: Hepatic Effects.

In the subset of the Sakr et al. (2007b) study in which persons using lipid/cholesterol control agents were excluded, serum PFOA was statistically significantly associated with elevated serum AST and ALT, in addition to elevated GGT noted by the draft Toxicological Profile. Age and family history were not statistically significant covariates for any measured serum liver enzyme or bilirubin and alcohol use was not significant for bilirubin. The models where PFOA was statistically significant explained 14 - 29% of the variance. This is important because it demonstrates that there was a greater association of liver chemistry endpoints with PFOA after obvious confounding was removed without over-adjusting.

Page 49 Inhalation: Hepatic Effects.

The Costa et al. (2004) study of the Miteni plant (Italy) has been published with updates (Costa et al., 2009). Testing in the 2000-2007 timeframe showed an association between PFOA and AST, ALT and GGT.

Pages 51 and 54 Inhalation: Endocrine Effects and Reproductive Effects.

The Toxicological Profile correctly notes that among male workers, estradiol and testosterone were elevated with higher serum PFOA in both the 3M (Olsen et al., 1998) and the DuPont (Sakr et al., 2007b) cross-sectional studies. (Unfortunately, the DuPont study did not give the units or further elaborate, so it is difficult to further interpret those findings.) However, the statement, "Taken together, the results showed no significant hormonal changes at the levels of PFOA measured [in the 3M study].", does not fit with

the acknowledgement of similar findings at DuPont. The statement refers to the small number of workers in the high exposure groups and confounding by BMI, but the commonality of findings should be the focus of attention.

Unfortunately, hourly changes in the release of many hormones and the pulsatile nature of that release means that multiple samples should be taken and that time of day and, for occupational studies, shift, should be included in the analyses. In these studies there was only one sample.

Page 51 Inhalation: Renal Effects.

While it is not clear whether renal function was affected, certain serum metals, calcium, iron, magnesium, potassium, and sodium had higher serum levels with increasing serum PFOA among workers at the DuPont Washington Works (Sakr et al., 2007a). This is consistent with univariate results from the C8 Health Project.

Page 52 Inhalation: Endocrine Effects.

It should be noted that there is only one occupational study of thyroid hormones. In addition, iodine sufficiency (urinary iodide) should also be measured in any study of potential thyroidal impact.

The health claims study at the 3M Decatur plant (Olsen et al., 2004) found that claims for diabetes was marginally elevated (RR = 1.3, 95% CI 0.9, 2.0), based on 42 cases among those who worked $\geq$10 years in the chemical plant.

Page 54 Inhalation: Developmental Effects.

The Grice et al. (2007) study of the 3M Decatur plant should be dropped from consideration for developmental effects because gestational age, the single most important determinant of birth weight, was not available for inclusion in the analysis.

Page 55 Inhalation: Cancer.

Again, the study at the DuPont Washington Works (Leonard, 2006, Leonard et al., 2008) had no analyses based on exposure, except for the analysis of IHD (Sakr et al., 2009).

The DuPont Cancer Registry surveillance report from Leonard (2003) indicated that bladder and kidney cancer incidence among male employees was elevated during the 1959-2001 period. The Registry relies on data from active employees and SIRs were calculated based on internal comparison (5-year time and age categories) with company-wide incidence rates. The respective SIRs for bladder and kidney cancer were 1.9 (95% CI 1.2, 3.1) and 2.3 (95% CI 1.4, 3.6), based on 18 cases each. They point out that the incidence of both types of cancer was higher in West Virginia than in the U.S. or in neighboring Ohio. However, elevated bladder cancer is consistent with the analysis of mortality among workers at the 3M Decatur facility (Alexander et al., 2003; see above).

