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October 31, 2009

Submitted Via E-Mail

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

Re: Draft Toxicological Profile for Perfluoroalkyls

Dear Sir/Madam:

3M is responding to the Agency for Toxic Substances and Disease Registry's draft Toxicological Profile for perfluoroalkyls. We very much appreciate the amount of effort and in general the grasp of the literature reflected in the draft document. We also appreciate the opportunity to comment on ATSDR's draft Toxicological Profile.

3M agrees with ATSDR that it is important to characterize the literature on perfluoroalkyls. We believe the draft Toxicological Profile will support and inform public health activities by ATSDR and other agencies, and we support the agency's efforts.

We appreciate that ATSDR points out in the first paragraph of text in the Foreword that perfluoroalkyls are not found on the ATSDR list of Priority Hazardous Substances. Indeed, perfluoroalkyls are not classified as "hazardous substances" under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), section 101(14), 42 U.S.C. §9601(14). However, it would be useful for ATSDR to point out in the draft Toxicological Profile itself that the agency has legal authority to address substances in addition to CERCLA hazardous substances, for example, under CERCLA Sections 104(i)(1)(B) and 104(i)(4). Lest there be any confusion, we would encourage you to be clear in stating that no perfluoroalkyl compound, including PFOS and PFOA, has been listed or declared as "hazardous substances" under CERCLA or any other U.S. law. The draft Toxicological Profile should note this fact on pages v and vi, where the agency lists its authority as deriving from CERCLA. It would also be beneficial to restate this fact on pages 303 and 313, where the draft profile states that CERCLA directs the Administrator of ATSDR to assess whether adequate information on the health effects of perfluoroalkyls is available.

In the attached comments from 3M's Medical Department, we provide detailed scientific input. We have also provided a list of key literature that needs to be addressed in the Toxicological Profile.

We hope the comments are helpful in improving the scientific accuracy of the draft Toxicological Profile. 3M would be pleased to provide any additional information that would be helpful to the Department, or to provide copies of any references not readily available to you.

Please do not hesitate to call me at 651-733-6374 if you have any questions or would like any additional information.

Sincerely yours,

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# COMMENTS OF 3M COMPANY ON ATSDR'S DRAFT TOXICOLOGICAL PROFILE ON PERFLUOROALKYLS

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3M Company appreciates the opportunity to comment on ATSDR's draft Toxicological Profile.

In these comments, 3M attempts to point out additional information that ATSDR may wish to consider. As authors or sponsor of many of the studies discussed in the draft documents, we would be pleased to answer any questions or to provide any additional information that would be helpful.

We initially wish to note that we agree with ATSDR's conclusion at page 207, which states, "it is difficult to envision a health condition that could be attributed solely to exposure to perfluoroalkyls." In fact, it is difficult to envision that any health condition could be attributed to perfluoroalkyls at all, given the well-characterized exposure levels in the general population and exposed communities, the decades of medical surveillance of highly-exposed perfluoroalkyl production workers, the mortality studies in multiple cohorts, and other studies of potential health effects in workers and the general population -- all without any indication that perfluoroalkyls have ever caused any health effect in humans. There is also a robust toxicological database, which has clearly shown the range of serum levels at which various endpoints seen in laboratory animals begin to occur. The ability to compare biomonitoring data for workers versus general population or exposed populations, and for humans versus laboratory animals, and current understanding of pharmacokinetics and mode of action, lend additional confidence in reaching the conclusion set forth by ATSDR. This is a critical point, and one we think should be repeated and emphasized throughout the draft profile.

Our comments below are directed to specific pages, but we have attempted to group them into some general topics, as many of the issues occur in multiple places throughout the document. As a general proposition, we first address topics related to human evidence, and then those related to the toxicology studies.

We also want to emphasize that ATSDR's statements in chapters 1 and 2 should be amended once the issues raised with respect to chapter 3 are addressed. For instance, in chapter 1, section 1.5 "How Can Perfluoroalkyls Affect My Health?", the document says, "The information available does not prove that perfluoroalkyls cause cancer in humans but the evidence is not conclusive. Some increases in prostate and bladder cancer have been seen, but the cause is not certain." As explained in more detail below, this sentence presents an overly simplistic attempt to summarize the data available. An increase in prostate cancer has not been demonstrated; rather, the results have been inconsistent due to a striking deficit of prostate cancer in the lowest exposed group in 3M's Cottage Grove study. Likewise, the occupational studies show inconsistent results with respect to bladder cancer: Importantly, a recent general population study (Eriksen et al. 2009) showed no association between PFOS or PFOA blood concentrations and prostate or bladder cancer. There is also no toxicological evidence for either cancer.

As further examples of necessary chapter 1 amendments, the second sentence in the first row of the table under section 1.6 (Effects in Children) should read, "However, several other studies that have looked at exposure to PFOA in drinking water and with individuals with higher PFOA concentrations have not found such associations." And, under Section 1.8 (Is there a Medical Test to Determine Whether

I Have Been Exposed to Perfluoroalkys), the second bullet regarding measuring perfluoroalkyls in the U.S. populations should state, "Serum concentrations of PFOS and PFOA have declined in the general population since 2000 by approximately 60 and 25 percent, respectively."

Again, we note that ATSDR, its staff and contractors are to be commended for this monumental task, and we offer these very detailed comments in the spirit of assisting with that effort.

## A. Key Literature Omitted from Draft

We appreciate the fact there inevitably must be a cut-off date for inclusion of literature in order for the drafters to complete the profile. There is a wealth of new data available, as well as several studies published in 2008 and 2009, which are not included in the draft. It is vitally important to include the most recent literature, given the pace at which the scientific community is exploring these compounds. This also speaks to the fact that this document will be 'out-of-date' with the most recent literature even before it is finalized for release to the public.

Pages 224-26 list several on-going studies at the time of writing the draft profile. Some of these studies, and many others, are now published in the literature. We attach to this letter a list of studies not included in the profile's references. (See Appendix A.)

3M respectfully urges ATSDR to determine the frequency with which it intends to update this profile, as it is in the public's best interest to have the most current information available when reviewing such a comprehensive compilation of the scientific literature.

## B. Perfluoroalkyl Substances Covered and Nomenclature

As stated on page 1, the Agency's draft profile covers 13 molecules: PFOS, PFOA, PFDoA, PFDeA, PFBA, PFHpA, PFNA, PFUA, PFHxS, PFBuS, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH. On page 2, the profile defines "perfluoroalkyls" as "stable chemicals made of a carbon chain surrounded by fluorine atoms and an acid or amide group located at the end of the carbon chain." This definition may be different from how chemists may define the term "perfluoroalkyls." (Technically speaking, the last two compounds are not "perfluoro"alkyls, as they contain hydrogenated carbons. The amide function is actually a "sulfonamide" function, as the amide functionality is not attached to a carbon, but to a sulfur.)

In addition to these 13 substances, there are many other molecules that may be labeled as "perfluoroalkyls" by an organic chemist, some of which were or are manufactured by 3M. For instance, "perfluoroalkyls" can refer to a substance that does not contain a terminal acid or amide group (one such class would be a different group of chemicals, not at issue here, known as "perfluoroalkyl inerts"). An example would be perfluorohexane.

With the understanding that the toxicological profile is limited to the 13 substances mentioned above, for the purposes of these comments any reference to "perfluoroalkyls" refers to these 13 substances or some subset of these 13 substances. 3M understands ATSDR's need to create a definition that fits the substances covered, and does not object so long as other substances in addition to the 13 enumerated above are not covered. (For example, on page 9 of the draft ATSDR notes that perfluoroalkyls do not occur naturally. This is believed to be true with respect to the substances on the list of 13. However, trifluoroacetate or TFA, the C2 carboxylate, does occur naturally.)

One additional caveat on terminology. It is commonplace to refer to the perfluoroalkyls as "acids" (e.g., draft document page 9). Use of the term "acid" may be taken to imply, however, that these substances exist in acid form under environmental and physiological conditions. Clarification is needed that, under most environmental and physiological conditions, these compounds are predominantly in the form of dissociated negative ions, even if they are informally referred to as acids.

## C. Human Exposure

### 1. General Population Exposure and Declining Serum Values

In reporting general population serum values, it is important to note that the presence of perfluoroalkyls (PFOS and PFOA) has declined substantially since 2000. Based on U.S. Centers for Disease Control and Prevention (CDC) data collected in 2003-2004, the average PFOS and PFOA concentrations in the U.S. general population approximated 20 ppb for PFOS and 4 ppb for PFOA. These concentrations have declined by approximately 25-30 percent since 2000. In comparing the geometric mean PFOS and PFOA concentrations in 600 individual American Red Cross adult blood donor samples obtained in 2006 each from six regional donation centers (100 samples per center) to the geometric means from the same approximate number of samples from the same regional centers obtained in 2000-2001, Olsen et al. (2008 ES&T 42, 4989-4995) found approximately 60% and 25% declines in the geometric means for PFOS and PFOA, respectively. Thus, any time values are provided, the date for the sampling being reported should also be provided. For example, values are given on pages 7 and 10.

In the paragraph on page 10, the mean general U.S. population blood concentrations are listed. This paragraph would benefit from inclusion of more up-to-date information published by Olsen et al. in 2008 ("Decline in perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross adult blood donors, 2000-2006"), as well as a sentence describing the conclusion of this study: between 2000 and 2006, PFOS concentrations declined approximately 60%, PFHxS approximately 30%, and PFOA approximately 25%. These percentages appear to be corroborated by the data presented by CDC NHANES for 2005-2006 that are now available for inspection on their website. See http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/lab05_06.htm.

Page 208 of the draft document states that no studies were located regarding methods to reduce body burden of perfluoroalkyl compounds in humans. However, several studies have shown such body burdens, as measured by serum concentrations,

have declined between 2000 and 2003/2004 in the general United States population (Calafat et al. 2007) and 2000 and 2006 among American Red Blood Cross donors (Olsen et al. 2008). Newborn infants have also shown corresponding declines (Spliethoff et al. 2008). Olsen et al. (2008) showed serum PFOS concentrations to have declined by approximately 60 percent for PFOS and 25 percent for PFOA between 2000 and 2006 in American Red Cross blood donors in six different locations (Boston, MA; Hagerstown, MD; Charleston, NC; Minneapolis-St. Paul, MN; Los Angeles, CA; and Portland, Oregon). Specific reasons for this decline are not identified but follow, to some extent, the phase-out of POSF-based chemistry by 3M Company, especially for PFOS. The decline mirrors the serum elimination half-life of PFOS (Olsen et al. 2007). This is less the case for PFOA due to a variety of non-3M manufacturing exposure sources that remained after 3M phased out of the perfluorooctanyl chemistry (e.g., other manufacturers of PFOA, manufacturers of fluorotelomers, manufacturers of perfluorinated phosphonic acids).

Similarly, Section 6.5, beginning on page 286, suffers from not including the recent Olsen et al. 2008 paper. The Olsen et al. (2008) data also need to be added to Table 6-11 and Table 6-12.

Although listed in the references, we noticed that the study by Kannan et al. (2004) which contains serum samples of PFOS and PFOA collected in various locations in the United States, is not included in Table 6-11. We support that decision, as some erroneous measurements in this study occurred due to a lack of matrix- matched internal calibration standards (Reagen et al. 2008).