In addition, myeloid leukemia incidence was marginally significantly elevated, SIR = 2.0 (95% CI 0.86, 4.0), based on 6 cases, and multiple myeloma incidence had an SIR of 1.7 (95% CI 0.69, 3.6), based on 7 cases. Including 2 cases (0.14 expected) among females attributed to combined multiple myeloma and immunoproliferative neoplasms, resulted in an SIR of 2.1 for the entire group with an estimated 95% CI of 1.0 – 4.1 (using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987). There was no analysis by exposure, duration or personal lifestyle (e.g., tobacco and alcohol use), BMI or SES.

Leonard (2003) also reported on internally-based SMRs among males from the DuPont Mortality Registry from 1959 through 2000. In general there were too few female employees and too few deaths, with one exception, noted below. Death from bladder (N = 7) and kidney (N = 8) cancer had SMRs of 1.6 (95% CI 0.64, 3.3) and 1.5 (95% CI 0.68, 3.0), respectively, which is consistent with the incidence results. Similarly, death from myeloid leukemia (N = 6) and combined multiple myeloma and immunoproliferative neoplasms (N = 5) had SMRs of 1.7 (95% CI 0.62, 3.7) and 1.4 (95% CI 0.46, 3.4), respectively. Including 2 deaths (0.11 expected) among females attributed to combined multiple myeloma and immunoproliferative neoplasms, resulted in an SMR of 2.0. Death from non-cancer blood and blood-forming diseases had an SMR of 3.0 (95% CI 0.95, 6.9).

The SMR for diabetes deaths (N = 12) was 1.6 (95% CI 0.81, 2.75). The SMR for acute myocardial infarction was 1.4 (95% CI 1.2, 1.6), based on 126 cases and the SMR for atherosclerosis and aneurysm was 2.0 (95% CI 1.2, 3.1), based on 18 cases, respectively. There was no analysis by exposure measures (job, serum PFOA, or duration) or personal lifestyle, BMI or SES.

In addition, there was an elevated incidence of carcinoid tumor at the Washington Works (Morel-Symons et al., 2007).

Epidemiological investigations at the 3M Decatur plant also included a health claims study. Analysis of 1993-1998 health claims compared workers at the POSF ("chemical") plant with workers at the film plant (Olsen et al., 2004). (This time frame is prior to the start of PFOA production, but biomonitoring in 1998 (Olsen et al., 2003b) showed serum PFOA levels as high as PFOS levels.) There were 652 and 659 workers, respectively, included in the analysis, including 211 and 345 workers employed for $\geq$10 years before 1993. Some workers had worked in both plants, but were not analyzed separately, which might mask associations. The expected number was based on "a normative database, which consisted of the remainder of the 3M manufacturing population" in the U.S. (approximately 20,000 workers) and calculated with an "employee health claim grouper (EHCG) software used by the Ingenix Employer Group.

It found that among male workers (N = 530) there were 5 prostate cancer "episodes of care" (involving 5 unique individuals) versus an age-adjusted expected number of 3.1, an RR = 1.6. (In this instance that means 5 unique cases.) A relative comparison with male workers at the neighboring "film" facility, which did not have direct exposure to POSF,

yielded an RR of 7.7 (95% CI 0.9, >100). Among long-term workers, the RRs were increased: RR = 2.7 (based on 4 unique cases) and employment in the chemical versus the film plant, RR = 8.2 (95% CI 0.8, >100). In addition, there were 59 episodes of care for enlarged prostate (involving 53 unique individuals) versus an expected 40.6, an RR = 1.5. Likewise, the number of acute prostatitis episodes was increased, 73 versus 39.2 expected based on 55 unique individuals. However, these latter two conditions were also elevated among male workers at the neighboring "film" facility. Therefore, it is possible that the workplace population in that location was more prone to prostate ailments. An important limitation is that the analysis was not adjusted for possible confounders, including smoking.

Gastrointestinal tract problems that were increased among long-term chemical plant versus film plant workers included malignant and benign colon cancer. There were 3 unique malignant cases (versus an expected 0.8) in the chemical plant compared to zero cases (versus an expected 1.6) in the film plant. Among long-term workers, the RR for benign colon cancer in the chemical plant was 2.4, based on 20 unique individuals, while it was approximately 1.0 in the film plant, based on 18 unique individuals. The internal comparison RR was 2.4 (95% CI 1.3, 4.5).