### 2. Children's Exposure

The last sentence on page 220, like a number of other places in the draft document, states that "Data on serum levels in young children are lacking, but presumably will be available in future NHANES reports." This is not accurate. Olsen et al. 2004 "Quantitative evaluation of perfluorooctanesulfonate (PFOS) and other fluorochemicals in the serum of children," which is cited elsewhere in the ATSDR profile, found that children's serum concentrations were generally comparable to the adult general population levels. This study is discussed on page 295 and in Table 6-14.

Data on serum levels in young children also include more recent studies by Kato et al. (2009), and Toms et al. (2009) et al. In contrast to the statement on page 306 in the third paragraph, NHANES surveys have now included children below 12 years of age, given the recently published paper by Kato et al. (2009). Pooled serum concentrations reported by Kato et al. (2009) of United States children representing three races (nonhispanic white, nonhispanic black, and Mexican American) need to be added to the data in Table 6-14 and Table 6-15, as do data from Australian pooled infant and children serum samples published by Toms et al. (2009).

For the U.S. NHANES data, Kato et al. (2009) reported from pooled children data age 6 – 11 the following arithmetic mean concentrations (95% CI) by race:

| | | Age 6 - 11 | |
|---|---|---|---|
| | PFOS | PFOA | PFNA |
| Nonhispanic white | 42.5 (36.4-48.5) | 7.6 (7.0-8.2) | 0.9 (0.74 – 1.1) |
| Nonhispanic black | 39.2 (33.1 – 45.2) | 7.4 (6.8-8.0) | 1.2 (1.0-1.3) |
| Mexican American | 30.5 (24.4-36.5) | 6.1 ((5.5-6.7) | 0.6 (0.5-0.8) |

Among 3-5 year old children, specific data from pooled samples were provided only for PFNA. Concentrations for nonhispanic white, nonhispanic black, and Mexican Americans were 0.9 ng/mL (0.7 – 1.1), 1.2 ng/mL (1.0 – 1.4) and 0.7 ng/mL (0.5-0.9), respectively.

Among the Australian samples (Toms et al. 2009), pooled serum mean concentrations were provided for 11 age groups under 16 years of age for PFOS, PFOA, and PFHS and five other perfluorochemicals. Serum concentrations increased from the 0-0.5 age bracket through the 12-15 year age bracket going from 7.0 ng/mL to 16.6 ng/mL for PFOS, 4.5 ng/ml to 5.8 ng/mL for PFOA, and 0.9 to 4.4 ng/mL for PFHS, respectively. No gender differences were apparent in the pools from children < 12 years of age.

In the discussion on pages 202-207, several references are missing in this section, including Monroy et al. (2008) and Stine et al. (2009), and Olsen et al. (2009).

The last sentence on page 10 states that doses to children estimated by theoretical models "are significantly lower than the doses administered to laboratory animals." We agree, but think that it would be even more helpful if you could provide an example of the magnitude of the difference in dose between the calculated dose to children and, for example, some of the key developmental toxicology studies.

### 3. Occupational Exposure

3M has studied its perfluoroalkyl production workers at its plants in Cottage Grove, Minnesota; Decatur, Alabama; and Antwerp, Belgium. Workers were exposed to both PFOA and PFOS at each of these plants. See Olsen et al. (Am Ind Hyg Asso J 2003). It should be noted that the Cottage Grove workers studied in Gilliland and Mandel (1993) (page 35) were also exposed to PFOS in addition to PFOA, although the researchers were not as cognizant of that at the time. Similarly, 3M's Decatur plant workers also had exposure to both PFOS and PFOA. This should be noted with respect to the Alexander (2003) study on page 36 of Decatur employees, which focuses on PFOS.

It is also important to emphasize, for example in the second paragraph at page 212, that subjects exposed in occupational settings are more highly exposed than general population. See http://solutions.3m.com/wps/portal/3M/en_US/PFOS/PFOA/Information/Health-Environment/.

On page 4, in Section 1.5 of the summary, it is important to note the concentrations in worker serum compared to the general population or exposed communities.

The occupational biomonitoring data from an Italian fluorochemical production facility (Costa et al. 2009) need to be added to the data presented in Table 6-13.

**4. Populations With Point Source Exposures**

Two major populations with potentially higher exposures due to environmental exposure through water are not included in section 6.7. The first is the C8 Health Project, for which serum concentrations have now been reported for 6 water districts (Little Hocking, Lubeck, Belpre, Tupper Plains, Pomeroy, and Mason), and have been published by Steenland et al. (2009). Median PFOA concentrations reported were 224.1 ng/mL, 66.9 ng/mL, 35.0 ng/mL, 37.2 ng/mL, 12.1 ng/mL, and 12.4 ng/mL, respectively.

The second population is from Washington County, Minnesota (Minnesota Department of Health 2009) exposed via drinking water, where serum concentrations for seven perfluorochemicals (PFOS, PFOA, PFHS, PFBA, PFPeA, PFHxA, and PFBS) were measured. PFOS, PFOA and PFHS concentrations were all above the limit of quantitation; whereas most of the PFBA, PFPeA, PFHxA and PFBS were not. See http://www.health.state.mn.us/divs/eh/tracking/biomonitoringpilot.htm.

A random sample of 198 members from three communities (Oakdale, Lake Elmo, and Cottage Grove, Minnesota) in Washington County, Minnesota were selected for the pilot study to determine the serum concentrations. The overall median concentrations (regardless of municipal or well) were measured at 16 ng/mL (range 1.6 – 177) for PFOA, 41 ng/mL (range 3.2 – 448 ng/mL) for PFOS, and 8.9 ng/mL (range 0.3 – 31.6 ng/mL) for PFHS, respectively, which is approximately 4, 2, and 4 times higher than the median general population's concentrations in the comparable time period.

**5. Relative Source Contribution**

Identifying the pathways of external exposure to perfluoroalkyl compounds in the general population has posed significant challenges.

At pages 3, 10, and 162, the document states, based on one reference, that food is expected to be an important source for exposure to perfluoroalkyls, and provides estimates of external doses to the general population. We do not believe ATSDR can support such a definitive statement as to the sources of exposure for PFOS or PFOA, much less other perfluoroalkyls. What has been demonstrated, however, is that when PFOS or PFOA is present in drinking water at elevated levels, drinking water becomes the dominant source of exposure.

Moreover, the United Kingdom Food Standards Agency has recently released a report of a food survey that estimated upper-bound average daily food-borne intake of PFOS and PFOA to be 0.01 μg/kg body weight for each compound, with 97.5 percentile daily intakes estimated at 0.02 μg/kg body weight

(http://www.food.gov.uk/multimedia/pdfs/fsis0509.pdf). Assuming a 70 kg standard human, this level of exposure via diet falls under the United States Food and Drug Administration's Threshold of Regulation for food additives of 1.5 μg/day. In addition, Fromme et al. (2009) provide an "exposure assessment for the general population in western countries" and estimate average daily exposures to be 1.6 ng/kg body weight and 2.9 ng/kg body weight for PFOS and PFOA, respectively.

The role of drinking water in aggregate exposure (referred to as relative source contribution) arises in several places in the draft document, including pages 3, 10, and 162. The information provided in the draft as written is accurate but we think incomplete. For instance, as currently drafted, the chart at page 3 illustrating how a person might be exposed to perfluoroalkyls leaves the impression that food is as important a source of exposure as drinking water. Similarly, the document states at page 10 that "one study has proposed that the major exposure pathways for PFOS for the general population . . . were food and water ingestion, dust ingestion, and hand-to-mouth transfer from mill-treated carpets," again indicating drinking water exposure is on equal footing with other pathways of exposure. While it is accurate that the single general population study referenced supports this conclusion, we think it is equally important to reference the available data on relative source contribution for drinking water in populations that have been exposed to elevated levels of perfluoroalkyls in their drinking water supplies. These data, which show drinking water is the predominant source of exposure when the drinking water contains PFOS or PFOA at elevated levels, has implications for exposure pathways in the general population as well.

The levels of PFOS and PFOA in general population serum have been well characterized. In addition, serum data are available for two communities that were exposed via drinking water, one in Minnesota and one in Ohio/West Virginia. By comparing the levels in the general population versus levels in populations exposed via drinking water, the relative contribution from the drinking water exposure is apparent. Based on data from two different communities, the contribution from the presence of elevated PFOS or PFOA in drinking water to the aggregate exposure reflecting in serum values are in the range of 60% to 80% for these compounds.

The table below shows serum concentrations of an exposed population from the 2009 Minnesota Department of Health East Metro Perfluorochemical Biomonitoring Pilot Project, compared to generally contemporaneous serum concentration data in the general population from 3M's published study presenting data from Red Cross blood banks. The geometric mean PFOA serum concentration in a population exposed to water supplies with elevated PFOA is 15.4 ng/mL. The geometric mean in a population not exposed to contaminated water supplies -- in this representation, 2006 Red Cross blood donor data -- is 3.4 ng/mL. From this, we subtract 3.4 from 15.4 to show the amount contributed by drinking water. We can then express that as a percentage of the total exposure. Based on these data for the Minnesota community with drinking water exposure, approximately 78% of the serum concentration of PFOA is attributable to drinking water -- a far cry from the typical default RSC estimate of 20%.

| | PFOA | | | PFOS | | |
|---|---|---|---|---|---|---|
| | Geometric Mean | Arithmetic Mean | Median | Geometric Mean | Arithmetic Mean | Median |
| Exposed through water (ng/mL) | 15.4 | 22.5 | 16.0 | 35.9 | 47.7 | 41 |
| Control: 2006 Red Cross (ng/mL) | 3.4 | 3.9 | 3.6 | 14.5 | 16.9 | 14.2 |
| RSC from water (%) | 78 | 83 | 78 | 60 | 66 | 65 |

The next chart reflects a comparison of the median serum concentrations of populations in Ohio and West Virginia that were exposed to PFOA-containing drinking water versus the median serum concentration in the 2006 Red Cross donors (i.e., general population without particular exposure to elevated levels of PFOA in drinking water). Following the formula set forth above, we can see the relative source contribution from water is 90%.

| Water District | Median Serum [PFOA] (ng/mL) | RSC (%) |
|---|---|---|
| **Belpre** | **35.0** | **90** |
| **Tupper Plains** | **37.2** | **90** |
| **Little Hocking** | **224.1** | **98** |
| **Lubeck** | **66.9** | **95** |
| **Mason County** | **12.4** | **71** |
| **Pomeroy** | **12.1** | **70** |

## D. Half Life Information

### 1. Half Life in Humans

Table 3-8 in the draft document provides summary serum elimination half-times for perfluoroalkyls estimated in humans and experimental animals. Under the human section of Table 3-8, the following information needs to be added for PFBS following the column headers of Table 3-8.

| | | | | | |
|---|---|---|---|---|---|
| PFBS – Human<br>Human (n = 6)<br>Adult, M(5) F(1) | NA | NA | NA | 25.8 days<br>(95% CI 16.6 – 40.2) | Olsen et al. (2009) |

It should be noted both in Table 3-8 as well as in the second paragraph on page 179 that the serum elimination half-lives cited for humans are geometric means. We agree with the use of geometric means is the appropriate measure of central tendency to use to describe the data in the Olsen et al. (2007) report because the distribution appeared to be log normal.

Also, in this paragraph, the ATSDR may want to cite two other studies that have recently provided serum elimination half-life estimates for PFOA. Costa et al. (2009) reported a serum elimination half-life of 4.8 years based on a 7-year follow-up of 16 formerly exposed workers, who retired or were transferred to other work departments at an Italian fluorochemical manufacturing company. Given several caveats, they have calculated a geometric mean of 4.8 years (arithmetic of 5.1 years, standard deviation 1.7). The range was 2.6 years to 9.7 years. These values may be biased upwards due to ongoing exposure that may have occurred for those former production employees who remained on the plant's premises doing other nonproduction jobs.