Page 116 Oral: Hepatic Effects.

The low participation, 30-50% in the randomly selected portion of the Emmett et al. (2006) study subjects (N = 343 in 161 households) and the additional group of subjects (N = 54 in 35 households) who were volunteers selected by lottery potentially allows for significant selection bias.

The median serum PFOA concentration, 354 ng/mL, was much higher in this study than in the C8 Health Project (28 ng/mL, see below). (Eighteen subjects were occupationally exposed and probably accounted for the top 5% of the serum PFOA levels.)

Despite those negative findings of the small Emmett study, descriptive statistics from the large, high participation C8 Health Project (2009) showed that serum levels of the liver enzymes, AST and ALT, are elevated with increasing serum PFOA levels in the C8 Health Project, while in the Emmett et al. study the slope estimates are negative. However, in the Emmett study the AST and ALT levels over the serum PFOA interquartile range (25%-ile - 75%-ile, 184 – 571 ng/mL) are 18 and 27 IU/L and 15 and 27 IU/L, respectively. In addition, serum levels of the liver enzyme, GGT, over the interquartile range of serum PFOA were 14 and 27 IU/L. Similarly, the interquartile range for total cholesterol was 172 and 220 mg/dL. These results were univariate (i.e., not adjusted by age, gender or medications).

Recently, analysis of total cholesterol by the C8 Science Panel (Steenland et al., 2009a) showed that the OR for cholesterol levels being above the clinical reference range (>240 mg/dL) in adults in the C8 Health Project were 1.2, 1.3 and 1.4 for the second, third and fourth quartiles, respectively, of serum PFOA versus the first quartile. All ORs were statistically significant. Similar results were seen for PFOS. In addition, extensive regression analyses showed statistically significant associations of both PFOA and PFOS

with total cholesterol, LDL cholesterol, total non-HDL cholesterol, triglycerides and the total cholesterol/HDL cholesterol ratio. Analysis only of subjects taking lipid control medications results in similar, though muted, associations with PFOA, but there was "no consistent trend" for PFOS. All analyses were adjusted for age, gender, BMI, education, exercise level and current alcohol consumption.

Also recently, Steenland et al. (2009b) found that uric acid was associated in a dose-response manner with increasing deciles of both PFOA and PFOS. Elevated uric acid has been linked to hypertension, and with less evidence to stroke, diabetes and metabolic disease. They also showed a dose response by quartile categories set up within the ≤20 ug/L subgroup, i.e., the response is present within the range of general population exposure.

These results have also been found in children (C8 Science Panel, 2009b).

One question that arises is whether the relationships that seem obvious in the much larger C8 Health Project, a clear dose-response, are not observed in the Emmett et al. study because the effects (e.g., total serum cholesterol) occurred within the lower exposure ranges and plateaued at higher serum PFOA concentrations. This is especially significant because the associations exhibited no threshold down to the lowest deciles of exposure (see figure in Steenland paper), 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).

Page 124 Oral: Renal Effects

While it is not clear whether renal function was affected even though creatinine levels were not changed (Steenland et al., 2009b), certain serum electrolytes, calcium, iron, magnesium, sodium among adults, and potassium among women, had higher serum levels with increasing serum PFOA in the preliminary descriptive statistics (C8 Health Project, 2009). This finding is consistent with that observed by Sakr et al. (2007a) at the DuPont Washington Works. No other study reported on that, though the data was probably collected.

Page 125 Oral: Endocrine Effects.

Regarding the overall negative findings in the Emmett et al. (2006) study, the low participation, 30-50% in the randomly selected portion of the study subjects (N = 343 in 161 households) and the additional group of subjects (N = 54 in 35 households) who were volunteers selected by lottery potentially allows for significant selection bias.

Regarding the lack of effect on thyroid hormones, iodine sufficiency (urinary iodide) should also be measured in any study of potential thyroidal impact. In addition, the pulsatile nature of protein or peptide hormone release means that multiple blood sample should be taken for greater accuracy.

Recently, Lin et al. (2009) examined a subpopulation of NHANES participants at least 12 years old (N = 3,685) tested for perfluoroalkyl chemicals. This study had a great amount of biochemical, health behavior and body measurement data available for inclusion in the analysis, as well as diabetes diagnostic methods. However, NHANES is a cross-sectional study and it cannot be easily determined whether the diabetes symptoms preceded the exposure or the reverse.

Serum PFOA was significantly associated with pancreatic beta-cell function (all three step-wise statistical models), and with blood insulin measurement (in the fully saturated model). Covariates included age, gender, BMI, family history of diabetes, and use of relevant medicines. PFOS was associated with both measures and with the calculated measure, homeostasis model assessment – insulin resistance (HOMA-IR). Since the authors chose to show probabilities only for statistically significant associations, there may be more diabetes diagnostic indicators that have marginal statistical significance.

Also recently, MacNeil et al. (2009) reported on the incidence of self-reported adult-onset diabetes (diabetes 2) that had been validated by medical record check and its relationship to serum PFOA in the C8 Study population. The data was analyzed as a case-control study, and controls were non-cases among the eligible population. The study population was restricted to a subset with at least a 20-year residency in the area prior to diagnosis, though the entire group (without restrictions) was also examined. No association was found in any decile of serum PFOA. Fasting blood glucose levels were also not associated with serum PFOA, though properly treated individuals would be less likely to show elevated glucose levels.

There are several limitations. Cases were lost because of missing residency data even though the serum PFOA and PFOS were used in the analysis. This could have introduced an ascertainment bias. In addition, since the study group is based on self-reporting before medical record validation, that may exclude many who are unaware of their adult-onset diabetes, since there is evidence that insulin-resistance is significantly under-diagnosed in the general population, depending on access to health care (U.S. Preventive Services Task Force, 2008). The proportion of unidentified cases was estimated to be 30-50% of the total number of cases. Another concern, which the authors also noted, is that the covariates they used in their analysis "may be intermediates on the pathway from exposure to disease, and therefore arguably should not be controlled in the analysis". Lastly, the authors also noted that since the study was cross-sectional in nature (even though they used a case-control type of analysis), it cannot be used for causality, i.e., one can't determine whether "exposure preceded disease".

In the crude descriptive data for estradiol, testosterone and prolactin (C8 Health Project, 2009), there appear to be notable changes with serum PFOA, especially in the tables and figures divided by age and gender.

Page 131 Oral: Immunological and Lymphoreticular Effects.

The C8 Health Project (2009a) descriptive statistics and the C8 Science Panel (2009) Status Report on immunological effects showed increased levels of anti-nuclear

antibodies (suggestive of autoimmune disease) as well as occurrence of self-reported scleroderma and Sjögren's syndrome (autoimmune diseases) in women with higher serum PFOA.

In addition, it is interesting that C-reactive protein levels are notably decreased with increasing PFOA. The change in CRP is of large magnitude and indicates that PFOA at these levels is having a biological effect consistent with known effects of PPAR alpha activators, such as the fibrates, in humans.

Serum levels of immunoglobulins A and E also showed a steady, though small, decrease with increasing serum PFOA.

Page 135 Oral: Reproductive Effects.

The C8 Health Project (2009) descriptive statistics showed notable effects on estradiol and prolactin levels in females with higher serum PFOA. In both girls and women estradiol was lower with higher PFOA, while lower prolactin was associated with higher serum PFOA in females over the 16 years old.