The other serum elimination half-life estimate has now been reported by the C8 Science Panel (Bartell et al. 2009), where they have estimated for 200 individuals, after one year of treated (filtered) municipal or private water, a serum elimination half-life of PFOA of 2.3 years (95% CI 2.1 – 2.4). Individual estimated half-lives varied with most between 1.5 to 4.6 years.

At page 180, second paragraph, as with PFOS and PFOA, the estimated serum elimination half-life of PFHS should be referred to as a geometric mean.

On page 180, third paragraph, the PFBA human data have the wrong units. The units should be <u>hours</u> *not days* per the statements made in this paragraph (i.e., 81 hours, 72 hours, 56 hours, 118 hours, 75 hours).

As a result of the presence of PFBA in municipal water and private wells in Washington and Dakota counties reported by the Minnesota Department of Health, 3M studied stored blood samples of current and former 3M employees who reside in the affected communities and analyzed them for PFBA. Occupational exposure to PFOS and PFOA was the likely primary source. The final study database consisted of 127 former and 52 current employees. The low ng/mL concentrations of PFBA that were measured were consistent with a relative rapid half-life of PFBA in humans estimated to range between 2 and 4 days. See Olsen, et al., Descriptive Analysis of Perfluorobutyrate (PFBA) in Sera Collected in 2005 from Former and Current 3M Cottage Grove Employees Who Resided in Selected Communities of Washington and Dakota Counties, 3M Final Report, July 20, 2007, in 3M's Submission to U.S. EPA Docket AR226, dated July 8, 2008. This is covered in Chang et al. (2008) Toxicol. Sci 104, 40-53. In this study 71.8% were below the lower limit of quantitation of 0.5 ng/mL. The highest measured value was 6.2 ng/mL, and 96.1% were less than 2 ng/mL.

### 2. Half Life in Animals

On page 10, the half-life of 75 days for PFBA in incorrect; this should be 75 <u>*hours*</u>. (Chang et al., 2008a).

Under the nonhuman primate section of Table 3-8, the following information needs to be added for PFBS following the column headers of Table 3-8.

PFBS – Nonhuman primate

Cynomolgus

| | | | | |
|---|---|---|---|---|
| monkey, adult, M IV | 10 mg/kg | 31 days | 95.2 hours (SD 27.1) | Olsen et al. (2009) |
| Cynomolgus monkey, adult, F IV | 10 mg/kg | 31 days | 83.2 hours (SD 41.9) | Olsen et al. (2009) |

Under the rat section for Table 3-8, the following information needs to be added for PFBS following the column headers of Table 3-8.

| | | | | |
|---|---|---|---|---|
| PFBS – Rat | | | | |
| Rat (SD), adult, M, Oral | 30 mg/kg | 1 day | 4.7 hours (SD 0.4) | Olsen et al. (2009) |
| Rat (SD), adult, F, Oral | 30 mg/kg | 1 day | 7.4 hours (SD 0.8) | Olsen et al. (2009) |
| Rat (SD), adult, M, IV | 30 mg/kg | 1 day | 4.5 hours (SD 2.2) | Olsen et al. (2009) |
| Rat (SD), adult, M, IV | 30 mg/kg | 1 day | 4.0 hours (SD 0.2) | Olsen et al. (2009) |

## E. Organization of Data by Route of Exposure

The organization of the draft document places primary emphasis on route of exposure. The routes of exposure in human data may not be entirely documented, and it could be more helpful for the reader to have all of the human data collected together. Because perfluoroalkyls are bound in blood plasma, body burden can be directly measured via blood concentration, which represents aggregate exposure by all routes. Animal data might be clearly presented based on route of exposure, but it does not make as much sense to present the human data based on route of exposure under the circumstances applicable to perfluoroalkyls.

While we appreciate ATSDR's efforts to divide the presentation of data by exposure route, the draft profile concludes: "It should be made clear, however that based principally on results from studies in animals that indicate that the health effects of these substances are independent of the route of exposure, conclusions can be drawn across exposure routes." 3M does not necessarily agree with this statement, but notes that it provides further basis for considering whether organization of data by route of exposure is the clearest way to present the data in this document.

ATSDR provides no information suggesting that inhalation is the sole exposure source within the occupational setting, yet the occupational epidemiology data are reviewed solely under 'Inhalation Exposure.' ATSDR recognizes at page 34 that workplace exposure to perfluoroalkyl compounds "may occur by the inhalation, oral, and dermal routes," but nevertheless asserts the basis for discussing workplace studies in that section is "[the inhalation] route may be more important than oral and dermal in occupational settings." See also the statement on page 161 indicating that serum levels probably reflect a predominant contribution from inhalation. That is an assumption.

PFOS and PFOA have low volatility. However, at 3M's Decatur and Antwerp plants where PFOS precursor products were manufactured, the starting material, POSF, was volatile, and some of the precursor products had some degree of volatility. Thus, potential inhalation exposure in the workplace could have occurred. With respect to PFOA, while volatility was low, 3M for a number of years manufactured

the ammonium salt of PFOA in powdered form, also resulting in potential inhalation exposure.

In reality the predominant route of PFOA exposure for most exposed employees at 3M production facilities is not known. Ingestion, through hand contamination and then hand to mouth activity such as eating or smoking probably played some role, possibly a major one. There may have been drinking water exposure at some point in time at one facility (Cottage Grove), but its relative significance is unclear. Dermal exposure may also contribute (see Olsen 2003) but is not likely to be major.

However, we question the statement on page 11 that workers may have high exposure based on the presence of these compounds in the environment surrounding the facilities, including air, soil, sediment, surface water, groundwater, and vegetation. Although we cannot speak for others, this has not been the case for 3M facilities. For example, exposure estimates prepared for EPA do not suggest significant occupational exposure from the external environment.

The worker serum values represent aggregate exposure from all potential routes of exposure, whatever they may be, including their background general population exposure as well. It is therefore inappropriate to suggest that the extensive occupational studies, including both medical surveillance, mortality studies and other studies, represent only inhalation exposure. For instance, at page 52, it should be noted that occupational exposure included dermal exposures, and thus if any dermal effects were occurring, they likely would have been revealed by worker studies. In Section 1.5 of the summary of the draft document, ATSDR should note that the exposure pathway is a combination of inhalation/ingestion/dermal. Figure 3-10 also needs to be revised to reflect multiple pathways studied in the occupational studies. Similarly, while there are studies specifically of certain populations known to have exposure via drinking water, there are also a number of studies on the general population. As with workers, the blood levels of perfluoroalkyl compounds present in the general population represent aggregate exposure from all exposure pathways.

Finally, given the agency's decision to organize the document by route of exposure, we think ATSDR should qualify certain absolute statements, such as "No studies were located regarding reproductive effects in humans following oral exposure to perfluoroalkyl compounds" at page 135, and "There are no studies of cancer in humans exposed orally to perfluoroalkyl compounds" at page 148 to caution the reader that such data are available.

At the very least, ATSDR should add sub-headings and paragraph breaks to divide human data from animal data and potentially to divide further by chemical substance. We believe the structure of Section 3 would be improved by placing emphasis on whether the data was from human studies or animal studies, then separating the data by endpoint and substance.

**F. Limitations of Human Studies**

The draft document does a thorough job of cataloging limitations that pertain to various epidemiologic studies. This database has strengths that should also be

noted, however. In particular, the database includes a large number of studies of occupationally-exposed cohorts at 3M's Cottage Grove, Decatur and Antwerp plants. These workers had some of the highest known exposures, and their health has been studied for decades. There are now over 12,000 workers and 250,000 person-years of follow-up in the 3M and DuPont cohort mortality studies, for example. There are also multiple cross-sectional studies at each of the 3M plants, as well as other types of studies, in addition to studies of exposed workers at other manufacturers' facilities.

3M will continue to follow the Cottage Grove and Decatur cohorts. However, given that ATSDR encourages future studies, you should be aware that exposure levels in members of these cohorts has continued to decline since 3M phased out of production of PFOA and PFOS-related products from 2000-2002.

In discussing limitations of the human studies on page 35, the draft document lists eight "inherent" limitations that "bias the results both towards finding nonexistent effects and failing to detect a true effect." This is a gross oversimplification of complex occupational epidemiology issues for any one (or all) of the limitations listed. It is also erroneous to assume that bias would only occur in the direction of not finding existing effects or failing to detect a true effect. Epidemiologists need to be equally concerned about false positive as well as false negative results.

The paragraph on page 35 appears to be a stock listing of limitations of epidemiologic studies generally. Some specific comments:

- To make the argument, as the draft document does, that these studies have relatively "poor measures of exposure" is indefensible. Few occupational epidemiology studies have been conducted with the degree of biomonitoring that these perfluorochemical epidemiology studies have undertaken. If anything, the occupational studies conducted of perfluoroalkyl production workers are greatly strengthened by the availability of biomonitoring data – especially given that these compounds have long serum half-lives indicating past exposures.

- ATSDR offers no definition of what constitutes a "low participation rate." If the participants reflect the exposures in an occupational setting, it does not necessarily follow that an effect cannot be detected because there are "low participation rates." Precision may be affected but not necessarily accuracy. Sensitivity analyses, which have been reported in the perfluorochemical epidemiology literature (such as that in Alexander and Olsen 2006), can be used to address such concerns.

- The healthy worker effect is the most common example of confounding in occupational studies. Aspects include preferential hiring of healthy persons for employment as well as self-selection of persons of poor health out of the workforce. It also includes the selection of a less than ideal reference group i.e., the general United States population. In cohort mortality studies, the healthy worker effect is most often observed for all causes combined and deaths from

cardiovascular diseases, diabetes mellitus, and nonmalignant respiratory diseases. It is much less likely to affect malignant neoplasms – especially those of adults that are diagnosed with rapidly fatal cancers. This would most definitely be the case with liver and pancreatic cancers which are two critically important *a priori* cancers to study with perfluorochemicals due to the findings of an increased incidences of benign hepatocellular adenoma and benign pancreatic acinar cell adenoma (without increases in malignancies (cancers) related to these tumor types) in a two year bioassay of rats fed PFOA (ammonium salt) (Biegel et al. 2001). Thus, to dismiss occupational studies due to the healthy worker effect becomes an irrelevant argument when studying these two specific cancers for this specific exposure. Yet this paragraph makes no exception, and appears to apply a 'healthy worker effect' argument with respect to all outcomes. Furthermore, this paragraph does not acknowledge the fact that 'internal' comparisons were used, in addition to general population comparisons, for the 3M Decatur (Alexander and Olsen 2007), 3M Cottage Grove (Lundin et al. 2009), and Sakr et al. (2009) DuPont occupational cohort studies. Nor does it acknowledge the DuPont referent (an external population) used by Leonard et al. (2008).

- Clearly, medically validated reports are preferred over self-reports. Yet, the draft document implies that all self-reports of health conditions are 'unreliable measures.' But whether such reports are reliable, and the extent of unreliability, depends on the outcome studied. (For example, mothers tend to reliably recall the birth weight of their babies.) Also, if unreliably recalled, it does not necessarily mean that self-reports would only result in a 'bias towards the null' as this paragraph in the draft document assumes. Over reporting due to preconceived concerns (for whatever reason) of the participant's perceived exposure may, indeed, bias measures of effect upwards.

- The blanket statement that a comparison group is not a true control group unless it is unexposed appears to be overly dismissive. Given the likely fact that everyone, regardless of occupational or nonoccupational setting, has some concentration of certain perfluoroalkyls in their blood, this argument about an entirely unexposed control group appears uninformed. What is examined is the biologic gradient (dose-response) among the exposed.

- The argument about 'small study size that have inadequate statistical power to detect relationships between exposures and adverse outcomes' is an *a priori* argument. Clearly, statistical power is an *a priori* concern. As stated by Beebe (1984), small size studies that have inadequate statistical power tend to also result in false positive findings that are preferentially written and published in the literature. As Ionnidis (2008) has aptly observed, even "newly discovered true (non-null) associations often have inflated effects compared with the true effect size." Ultimately, upon completion of a study, it is the measure of effect and its precision (as well as all other aspects of the study

design and conduct) that drive study inferences – not the mere fact of *a priori* 'study sample size.'

The collective 3M and DuPont cohort mortality studies on perfluorochemical production workers account for more than 12,000 workers approaching 250,000 person-years, some followed for upwards of 50 years in the three major cohort mortality studies published. There are a series of cross sectional investigations conducted since the 1970s examining a variety of clinical chemistries in highly exposed workers. The occupational studies include actual biomonitoring data, which is the preferred measure of exposure, as well as exposure estimates based on work assignments coupled with these biomonitoring data. (Lundin et al. 2009; Sakr et al. 2009; Kreckmann et al.). The biomonitoring data indicate average occupational exposure among PFC production workers is approximately 50-fold higher than the general population's blood levels to PFOS or PFOA, which have also been well-characterized. These unusual strengths of the epidemiologic database need to be highlighted along with the limitations. The extent of medical monitoring and biomonitoring data available for these compounds differentiate the literature on PFOS and PFOA from that of many other compounds.

## G. Developmental and Reproductive Studies in Humans

### 1. Developmental Studies in Humans

In a number of places, the draft document discusses general population studies of birth outcomes. (This includes page 6, under Effects in Children, in the second paragraph; pages 13-14, and a list of citations at the bottom of pages 21, 138-142, and 204.) Additional data have now been reported in the literature, and the available data are summarized in a review paper, Olsen et al. Perfluoroalkyl chemicals and human fetal development: An epidemiologic review with clinical and toxicological perspectives, *Reproductive Toxicology* 27 (2009) 212-230. The table presented there demonstrates the validity of ATSDR's conclusion that the inconsistent reported associations are not causal. In discussing developmental effects at pages 138-142, the draft document should direct the reader to the published review paper, as it is much more comprehensive than what is presented within this ATSDR draft document. The ATSDR should also note the commentary by Savitz (2007, Environ Health Perspect 115, A528-A529) regarding the Apelberg and Fei papers that were published in *Environmental Health Perspectives*.

With regard to Section 1.6 of the summary, there is only one study that showed a statistically significant decrease in mean birth weight (Fei et al. 2007). Apelberg et al. did not – although the mean birth weights were lower for both PFOA and PFOS. Fei et al. reported no association with PFOS. As for the other studies, Grice et al., Monroy et al., Washino et al. (except for females with PFOS), Nolan et al., and Stine et al. all did not show any association with birth weight and PFOA. Therefore, the numbers used in this paragraph are not correct. Stine et al. did show a birth weight association with PFOS.

Given more than 10 studies on developmental effects in humans, the ATSDR draft document needs to be much more specific with its criticism (page 217) about 'limited' information regarding developmental effects in humans. As reviewed by

Olsen et al. (2009) and with the addition of the Stine et al. paper (2009), the one major theme across the studies published, to date, is the inconsistency of the associations of the outcomes measured and the lack of associations with birth weight or gestational age with higher exposed populations compared to the general population across these studies.

On pages 13, 54-55 and 204, the profile describes the Grice et al. study of self-reported conditions among workers at the 3M Decatur production facility. We appreciate that ATSDR points out one important finding of the study: that birth weight did not vary between exposed and non-exposed groups. However, the draft document critiques the study for not analyzing length of gestation, which is "an important determinant of birth weight." Given that all birth weights in the study were above the definition of low birth weight of 2.5 kg, the bias induced by not collecting this information is unclear. We also suggest noting that this study is important because it includes an occupational group exposed at levels two orders of magnitude above the general population level and found no low birth weight disparity. The Grice et al. study had a significantly higher body burden of PFOA and PFOS than the general population studies performed by Fei et al., Apelberg et al., or others, and also substantially higher than the population in the Stine et al. study of the C8 Health Project. (While Grice reported on POSF-exposed workers, those workers had exposure to both PFOS and PFOA. See Olsen, et al. 2003, and the underlying 3M Final Report, Olsen et al. 1999, U.S. EPA docket AR226-0950).

At the top of page 14, without citations, it is impossible to evaluate the thoroughness of the discussion of birth outcomes. For example, is the third Fei et al. paper, which evaluated development of children at 18 months, included?

In the "Developmental Effects" discussion at pages 138-140, ATSDR should make clear where developmental study results were inconsistent, as consistency is a key component of analyzing association versus causation. For example, some of Fei et al. results were inconsistent with Apelberg et al. (2007). Like Apelberg et al., Fei et al. 2007 observed an inverse relationship between PFOA and birth weight, but at a lower magnitude of association. And unlike Apelberg et al., Fei et al. 2008a did not find a statistically significant inverse association between PFOA and head circumference or placental weight, but did with birth length and abdominal circumference.

Indeed, it may be useful to present the data in tabular form. The table below is based on the Olsen review paper, with the addition of the subsequent Stine et al. study:

**Table**

| Endpoint | PFC | Olsen | Grice | Inoue | Apelberg | Fei | Monroy | Washino | Nolan | Stein |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gestational age** | PFOS | | | | N.S. | N.S. | N.S. | | | N.S. |
| | PFOA | | | | N.S. | N.S. | N.S. | | N.S. | N.S. |
| **Birth weight (g)** | PFOS | | N.S. | N.S. | N.S. | N.S. | N.S. | S.S.[females] | | S.S. |
| | PFOA | | N.S | | N.S. | S.S. | N.S. | N.S. | N.S. | N.S. |
| **Birth length (cm)** | PFOS | | | | N.S. | N.S. | | N.S. | | |
| | PFOA | | | | N.S. | S.S. | | N.S. | | |
| **Head circumference (cm)** | PFOS | | | | S.S. | N.S. | | N.S. | | |
| | PFOA | | | | S.S. | N.S. | | N.S. | | |
| **Abdominal/chest circumference (cm)** | PFOS | | | | | N.S. | | N.S. | | |
| | PFOA | | | | | S.S. | | N.S. | | |
| **Apgar score** | PFOS | | | | | N.S. | | | | |
| | PFOA | | | | | N.S. | | | | |
| **Ponderal index** | PFOS | | | | S.S. | N.S. | | | | |
| | PFOA | | | | S.S. | N.S. | | | | |
| **Placental weight (g)** | PFOS | | | | | N.S. | | | | |
| | PFOA | | | | | N.S. | | | | |
| **Miscarriage** | PFOS | N.S. | N.S. | | | | | | | N.S. |
| | PFOA | N.S. | N.S. | | | | | | | N.S. |
| **Birth defects (non-specific)** | PFOS | N.S. | | | | | | | | |
| | PFOA | N.S. | | | | | | | | N.S. |
| **Preeclampsia** | PFOS | | | | | | | | | S.S. |
| | PFOA | | | | | | | | | N.S. |
| **Developmental milestones** | PFOS | | | | N.S. | | | | | |
| | PFOA | | | | N.S. | | | | | |

Olsen et al. actually displayed the specific coefficients of measurements from these studies and discussed the various covariates that were (or were not) adjusted for the birth endpoints examined. Adjustment, or lack of adjustment, for these covariates may result in biased estimates and inconsistency across the studies.

Missing from the draft document is the developmental paper by Monroy et al. (2008), who studied a nested subset (n = 101) of women involved in a large cohort study at MacMaster University. Monroy et al. did not find statistically significant associations between birth weight and maternal serum or umbilical cord serum levels of PFOS or PFOA with birth weight or gestational age.

A paper that has been recently published by Stine et al. (2009) investigated birth weights and other neonatal parameters among a large number of births in the C8 Health Project database. Stine et al. used the < $50^{th}$ percentile of PFOA or PFOS exposure as a referent group. Using higher percentile cutpoints of $75^{th}$ – $90^{th}$ percentile and greater than $90^{th}$ percentile, they reported no statistically significant adjusted odds ratio for PFOA for miscarriage, preeclampsia, gestational age or birth weight of less than 5.5 pounds within 5 years of enrollment. For PFOS, there were no statistically significant associations for miscarriage but there were 'modest' associations, as described by Stine et al. for preeclampsia at > $90^{th}$ percentile compared to those below the $50^{th}$ percentile had an adjusted odds ratio of 1.6 (95% CI 1.2 to 2.3) and low birth weight (adjusted odds ratio 1.8, 95% CI 1.2 to 2.8). The generic term "birth defects" were not significantly associated with exposures above the $90^{th}$ percentile for PFOA (adjusted odds ratio 1.7, 95% CI 0.8 to 3.6) or PFOS (adjusted odds ratio of 1.3, 95% CI 0.8 to 2.1). All data were based solely on self-reported health outcomes.

Page 138 of the draft discusses the Apelberg et al. study. The 95% confidence intervals appear to be incorrect for the Apelberg study. They should be (-149 to +10) for the 69 g decrease for a 2.7 fold increase in PFOS and -213 to +5 for a 104 g decrease reported for a 2.7 fold increase in PFOA.

The ATSDR draft document does not discuss the discrepancy in head circumference by method of delivery in the Apelberg et al. study. The decrease in head circumference of 0.32 and 0.41 cm, per 2.7 fold increases in PFOS and PFOA, as reported by Apelberg et al., was for all births. However, this difference was dependent upon mode of delivery. Vaginal delivered births had decreased head circumferences of 0.46 and 0.62 cm, respectively, but among C-section births head circumference increased 0.31 and 0.23 cm, respectively, per a 2.7 fold increase in PFOS and PFOA, respectively. As discussed by Fei et al., because of the head molding with vaginal births, the accuracy of this measurement is questionable.

At page 139, the draft ATSDR document discusses the first Fei et al. publication and cites the PFOA data from this publication. The 95% confidence interval that is presented for birth weight with PFOA appears to be incorrect. It should read (95 CI -20.79 to – 0.47). However, nothing is mentioned about PFOS in this write-up of the original Fei et al. paper. This omission needs to be corrected. Unlike Apelberg, Fei et al., did not find birth weight to be associated with PFOS. There was a 0.46 gram decrease in birth weight associated with a 2.7 fold increase in

PFOS (95% CI -2.34 to +1.41). The ATSDR needs to add these PFOS data to this paragraph.

The Washino et al. (2007) paper is discussed on page 141. Because there is a striking inconsistency in the mean birth weights recorded for male and female infants, these data should be presented in this paragraph in addition to the overall decrease of 148.8 grams. (Note: the 95% Confidence interval should be -297 to – 0.5) for all subjects.) For females, the decrease was -269.4 grams (-465.7 to -73.0); however for male births, the birth weight was increased at +12.1 grams (-217.7, +242.0).

On page 204, the sentence beginning "Similar studies of Danish women reported that birth weight, birth weight, and abdominal circumference were inversely associated with plasma levels…" references "birth weight" twice. One of these references should be to "birth length".