The new study by Fei et al., (2009) showed a longer time to conception with increasing maternal serum PFOA and PFOS in the general population. Women in each of the three highest quartiles of each chemical exhibited approximately one-third greater risk of having a time-to-pregnancy >12 months than those in the respective lowest quartile.

The new study by Joensen et al. (2009) showed an association between serum PFOA and spermatozoa quality and number in young Danish men.

Page 141 Oral: Developmental Effects.

In the Washino et al. (2009) study maternal serum PFOS was statistically significantly associated with birth weight of females, but not males. Maternal PFOA was not associated with birth weight. However, adjustment only for gestational age, the most significant confounder, resulted in a statistically significant slope coefficient for PFOA versus birth weight of all infants and of female infants and a marginally significant slope coefficient for PFOA versus head circumference among males. One potential major limitation of this study was the low participation rate, 29%, which could have resulted in selection bias. In addition, maternal age, parity and BMI, included as covariates in the fully adjusted models, were also related to serum PFOA level (i.e., they are probably intermediate variables). This could have reduced the regression coefficients in the fully adjusted models. Lastly, the relatively low levels of PFOA in serum in this study may have limited the accuracy of the exposure assessment, given the detection limit of 0.5 ug/L (7% of women had no detectable PFOA).

The new study by Monroy et al. (2008) was a small hospital-based prospective study (N = 101) that was part of a larger Family Study cohort recruited during 2004-2005 in Hamilton, Ontario. A significant limitation of this study was the very low (10%) recruitment rate, which could allow substantial selection bias. No association was found

between PFOA or PFOS and birth weight, but no detail was reported on the regression analysis to find out whether there was a trend that would have been statistically significant in a larger study.

Page 142 Oral: Developmental Effects.

In addition to the extensive limitations of the Nolan et al. (2009) study discussed in the Toxicological Profile, including the lack of any individual-based data on exposure or key confounders known to influence birth weight and gestational age (e.g., parity, smoking status, nutrition, and socioeconomic status), one should also include potential misclassification of residential history related to moving to a residence more appropriate to a larger family prior to the birth, but with a different PFOA exposure level). This is more important for this study since serum PFOA data was not available for incorporation into the analysis.

The C8 Science Panel (Stein et al., 2009) reported results of a case-control study on the outcome of pregnancies during the 5 years before enrollment (August, 2005 through July, 2006) among women whose residence during their live or stillborn singleton pregnancy was completely in one of the water districts targeted by the C8 Health Project or whose residence during the 90 days before their miscarriage was in one of the targeted water districts. In addition, there was a separate analysis of serum PFOS that was not focused on water districts, which looked at all pregnancies regardless of drinking water source. There were 5262 singleton pregnancies in women whose serum was analyzed for PFCs among 3996 unique women. The water system-based PFOA study excluded 3290 pregnancies mostly due to missing data on water district, for a total of 1972. That analysis centered on white women with no history of pre-pregnancy diabetes for whom there was a complete set of data, 1845 pregnancies. The PFOS analysis included all 5262 pregnancies.

Preeclampsia, a potentially dangerous syndrome that can occur late in pregnancy, was marginally associated with serum PFOA above the median (adjusted OR = 1.3, 95% CI 0.9, 1.9), compared to those below the median, but the risk was lower above the 75th percentile. Miscarriage, low birth weight (LBW, < 5.5 pounds) and preterm birth (≥3 weeks early) were not associated. Neither birth weight nor gestational age at birth was analyzed as a continuous variable. Serum PFOS level above the 90th percentile was associated with preterm birth. The 75th – 90th and the 90th percentile of PFOS were associated with a higher risk of LBW in comparison to PFOS less than the median. Preeclampsia was also associated with PFOS, both above versus below the median and above the 90th percentile versus below the median. Birth defects were not associated with PFOS.

Important limitations are 1) the quality of the self-reported information, especially since birth records had not been accessed for this study, 2) the PFOA study design that excluded approximately 60% of pregnancies mostly because of incomplete data on residency in water system of concern during pregnancy even though the analysis was based on the serum PFOA level, and 3) lack of data on maternal BMI and infant gender.