Key milestones in child development through 18 months of age were studied in association with maternal serum PFOS and PFOA concentrations in a subset of the Danish National Birth Outcomes cohort (Fei et al. 2008, Environ Health Perspect 116, 1391-1395). The study found that "mothers who had higher levels of PFOA and PFOS gave birth to children who had similar Apgar scores and reached virtually all of the development milestones at the same time as children born to mothers with lower exposure levels."

**2. Reproductive Toxicity**

With respect to pages 135 and 216, there have now been two reproductive studies in humans – one evaluating sperm characteristics (Joensen et al. 2009) and the other time to pregnancy (Fei et al. 2009). Caution needs to be exercised in the interpretation of both of these studies due to the very small study population used by Joensen et al. (n = 100) and a questionable causal model used by Fei et al., as a longer time to pregnancy may actually have resulted in lowered perfluorochemical concentrations rather than the other way around (Olsen et al. 2009).

As part of the same series of papers by Fei et al., that have examined birth and developmental milestone measurement among a cohort of women from the Danish National Birth Cohort, this Fei et al. (2009) study examined time to pregnancy defined as taking more than 12 months to become pregnant when planned. Mean plasma PFOS concentrations for women who took < 6 months, 6 – 12 months and > 12 months were 34.6 ng/mL, 36.6 ng/mL, and 38.3 ng/mL, respectively. The comparable mean concentrations for PFOA were 5.4 ng/mL, 6.0 ng/mL, and 6.3 ng/mL. Analyzing their data in quartiles of PFOS concentrations, the odds ratio for infertility, defined as time to pregnancy > 12 months were 1.00 (referent) , 1.70 (95% CI 1.01 – 2.86), 2.34 (1.40 – 3.89) and 1.77 (1.06 – 2.95). The range of concentrations in the four quartiles were 6.4 – 26.0 ng/mL, 26.1 – 33.3 ng/mL, 33.4 – 43.2 ng/mL, and $\geq$ 43.3 ng/mL. Likewise, for PFOA, the odds ratios for the four quartile were 1.00 (reference), 2.06 (1.22 – 3.51), 1.60 (0.93 – 2.78), and 2.54 (1.47 – 4.39), respectively. The concentration ranges within the PFOA quartiles were < LLOQ – 3.91 ng/mL, 3.91 – 5.20 ng/mL, 5.21 – 6.96 ng/mL, and $\geq$ 6.97 ng/mL. The ranges within PFOA quartiles, especially from the first through third quartiles, are narrow and, likely because of analytical precision issues, resulted in substantial

misclassification. These odds ratios were adjusted for maternal age at deliver, parity, prepregnancy BMI, maternal socio-occupational status, paternal education, paternal age and alcohol consumption before pregnancy. As seen throughout the Fei et al series of papers, the first quartile (lowest exposure) always had the highest parity.

Besides time to pregnancy, Fei et al. also presented fecundity odds ratios which is the measure of the odds of a successful conception. Compared to the first quartile, these odds ratios were approximately 0.7 for the second, third, and fourth quartiles for both PFOS and PFOA. Fei et al. interpreted their data to suggest that PFOS and PFOA may result in a delayed time to pregnancy and may be another risk factor for subfecundity. However, Olsen et al. (2009) suggested Fei et al. may have their association backwards. For women of the same parity and all other factors being equal, they suggested those women with longer time to pregnancy will have longer intervals of time between births and so may have higher perfluorochemical levels prior to the next pregnancy. This would result in longer time to pregnancy measures associated with perfluorochemical levels, but the direction of the causality would be backwards. The longer time interval between births, including time to pregnancy resulted in higher perfluorochemical concentrations.

Joensen et al. (2009) analyzed for 10 different perfluorinated chemicals, including PFOS and PFOA, in relation to semen quality, in young Danish men who reported for the military draft. Each subject provided one semen sample and a blood sample. Joensen et al. selected 105 subjects with the highest and lowest testosterone levels. Their median PFOS and PFOA concentrations were comparable to general population levels. Adding serum concentrations, the investigators categorized concentrations as low PFAA (lowest 25% of subjects), intermediate PFAA (interquartile range) and high PFAA (upper 25% of subjects) and then examined the adjusted means across various sex hormones and semen quality. The only statistically significance among the groups was percent morphologically normal sperm. In conducting a regression analysis of a 1 ng/mL change in PFOS, PFOA or the sum of the two concentrations, Joensen et al. reported no statistically significant trends although most semen quality trends were in a negative (coefficient) direction. Joensen et al. concluded that high levels of PFAAs may contribute to low semen quality; however, they warned their preliminary study results should be corroborated in larger studies. Joensen et al. did not comment on the inconsistency of their preliminary investigation and the lack of reproductive toxicity, including lack of sperm abnormalities, reported in rat reproduction studies for PFOA and PFOS.

In discussing reproductive issues at page 54, we suggest adding the description of the 11 hormones analyzed in relation to PFOS at the 3M Antwerp and Decatur facilities. See Olsen et al., 3M Final Report, 1998, U.S. EPA docket AR-226-0030.

### 3. Maternal Transfer

In noting on page 3 that exposure occurs via human breast milk, it would be useful to note that the concentrations in breast milk are much lower compared to serum.

On page 24, the draft is missing the Monroy e al. (2008) paper.

Data from Fei et al. (2007 – see first paper published in Environ Health Perspect) could be added at page 171. Those authors reported mean 1st trimester maternal blood plasma PFOS and PFOA concentrations of 35.3 ng/mL and 5.6 ng/mL, respectively, based on 1,399 samples. Although not presenting paired data, a sample of 200 2nd trimester blood plasma PFOS and PFOA concentrations resulted in mean levels of 29.9 ng/mL and 4.5 ng/mL, respectively. Finally, 50 umbilical cord blood samples resulted in PFOS and PFOA concentrations of 11.0 ng/mL and 3.7 ng/mL, respectively, for which Fei et al. stated there was good correlation between maternal umbilical cord sample concentrations.

There are also data available regarding concentrations of perfluoroalkyls in human milk in the U.S. populations. Kukleynik et al. analyzed milk samples prepared from two pooled breast milk purchased from a milk bank in San Jose California. They did not detect most perfluorochemicals in these samples.

The study by Tao et al. analyzed 45 human breast milk samples from Massachusetts. For the higher chain carboxylates PFDA, PFUnDA, PFDoDA, as well as PFHpA and PFBS, few samples were measured above the limit of quantitation. For PFOS, PFOA, PFHS and PFNA, there were 43, 40, 23, and 29 samples measured above the limit of quantitation. The median breast milk concentrations (range in parentheses)were 0.106 ng/mL (<0.032 – 0.617), 0.0361 ng/mL (0.0301 – 0.161), 0.0121 ng/mL (<0.012 – 0.0638), and 0.00697 ng/mL (<0.0052 – 0.0184), respectively.

The ATSDR draft document should also review the recently published paper by Ehrenstein et al. (2009), who conducted a pilot study of 34 breastfeeding women in North Carolina.

## H. Cancer - Human Studies

We agree with most of the assertion at page 14 that "[t]here is no conclusive evidence that exposure to perfluoroalkyl compounds produces cancer in humans based on a limited number of studies."

We take exception, however, to describing the epidemiological database as "limited" with respect to cancer studies. Use of the word "limited" needs to be defined. Mortality studies are available from three different production facilities (3M Decatur, 3M Cottage Grove, and DuPont Parkersburg), and a very large general population case-cohort study has recently been published (Erickson 2009).

The discussion on cancer studies at pages 214 - 215 should be updated with the recently published occupational study by Lundin et al. (2009) of the 3M Cottage Grove cohort, as well as adding Olsen et al. (2000), Leonard (2008) instead of Leonard 2006, and Sakr et al. (2009). In particular, the Lundin et al. (2009) and Eriksen et al. (2009) papers specifically address cancer outcomes in occupational and general populations, respectively.

### 1. Bladder Cancer

The high, but imprecise SMR estimate for bladder cancer that was reported by Alexander et al. (2003) was not replicated with a self-reported/validated bladder cancer incidence study, although given the small number of cases, an exposure response analysis could not rule out a small association in a dose response analysis (Alexander and Olsen 2007). Bladder cancer excesses were not observed in the 3M Decatur or DuPont cohorts, nor in the general population case-cohort cancer incidence study.

In referring to the occupational mortality studies on pages 5 and 14, it is important to note that the findings of bladder cancer in the Decatur cohort are not confirmed in the 3M Cottage Grove or the DuPont cohort mortality studies, or by the bladder cancer incidence study among Decatur workers. Nor is there any biologically plausible mode of action demonstrated. A study of POSF, which is a PFOS precursor, showed no bladder effects in laboratory animals. Final Report, Perfluorooctanesulfonyl Fluoride (POSF; T-7661.1) Toxicity Study by Inhalation Administration to CD Rats for 13 Weeks Followed by a 4 Week Recovery Period, Huntingdon Life Sciences Ltd., Study No. MIN 313/023622, September 28, 2005. U.S. EPA Docket AR226-3573.

The description of the results from the Alexander and Olsen (2007) study in the second paragraph on page 36 is inadequate given the importance of this study in its ascertainment of the risk of bladder cancer at the 3M Decatur facility. ATSDR's discussion about this particular paper appears to be almost entirely from the study's abstract. Given the generic concerns about occupational studies expressed by the ATSDR on page 35, ATSDR should note some of the ways the Alexander and Olsen (2007) study tried to address the 'limitations of occupational epidemiology studies'.

For instance, there is no mention in this ATSDR paragraph of the attempt by Alexander and Olsen (2007) to validate the self-reports of bladder cancer from medical records, although only 2 of 6 self-reported cases consented to release of medical records to confirm the diagnosis. There is no discussion about the need to address smoking as an important risk factor bladder cancer, as discussed by Alexander and Olsen (2007). There was no discussion by ATSDR of the use of external (NCI SEER cancer rates) and internal analyses used in this study. There was no discussion by ATSDR about participation rates (75 percent). There was no discussion about the sensitivity analyses conducted by Alexander and Olsen (2007) to address the 25% of the study population that did not participate.

As for what the draft document does state in this paragraph, that "while the results did indicate an excess risk of bladder cancer among the highest exposed workers," this is not what the investigators wrote. Rather, they wrote, "overall, the results of this study do not confirm the high excess risk of bladder cancer that was reported in the mortality study of this population of fluorochemical manufacturing workers. The possibility remains for a smaller risk (approximately 1.5 to 2 fold) in the higher exposed workers, but the limited size of the population prohibits a conclusive exposure response analysis, including an analysis of latency."

Alexander and Olsen do *not* conclude, as ATSDR suggests, that the results indicate an excess risk of bladder cancer among the highest exposed workers. Also, it is misleading to provide the 1.5 – 2.0 fold increased risks compared to the lowest cumulative exposure category without measures of precision (i.e., 95% confidence intervals). Based on the Alexander and Olsen (2007) results, total cumulative exposure, based on an internal referent population analysis (Poisson regression), showed relative risks of 1.0 (referent), 0.83 (95% CI 0.15 – 4.65), 1.92 (95% CI 0.30 – 12.06), and 1.52 (95% CI 0.21 – 10.99) for cumulative exposure cutpoints of 1, 1-5, 5- <10, and ≥ 10 years of employment in high PFOS exposed jobs. The lack of precision as well as non statistical significance in the relative risks for the 5 - < 10 and ≥ 10 years categories is quite evident.