The study did not conduct a sensitivity analysis by examining the full group, i.e, the same set of subjects analyzed for PFOS. The investigators are developing exposure reconstruction models, which will allow inclusion of greater numbers of pregnancies

Page 148 Oral: Cancer.

As noted above, the occupational exposures were thought to be primarily from inhalation. However, this has not been studied and at least one author has suggested that oral exposure may have accounted for a significant amount of the absorbed perfluoroalkyl chemicals.

Cancer incidence was prospectively studied in a subset of a cohort (N = 57,000) assembled from 50-65 year olds in the Danish general population during December, 1993, through May, 1997 (Eriksen et al., 2009). Cancer cases (713 prostate, 332 bladder, 128 pancreas and 67 liver) that occurred in this cohort were ascertained from the Danish Cancer Registry and the Danish Pathology Data Bank after a median 7 years of follow-up ending at the start of July, 2006. Those cases (N = 1111 males and 129 females) and a random sample (N = 680 males and 92 females) of those not diagnosed with cancer were tested for serum PFOA and PFOS.

PFOA and PFOS were high correlated (R = 0.70), and median levels were 6.9 and 35 ug/L, respectively, among control males, and 5.4 and 29 ug/L, respectively, among control females. Females with cancer had slightly higher PFOA, 6.0 ug/L.

Only pancreatic cancer exhibited a notably increased, but not statistically significant, RR = 1.6 among those in the fourth quartile of PFOA. Bladder and liver cancer cases had a reduced incidence with higher PFOA, while prostate cancer incidence was slightly elevated. However, PFOS was marginally associated with increased prostate cancer in the 2nd, 3rd and 4th quartiles. The RR for the 4th quartile was 1.4 (95% CI 0.99, 1.9).

Page 190 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models. Risk Assessment.

Extrapolations based on serum levels, as discussed by Post et al. (2009) and Tardiff et al. (2009) avoids the limitations of extrapolating between pharmacokinetic models for different species.

Page 198 Animal-to-Human Extrapolations.

The text states that "**No significant health conditions** have been associated with the serum levels of perfluoroalkyls..." and "Health evaluations of perfluoroalkyl workers ... or of people undergoing high environmental exposure ... have **not provided evidence of adverse effects**". The summary of human health and serum chemistry results should reflect the concordances noted in these Comments. The weight of evidence is not that clear cut.

In addition, there is little rationale for the statement,

"Thus, the lack of reported health effects at the reported body burdens precludes identifying the animal model that would be most appropriate for human risk assessment based on similar toxic effects.".

The epidemiology has numerous limitations, as discussed in this document; however, as also noted here, the health effects reported in the epidemiological literature are more concordant, given those limitations, than the opinion expressed in the Toxicologic Profile. ATSDR should not use that rationale to avoid development of Maximum Risk Levels (MRLs).

In addition, as noted in the comments by Dr. Post, the public health logic of this sentence is unclear:

"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."

Page 198-200 Toxicities Mediated through the Neuroendocrine Axis.

The Toxicological Profile correctly notes that among male workers, estradiol and testosterone were elevated with higher serum PFOA in both the 3M and the DuPont cross-sectional studies. (Unfortunately, the DuPont study (Sakr et al., 2007a) did not give the units or further elaborate, so it is difficult to further interpret those findings.)

It is interesting that the C8 Health Project findings suggest that estradiol decreased among females with increasing serum PFOA.

Page 203 Children's Susceptibility.

The ongoing C8 Health Study will also provide information on associations of many endpoints with PFOA exposure in children. Notably, children exposed to PFOA in drinking water had higher serum PFOA levels than adults (Emmett et al., 2006, Steenland et al., 2009c). This could be due to greater water consumption per kilogram body and/or differences in the toxicokinetics.