At page 215, after discussion of Alexander and Olsen 2007 results, we suggest noting that the high-exposed worker category has been reported to have average serum PFOS concentrations in the 1,000 ppb range for both PFOS and PFOA (Olsen et al. 2003a) -- much higher than general population levels.

**2. Prostate Cancer**

The prostate cancer findings in the 3M Cottage Grove cohort are not confirmed by the 3M Decatur or DuPont cohorts. In addition, there is now a general population case cohort cancer incidence study. We address the Cottage Grove studies in detail.

In discussing Gilliland and Mandel (1993), the report fairly recognizes the limitations of the study (*e.g*., the small number of prostate cancers observed; could have resulted from chance). This study used duration worked in the chemical division as a surrogate for exposure, and it has been shown that this is a very poor proxy measure, based on employee PFOA biomonitoring data at the 3M Cottage Grove facility (Olsen et al. 2003c). The lack of an association between PFOA biomonitoring data and duration worked has also been reported elsewhere at DuPont fluoropolymer production facility (Leonard 2006; Kreckman et al. 2009).

The study by Gilliland and Mandel (1993) (discussed on page 35) needs to be placed in a much better context. This study is actually the third of a total of 5 cohort mortality studies conducted of the employees at 3M's Cottage Grove manufacturing site. Preceding studies were reported by Ubel et al. (1980). See also Schuman and Mandel (1980), Mandel and Schuman (1989). Reports that followed were Alexander (2001) and Lundin et al. (2009). Readers may not understand that this cohort has been studied for many years and is the subject of multiple publications.

Lundin et al. is the most up-to-date cohort analysis of the 3M Cottage Grove site and was recently published (November 2009 issue, Epidemiology. 20(6):921-928) but has been available on-line since September 29, 2009. Since the Lundin et al. paper is the most recent published update, it should be thoroughly presented in this ATSDR document, rather than citing the third cohort mortality study of Gilliland and Mandel (1993).

The Lundin study has multiple strengths compared to the Gilliland and Mandel study (1993), including the obvious strength of having 13 years more follow-

up (vital status ascertained through 2002 instead of 1989), and the use of a qualitative exposure matrix for exposure to the ammonium salt partially based on biomonitoring data compared to just 'employment duration not specific to any job'.

As ATSDR will want to thoroughly review and comment on the Lundin et al. (2009) paper, we will not provide a detailed description. We should note, however, that in addition to the published paper, ATSDR should also avail itself of the supplementary information supplied on the Epidemiology journal's website.

We do note several points need to be considered in the ATSDR review of Lundin et al. (2009). Most importantly, the increased relative risks reported by Lundin et al. (2009) for prostate cancer based on internal analyses are driven by a deficit of prostate cancer among those with jobs not involved with PFOA production.

The 3M Cottage Grove study cohort consisted of 3993 employees of whom 807 died in the follow-up period. Analyses included both external (State of Minnesota) as well as an internal referent population where hazard ratios were calculated using time-dependent Cox regression models. Estimates of exposure intensity included a qualitative assessment in the form of relative exposure weights assigned to a job exposure matrix. The exposure weights were calculated, in part, from serum PFOA concentrations collected in 2000 from 131 employees in the chemical division of the plant. Based on using the Minnesota mortality rates, the authors reported SMR estimates (95% CI) for prostate cancer for the ever definite job exposure group of 2.1 (95% CI 0.4 – 6.1), for the ever probable/never definite job group of 0.9 (95% CI 0.4 – 1.8), and for the never employed in a PFOA exposure group of 0.4 (95% CI 0.1 – 0.9) based on 3 versus 1.4, 9 versus 9.7, and 4 versus 11.1 observed versus expected deaths, respectively.

Because of the statistically significant deficit of prostate cancer cases in the 'never' PFOA job exposure group, it is to be expected that internal analyses using Cox proportional hazard models would magnify the hazard estimate for the definite exposure group as well as the imprecision of the estimate. Lundin et al. cautioned, "While an internal referent population may provide a more valid comparison (assuming similar social and demographic determinant of disease), the interpretation of this internal analysis should consider the stratum-specific prostate cancer SMRs." Indeed, regardless of the exposure classification by job or by cumulative exposure as defined by Lundin et al., hazard ratios for prostate cancer for low, moderate and high exposure categories were 1.0 (referent), 3.0 (95% CI 0.9 – 0.7), and 6.6 (95% CI 1.1 – 37.7), or, for $< 1$ year, 1- 4.9, and $\geq 5$ cumulative exposure categories they were 1.0 (referent), 0.4 (95% CI 0.1 – 3.6), and 3.7 (95% CI 1.3 – 10.4), respectively. Lundin et al. discussed the inconsistency of these prostate cancer mortality results and concluded that to further elucidate these associations would require the use of nonfatal cases because of the incompleteness of case ascertainment by using death data only. Finally, Gilliland and Mandel (1993) also observed an association with prostate cancer in their earlier cohort study and, they, too, observed a lowered risk of prostate cancer mortality among the non-exposed (SMR 0.58, 95% CI 0.07 – 2.09) compared to an SMR of 2.03 (95% CI 0.55 – 4.59) for the exposed.

An incidence study of prostate cancer and other cancers in this cohort is underway at the University of Minnesota.

### 3. Other Cancers

Results from Lundin et al should also be added with regard to liver and pancreatic cancer. Using the Minnesota mortality rates, the authors reported SMR estimates (95% CI) for liver cancer of 'not estimatable' (0.0 – 7.6) for the ever definite job exposure group, 0.7 (0.1 – 2.6) for the ever probable/never definite job group, and 0.3 (95% CI 0.0 – 1.8) for the never employed in a PFOA exposure group. For pancreatic cancer, SMRs were 0.9 (95% CI 0.0 – 4.7), 1.0 (95% CI 0.4 – 2.1), and 0.7 (95% CI 0.2 – 16), respectively.

Indeed, the Alexander et al. (2003) and Lundin et al. (2009) studies did not find statistically significant SMR estimates for liver and biliary passages, pancreas, kidney and urinary tract, bronchus, trachea or lung. These results are consistent with the results of the Leonard et al. (2008) study, which are noted in the draft document.

### 4. General Population Case-Cohort Cancer Incidence Study

There is now more than a "little research" (page 4), "limited data" (page 212), or just a "relatively few studies conducted on the general population" (p. 34, third paragraph). Many of these general population studies that have been published were not included in this ATSDR draft review, likely due to the fact they were published after the writers of this document finished their draft.

For example, Eriksen et al. (2009) investigated the incidence of four cancers in relation to plasma levels of PFOA and PFOS among subjects enrolled in a prospective Danish general population cohort study designed to assess diet and health. A total of 57,053 individuals were enrolled from December 1993 through May 1997, aged 50-65 years, and had no previous diagnosis of cancer.

Over a 12 year time period (through June 2006) a total of 713 prostate cancer, 332 bladder cancer, 128 pancreatic cancer, and 67 liver cancer cases were newly diagnosed. Within the same cohort, a random sample of 680 men and 92 women, approximating the gender ratio in the cancer cases, were selected as the comparison group. Plasma samples at the time of initial enrollment were analyzed, in a blind fashion, for PFOA and PFOS concentrations.

For each specific cancer, adjusted incidence rate ratios were calculated for the three upper quartiles of plasma concentration of PFOA and PFOS compared with the lowest quartile (odds ratio = 1.00). Covariates included in the model were specific for each cancer type. Provided below are the adjusted incidence rate ratios and 95% confidence intervals (in parentheses). A trend analysis was also done which considered PFOA and PFOS as continuous variables and examined the increase in PFOA and PFOS concentrations for each increase of 1 ng/mL and 10 ng/mL, respectively.

| | | PFOA | PFOS |
|---|---|---|---|
| Prostate | Q1 | 1.00 (referent | 1.00 (referent) |
| | Q2 | 1.09 (0.78 to 1.53) | 1.35 (0.97 to 1.87) |
| | Q3 | 0.94 (0.67 to 1.32) | 1.31 (0.94 to 1.82) |
| | Q4 | 1.18 (0.84 to 1.65) | 1.38 (0.99 to 1.93) |
| | Trend | 1.03 (0.99 to 1.07) | 1.05 (0.97 to 1.14) |
| Bladder | Q1 | 1.00 (referent) | 1.00 (referent) |
| | Q2 | 0.71 (0.46 to 1.07) | 0.76 (0.50 to 1.16) |
| | Q3 | 0.92 (0.61 to 1.39) | 0.93 (0.61 to 1.41) |
| | Q4 | 0.81 (0.53 to 1.24) | 0.70 (0.46 to 1.07) |
| | Trend | 1.00 (0.95 to 1.05) | 0.93 (0.83 to 1.03) |
| Pancreas | Q1 | 1.00 (referent) | 1.00 (referent) |
| | Q2 | 0.88 (0.49 to 1.57) | 1.02 (0.57 to 1.84) |
| | Q3 | 1.33 (0.74 to 2.38) | 1.24 (0.57 to 2.31) |
| | Q4 | 1.55 (0.85 to 2.80) | 0.91 (0.51 to 1.65) |
| | Trend | 1.03 (0.98 to 1.10) | 0.99 (0.86 to 1.14) |
| Liver | Q1 | 1.00 (referent) | 1.00 (referent) |
| | Q2 | 1.00 (0.44 to 2.23) | 0.62 (0.29 to 1.33) |
| | Q3 | 0.49 (0.22 to 1.09) | 0.72 (0.33 to 1.56) |
| | Q4 | 0.60 (0.26 to 1.37) | 0.59 (0.27 to 1.27) |
| | Trend | 0.95 (0.86 to 1.06) | 0.97 (0.79 to 1.19) |

There were no statistically significant trends in the above data. Odds ratios tended to increase for pancreatic cancer by PFOA quartile and for prostate cancer for PFOS quartiles. On the other hand, odds ratios decreased by quartiles for both PFOS and PFOA for bladder cancer and liver cancer. Eriksen et al. discussed the positive association between PFOS and prostate cancer indicating it was either suggestive of a threshold response or that the different risk for the lowest quartile was due to chance. They felt the latter was more likely because there was no deviation from linearity. Eriksen et al. concluded that their results suggested that, the plasma PFOA and PFOS concentrations in the Danish population are not associated with increased risk of prostate, bladder, pancreatic, or liver caner.

### 5. Humans Exposed Orally

Page 148 says there are no studies of cancer in humans exposed orally to perfluoroalkyl compounds. However, as noted above, 3M's occupational cohorts did have some oral exposure, as did the general population cohort studied by Eriksen (2009).

In addition, studies of cancer rates in localities in which PFOS or PFOA have been present in drinking water are relevant to this discussion. While these studies admittedly are not specific to the exposed population, they are worth noting.

In addition to the Eriksen et al. study, the ATSDR draft document should consider the population cancer incidence study conducted by the Minnesota Department of Health of those Minneapolis and St. Paul metropolitan area communities who had municipal water and private well water PFOA and PFOS concentrations that were likely contributed to by leakage from landfills into the

surrounding aquifers. An ATSDR Public Health Assessment was written for this area ('Perfluorochemical Contamination in Lake Elmo and Oakdale, Washington County, Minnesota).