Page 207 Biomarkers Used to Characterize Effects Caused by Perfluoroalkyls.

The following sentence should be deleted, based on the comments provided here:

"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)."

Page 207 Populations that are Unusually Susceptible.

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.

Page 212 Existing Information of Health Effects of Perfluoroalkyls.

A variety of C8 Science Panel studies have recently been published in peer-reviewed publications and more are expected. As well, studies based on the NHANES are being published. It can no longer be said that there are "limited" data on environmental exposures.

Page 213 Identification of Data Needs.

There is currently sufficient information with a "sufficient degree of certainty" to develop a chronic oral MRL for PFOA. This is also addressed in the comments on the Minimal Risk Levels portion of the Relevance to Public Health section.

***Page 214 Chronic-Duration* Exposure and Cancer.**

I disagree with the statement that "for the most part, no significant adverse effects have been identified", as outlined in the General Comments here and in the Specific Comments. This section should also discuss the DuPont incidence study (Leonard, 2003) the recent occupational 3M mortality study of Lundin et al. (2009), the blood chemistry study of Miteni workers in Italy, as well studies of chronic exposure in the community (Lin et al., 2009; MacNeil et al., 2009; Steenland et al., 2009a,b). There is more concordance among the studies than discordance.

Page 216 Reproductive Toxicity.

Both the study on spermatozoa quality and number (Joensen et al., 2009) and the study by Fei et al. (2009) on increased time to pregnancy found associations with PFOA and PFOS.

Page 218 Developmental Toxicity.

In addition to the extensive limitations of the Nolan et al. (2009) study discussed in the Toxicological Profile, including the lack of any individual-based data on exposure or key confounders known to influence birth weight and gestational age (e.g., parity, smoking status, nutrition, and socioeconomic status), one should also include potential misclassification of residential history related to moving to a residence more appropriate to a larger family prior to the birth, but with a different PFOA exposure level). This is

more important for this study since serum PFOA data was not available for incorporation into the analysis.

In the Washino et al. (2009) study adjustment only for gestational age, the most significant confounder, resulted in a statistically significant slope coefficient for PFOA versus birth weight and a marginally significant slope coefficient versus head circumference among males. A major limitation of this study was the low participation rate, 29%, which could have resulted in selection bias. In addition, maternal age, parity and BMI, included as covariates in the fully adjusted models, were also related to serum PFOA level (i.e., they are intermediate variables). This could have reduced the regression coefficients in the fully adjusted models.

The C8 Science Panel study of low birth weight, preterm birth, birth defects, miscarriage and preeclampsia of pregnancy by Stein et al. (2009) observed associations between PFOS and low birth weight, preterm birth and preeclampsia and marginally between PFOA and preeclampsia. However, neither birth weight nor gestational age at birth was analyzed as a continuous variable. Important limitations are 1) the quality of the self-reported information, especially since birth records had not been accessed for this study, 2) the PFOA study design that excluded approximately 60% of pregnancies mostly because of incomplete data on residency in water system of concern during pregnancy even though the analysis was based on the serum PFOA level, and 3) lack of data on maternal BMI and infant gender. The study did not conduct a sensitivity analysis by examining the full group, i.e, the same set of subjects analyzed for PFOS. The investigators are developing exposure reconstruction models, which will allow inclusion of greater numbers of pregnancies

Page 219 *Immunotoxicity*.

The C8 Health Project (2009) descriptive statistics and the C8 Science Panel (2009) Status Report on immunological effects showed increased levels of anti-nuclear antibodies (suggestive of autoimmune disease) as well as occurrence of self-reported scleroderma and Sjögren's syndrome (autoimmune diseases) in women with higher serum PFOA.

Page 220 Epidemiological and Human Dosimetry Studies.

I disagree with the statement that "No significant health conditions have been associated with the serum levels of perfluoroalkyls measured in these studies,..", as outlined in the General Comments here and in the Specific Comments. My disagreement stems from a critical review of old and new studies.

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