A random sample of 198 members from three communities (Oakdale, Lake Elmo, and Cottage Grove, Minnesota) was selected for a pilot study to determine their serum PFOA, PFOS, and PFHS concentrations. The overall median concentrations (regardless of municipal or well) were measured at 16 ng/mL (range 1.6 – 177), 41 ng/mL (range 3.2 – 448 ng/mL), and 8.9 ng/mL (range 0.3 – 31.6 ng/mL), respectively, which is approximately 4, 2, and 4 times higher than the median general population's concentrations in the comparable time period. Other perfluoroalkyls (PFBA, PFPeA, PFHxA, and PFBS) were primarily below the limit of quantitation.

As part of their overall investigation in the area, the Minnesota Department of Health also reviewed the cancer incidence of this population through its Minnesota Cancer Surveillance System database. The observed incidence from 1996 – 2004 for eight Washington County and Dakota County communities were tabulated and compared to an expected based on Minneapolis-St. Paul metropolitan cancer incidence rates. For this time period, the observed versus expected liver cancer incidence for Oakdale, Lake Elmo, and Cottage Grove communities were 9 versus 7, 0 versus 3 and 6 versus 7, respectively. For pancreatic cancer, the observed versus expected ratios were 13 versus 16, 5 versus 5, and 16 versus 14, respectively. For bladder cancer, the ratios were 40 versus 39, 5 versus 10, and 39 versus 30. Finally, for prostate cancer the observed versus expected ratios were 132 versus 137, 42 versus 43, and 118 versus 124.

None of the above ratios (i.e., Standardized Incidence Ratios) were statistically significant. The Minnesota Department of Health cautioned that causal inferences could not be derived from these data because the lack of a known latency period, unknown mobility of the community populations, and lack of adjustment for known risk factors and other confounding factors. The Minnesota Department of Health concluded that cancer rates in each of the 8 communities (including the three described above) must be interpreted cautiously, but that the data combined for all communities were virtually identical to the metropolitan area.

ATSDR should also be aware of an unpublished report by Colsher et al. that examined cancer mortality rates in Wood, Jackson, and Mason counties, West Virginia. Wood and Mason counties contain some of the water districts from the C8 Health Project database (Lubeck water district in Wood County and Mason water district in Mason county). Colsher reported no statistically significant cancer rates compared to West Virginia for liver, pancreatic, or bladder cancer. Both Wood and Mason counties had significantly higher prostate cancer rates than West Virginia.

The Ohio Cancer Surveillance System has displayed on its website (see below) prostate cancer incidence rates for areas in Washington County and Meigs County, Ohio that contain the other four C8 Health Project water districts. These are Belpre and Little Hocking water association (Washington County) and Pomeroy and Tupper Plains water districts in Meigs County. None of these water districts, as can be approximated from the census tracts on the website, had prostate cancer incidence

rates above average. See
http://www.odh.ohio.gov/odhPrograms/dis/ociss/profiles.aspx.

## I. Human Studies - Hepatic Effects

The main conclusion on health effects is on p. 11: "For the most part, no significant adverse effects have been identified in these populations, but some potentially adverse changes in clinical tests associated with serum levels of perfluoroalkyl compounds have been reported." The end of this sentence needs to clarify that these reports are "without consistency" and "without serious clinical impairment" or something to that effect. There are a large number of medical surveillance studies (about a dozen), and there has been no consistent pattern of hepatic effects observed over the decades of occupational studies. Nor have hepatic changes been observed in the Emmett study in Ohio/West Virginia.

The discussion of "Hepatic Effects" at page 48 describes Olsen and Zobel (2007) as having assessed 506 employees "who did not take cholesterol-lowering medications at three fluorochemical production plants". ATSDR should mention that analyses were in fact also conducted of individuals who self-reported taking cholesterol-lowering medications. These data are found in the full report on the EPA docket (Olsen et al. 2006, US EPA docket AR226-3678), and are referenced by Olsen and Zobel (2007). They observed no associations for the 46 individuals and the hepatic clinical chemistry measurements.

We suggest ATSDR note the inconsistent results regarding hepatic clinical chemistry found in the Sakr et al. studies. The cross sectional study by Sakr et al. found a modest, statistically significant association between PFOA and GGT, but no association for any other measure of liver function (AST, ALT, or bilirubin). According to the model used, a 1,000 ng/mL increase in PFOA resulted in an approximate 1 mg/dL increase in a 1 IU/L increase in GGT (need to exponentiate the PFOA beta coefficient because model is natural log GGT). In the longitudinal analysis, Sakr et al. found PFOA was associated with declines in bilirubin levels and increased AST levels, but not with GGT, ALT, or alkaline phosphatase. In fact, in the Sakr et al. longitudinal study, a 1,000 ng/mL increase in PFOA was associated with a 0.35 IU/L increase of AST. This is a clinically trivial change and should be noted.

In the discussion of Hepatic Effects in "Oral Route of Exposure" section at page 116, it would seem important to add that several studies of the workforce at 3M's Decatur facility have not reported statistically significant associations with hepatic diseases using a variety of data sources including death certificates and self-reports. See Alexander 2001a, Olsen et al. 2004c, and Grice et al. 2007.

At pages 207-208, the ATSDR draft states obese people may represent a susceptible population based on data from Gilliland and Mandel (1996) as serum ALT and AST activities may have increased because of an interaction of PFOA concentration (measured as total organic fluorine in this study) and obesity. However, this interaction was further studied in subsequent medical surveillance examinations at the 3M Cottage Grove manufacturing site by specifically measuring PFOA (Olsen et al. 2000).

In the Gilliland and Mandel study, the change noticed for ALT associated with a 10,000 ng/mL increase in serum total organic fluorine (proxy for PFOA) for three body mass indices (25, 30, and 35) were -3.0, +28.0, and +59.0 IU/L. Upon three subsequent medical surveillance examination years (1993, 1995, and 1997) among the same group of production employees of the ammonium salt of PFOA, this magnitude of change was not observed.

- In 1993, the changes in ALT at each BMI category (25, 30, and 35) were +2.2 IU/L, +0.9 IU/L, and -0.5 IU/L, respectively.
- In 1995, the change in ALT was +1.5 IU/L, +0.1 IU/L, and -1.2 IU/L, respectively.
- In 1997, the change was +5.3 IU/L, +0.8 IU/L, and -3.7 IU/L, respectively.

Olsen et al. 2000 concluded there was no significant clinical hepatic toxicity associated with PFOA levels measured in this workforce and that PFOA did not appear to modulate hepatic responses to either obesity or alcohol consumption. Limitations of this study included the cross-sectional design for each year and the voluntary participation that ranged between 50 and 70 percent.

## J. Human Studies - Lipid Effects

This ATSDR draft document does not cite the recently published study by Steenland et al. (2009) that analyzed serum PFOA and PFOS concentrations in relation to lipids that were analyzed in the cross-sectional study known as the C8 Health Project. A total of 46,294 residents 18 years of age or older were subjects of this analysis. Adjusting for age, gender, smoking, education, exercise, current alcohol intake, and BMI, Steenland et al. reported the predicted increase in cholesterol from lowest to highest decile for either PFOS or PFOA was 11 – 12 mg/dL. The odds ratios for high cholesterol (defined as $\geq$ 240 mg/dL) by increasing quartile of PFOA were 1.00 (1.21 (95% CI 1.12-1.31), 1.33 (95% CI 1.23-1.43), and 1.40 (95% CI 1.29-1.51) where quartile concentration were 0 – 13.1 ng/mL, 13.2 – 26.5 ng/mL, 26.6 – 66.9 mg/dL, and $\geq$ 67 ng/mL. It should be noted that 99 percent of the general population would be within the first decile (Calafat et al. 2007; Olsen et al. 2008).

Likewise, for PFOS, the adjusted odds ratios were 1.00, 1.14 (95% CI 1.05 – 1.23), 1.28 (95% CI 1.19 – 1.39), and 1.51 (95% CI 1.40 – 1.64) for cutpoints 0 – 13.2 ng/mL, 13.3 – 19.5 ng/mL, 19.6 – 28.0 ng/mL, and $\geq$ 28.1 ng/mL. For PFOS, the concentrations mirror those found in the general population.

Similar trends were reported for LDL (indirect calculation), non-HDL cholesterol, and the ratio of total cholesterol to HDL. Associations were not observed for the apolipoprotein A containing particle, HDL.

None of these analyses, however, appeared to adjust for current use of cholesterol-lowering medications and the fact that the lowest (first) decile has been reported to have a 33 percent increased risk for validated type II diabetes (MacNeill et al. 2009) as well as higher prevalences of self-reported diseases including

atherosclerosis and cerebrovascular disease (see C8 Health Project Website hosted by University of West Virginia).

Restricting the analyses to 10,746 adults who were taking cholesterol-lowering medications, who had a mean cholesterol level of 173 mg/dL compared to 206 mg/dL for those not taking cholesterol medication, Steenland et al. reported a consistent increasing trend in total cholesterol with increasing PFOA (although somewhat attenuated compared with the exposure–response for those not taking medication) but there was no consistent trend for PFOS.

Steenland et al. also analyzed for perfluorononanoic acid (PFNA) and perfluorohexanesulfonate (PFHS) at mean concentrations of 1.6 ng/mL and .1 ng/mL, respectively, and found a similar monotonic increase in cholesterol by increasing decile of each compound. All four of these compounds were correlated with each other.

Steenland et al. acknowledged the perfluorinated compounds did not explain a large portion of the variance in lipids. For total cholesterol, the most important predictors were the established risk factors of age, gender, and body mass index not PFOA or PFOS; although Steenland et al. did not provide what these $R^2$ contributions were.

Steenland et al. also examined the issue of 'reverse causation' because perfluoroalkyl compounds have been shown to bind to beta-lipoproteins (in other words, whether the positive associations observed between PFOS or PFOA and total cholesterol may be due to the fact that higher cholesterol levels result in higher PFOS and PFOA concentrations due to the lipid binding). To address this question, Steenland et al. considered taking cholesterol medication as the explanatory variable that might lead to a decrease in PFOA (response variable). Those individuals who took cholesterol medication did have a significantly lower log PFOA concentration with a modest decline of about 4 percent. There was no difference in PFOS levels between those taking and not taking medications.

Finally, the ATSDR should compare the magnitude of associations regarding lipids and PFOA across the studies. In their occupational studies, Sakr et al. did not report the same magnitude of dose response that Steenland et al. observed. Whereas Sakr et al., in their cross-sectional and longitudinal studies, observed 5 mg/dL and 1 mg/dL increases in total cholesterol associated with a 1000 ng/mL increase in PFOA, respectively, Steenland et al. reported a 10 - 11 mg/dL increase going from 1$^{st}$ decile (approximately 7 ng/mL PFOA) to 10$^{th}$ decile (approximately 200 ng/mL PFOA). If the Steenland et al. analyses were to be extrapolated to the Sakr et al. databases, the occupational studies by Sakr et al. should have seen an approximate increase of 50 mg/dL cholesterol per 1000 ng/mL increase in PFOA rather than 5 mg/dL. They did not.

## K. Clinical Significance of Reported Hepatic and Lipid Associations

From page 47 through page 50, there is a discussion of hepatic and lipid associations reported in the literature. The word "significant" by itself is often used throughout this discussion without clarifying what is meant. What is intended is

appears to be "statistically significant" findings. Therefore, both words should be used throughout this document when statistical significance is intended.

ATSDR should acknowledge that statistical significance does not necessarily imply biological significance – especially with clinical chemistries that are often well within the reference range of the tests and the 'statistical significance' reported may be due to sample size and not necessarily a biological/pathological condition.

Furthermore, the document often uses the word "association" without clarification that it is actually referring to a beta coefficient for PFOA from a regression model, and with no discussion of the magnitude of change. As an example, see the second paragraph on page 49. ATSDR does specifically discuss the 1.06 mg/dL increase in total cholesterol for a 1,000 ng/mL increase in PFOA. However, it then says, "In addition, PFOA was negatively associated with total bilirubin and positively with serum AST activity, but not ALT or GGT." This implied a statistically significant finding; however, no data are presented on the magnitude of the association.

In fact, as previously discussed, in the Sakr et al. cross-sectional study for AST, a 1,000 ng/mL increase in PFOA was associated with a 0.35 IU/L increase of AST. This is a clinically trivial change and that fact should be noted. To rely solely on regression coefficients without expanding what the unit of change of the response variable (Y) is per unit of 'X' (explanatory variable) can be highly misleading – with or without statistical significance – as this example shows with AST.

A similar issue arises where the draft document describes the "modest but statistically significant positive association between PFOA and total cholesterol, LDL, VLDL, and GGT activity." The document should elaborate on what this modest change means. According to the linear model used, a 1,000 ng/mL increase in PFOA resulted in a 4 mg/dL change in total cholesterol, a 2.8 mg/dL change in HDL, a 1 mg/dL increase in VLDL, and a 1 mg/dL increase in GGT (need to exponentiate the PFOA beta coefficient because model is natural log VLDL and natural log GGT). The statistically significant association is irrelevant for the general population, even if it were causal, given that it took a 1,000 ng/mL increase in PFOA to result in such a modest change in the statistical model used by Sakr et al. in their occupational population. General population serum PFOA concentrations are approximately 200 times lower than levels in the Sakr study (Calafat et al. 2007; Olsen et al. 2008).

On page 49, last paragraph, there is a published paper by Costa et al. (2009) that should be reviewed and cited. It is much more informative than what ATSDR currently references for Costa. Costa et al. reported a significant association of total cholesterol and uric acid with serum PFOA concentrations; although no clinical evidence "of any specific trouble or disease has been recorded over the 30 years, and all the biochemical parameters, including liver, kidney and hormonal functions, turned out to be within the reference range." Among the current exposed workers, their mean total cholesterol was 237 mg/dL compared to 206 for the non-exposed current workers. Uric acid was 6.29 mg/dL compared to 5.73 mg/dL, respectively. This difference was apparent in the multiple regression analysis provided where the coefficient for total cholesterol (exposed vs. all comparison) was 21.7 (95% CI 6.83 – 36.6) and 0.50 (95% CI 0.06 – 0.94) for uric acid. Results of a multivariate analysis

that examined individuals (current, former and never exposed) with serum PFOA concentrations measured in the last 6 years resulted in PFOA coefficients of 0.028 (95% CI 0.002 – 0.055) and 0.026 (0.001 – 0.053), respectively. There were also statistically significant regression coefficients (positive) for PFOA with ALT, GGT, and alkaline phosphatase and a negative coefficient for total bilirubin. The exact meaning of these coefficients is not well explained, but they appear to be the result of the natural log of the clinical parameter (response) with the explanatory variable (PFOA in 1000 ng/mL units). If so, the increase of 1000 ng/mL PFOA resulted in a clinically trivial change (no more than an approximate 1 unit difference) in ALT, GGT and alkaline phosphatase.

## L. Cardiovascular Effects

References on page 37 should be updated to reflect the published papers by Leonard et al. (2008) and Sakr et al. (2009) regarding the DuPont Washington Works cohort mortality study and the subanalysis on ischemic heart disease mortality, respectively.

The discussion of "Cardiovascular Effects" at page 46 should include the important fact that, at the 3M Cottage Grove facility, there was no evidence to suggest an increased risk for ischemic heart disease based on the use of external or internal comparison analyses. Also, at the 3M Decatur facility, the considerably lower than expected coronary ischemic heart disease mortality was consistent with that expected from the healthy worker effect.

In their internal analyses, Lundin et al. (2009) reported no increased risk for ischemic heart disease mortality. This information should be added on page 46. Based on PFOA (ammonium salt) exposure characterized by job classification, Lundin et al. calculated hazard ratios for ischemic heart disease mortality for low, moderate and high categorizations of 1.0 (reference), 1.2 (95% CI 0.9 – 1.7), and 0.9 (95% CI 0.4 – 2.1), respectively. Hazard ratios characterized by cumulative exposure years for the following categories, $< 1$, 1 – 4.9, and $\geq 5$ years, were: 1.0 (reference), 1.2 (95% CI 0.9 – 1.8), and 0.8 (95% CI 0.5 – 1.2) based on 138, 42, and 21 deaths, respectively.

The SMRs in Lundin et al. for cerebrovascular disease for the ever definite, ever probable/never definite, and never PFOA job categories were 1.6 (95% CI 0.5 – 3.7), 0.7 (95% CI 0.4 – 1.1), and 0.5 (95% CI 0.3 – 0.8). The observed versus expected number of cerebrovascular deaths for these PFOA job categories were 5 versus 3.1, 17 versus 24.2, and 13 versus 27.1, respectively, resulting in similarly magnified, albeit more imprecise, estimates for the highest exposure category using internal reference analyses.

## M. Renal Effects

The discussion on page 51 regarding renal effects, and on page 55 regarding bladder cancer should also cite to the 90-day POSF inhalation toxicology study conducted by Huntingdon Research for 3M. Final Report, Perfluorooctanesulfonyl Fluoride (POSF; T-7661.1) Toxicity Study by Inhalation Administration to CD Rats for 13 Weeks Followed by a 4 Week Recovery Period, Huntingdon Life Sciences

Ltd., Study No. MIN 313/023622, September 28, 2005. U.S. EPA Docket AR226-3573.

Other references that can be cited on page 51 -- all showing a lack of associations between BUN and creatinine with PFOS or PFOA -- include Olsen et al. (1998, 3M Final Report AR226-0030) and Olsen et al. (1998, 3M Final Report, U.S. EPA docket AR226-0474).

BUN and creatinine data are also provided in the publication by Costa (2009), and the study by Sakr et al. (2006, the cross-sectional study), showing no associations with PFOA concentrations.

On page 124-125, the draft document discusses renal effects in animals. The discussion focuses on BUN, noting an increase in BUN values in rats exposed for 14 weeks and 53 weeks. (Note that Seacat et al. 2003 discussed at page 124 and Thomford 2002b cited on page 125 are reporting on different time points in the same chronic bioassay.) However, there are many potential causes of increased BUN unrelated to the kidney. Given that the kidneys looked normal, changes in BUN could be a result of increased protein catabolism.

On Page 124, paragraph 2 the ATSDR should be aware of the C8 Science Panel report on uric acid which found a modest 5 to 6 mg/dL increase in uric acid from the 1$^{st}$ to 10$^{th}$ deciles in the C8 Health Project data. A weak association was observed for hyperuricemia as well. This report has yet to be published in the scientific literature. See C8 Science Panel Status report: Association of perfluorooctanoic acid (PFOA) and perfluoroctanesulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. January 27, 2009. http://www.c8sciencepanel.org/pdfs/Status_Report_C8_and_uric_acid_Jan2009.pdf. This observation is interesting because uric acid has also been positively associated with PFOA in two occupational studies although specific detailed analyses were sparse (Sakr et al. 2007b; Costa et al. 2009). An important question that remains to be resolved is whether these associations could be attributable to shared organic anion transporters for urate and PFOA.

## N. Gastrointestinal, Hematological and Other Effects

With respect to page 46, regarding gastrointestinal effects, besides gastric ulcers, Grice et al. (2007) also reported on colon polyps, colon cancer, cholecystitis, and liver disease (including cirrhosis and hepatitis). No associations were observed for any of these gastrointestinal effects.

Not mentioned in this paragraph are the numerous gastrointestinal disorders addressed by Olsen et al. (2004) (see also Olsen et al. 2004, 3M Final Report, U.S. EPA docket AR226-0030) in their analysis of health claims data at the 3M Decatur site. Although health claims data cannot provide a definite measure of risk, it is worth reporting the results of this study. The Olsen et al. (2004) published paper on 'episodes of care' (i.e., health claims data) reports only a subset of disorders, but the full 3M report (Olsen et al. 2004, 3M Final Report, U.S. EPA docket AR-226-1030a021) includes health claims data for the following disorders: infectious diseases, cancers and benign growths, endocrine, hematological, psychiatric, neurologic,

ophthalmologic, cardiovascular, pulmonary, ENT (ear, nose and throat), gastrointestinal, urologic, gynecologic and reproductive, pregnancy, dermatologic, musculoskeletal, congenital, perinatal, injury and poisoning, and miscellaneous conditions.

With respect to hematological effects addressed on page 47, although Olsen et al. (1999) did not specify the hematology studied, this information can be ascertained from the 3M Final Report (Olsen et al. 1998, 3M Final Report, U.S. EPA docket AR226-0030) from which the Olsen et al. (1999) paper was taken. These parameters included: hematocrit, hemoglobin, RBCs, MCH, MCHC, MVC, WBC, and platelets.

The draft profile states at page 220 that "Evaluations of other end points [besides liver] seem warranted." The medical surveillance studies have looked at several endpoints besides liver. The liver is the main concern because it is consistently the most sensitive endpoint in animal studies. Similarly, the statement on page 11 that most evaluations have focused on liver, endocrine and lipid effects misses the thorough medical surveillance of occupational groups that has included other endpoints.

## O. Hormone Measurements in Humans

In the discussions on pages 21, 52 and 199, ATSDR needs to consider a 3M Final Report (Olsen et al. 1998 U.S. EPA docket AR226-0030) which supplements data published in the Olsen et al. 1999 paper. In this report, 11 hormones were analyzed in relation to PFOS in 3M workers. These hormones were cortisol, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, 17-alpha hydroxyprogesterone, luteinizing hormone, prolactin, sex hormone binding globulin, free testosterone, bound testosterone, and thyroid stimulating hormone in relation to serum PFOS.

These hormones were assessed in fluorochemical production employees from 3M Antwerp and Decatur manufacturing facility from two time periods: 1995 (N = 178) and 1997 (N = 149). The two plant populations differed by age, body mass index and alcohol consumption. Adjusting for the differences in age, BMI, alcohol consumption, and cigarette smoking in the regression models, no statistically significant associations between PFOS and the hormones were observed, except for estradiol.

With estradiol, a quadratic model provided the best fit of the data and both PFOS terms were significant. Upon residual diagnostics, it was determined that this model was influenced by one employee with the highest PFOS serum level (12.83 μg/mL), an estradiol value of 92 pg/dL, and a high body mass index value (BMI = 33). Exclusion of this employee from the model resulted in a statistically nonsignificant quadratic equation. The variability of the data explained went from 7.6 percent to 2.1 percent upon exclusion of this employee. The model did predict the known positive association between estradiol and body mass index with or without the inclusion of this employee in the model.

At page 51, it should be noted that Olsen et al. (1998) concluded that the results in their study provided reasonable assurance that in this production setting

(i.e., higher exposure than general population) there were no significant hormonal changes associated with the serum PFOA concentrations measured. Also, because the primary hypothesis of the study was whether PFOA increased estradiol and decreased testosterone serum levels in a non-linear fashion, as initially reported by Gilliland (dissertation 1992), the Gilliland models were replicated without any significant associations between PFOA and serum estradiol, free testosterone, or bound testosterone.

Hormone measurements also are available in the papers by Costa (2009) and Sakr (2007b) (i.e., the cross-sectional study). Page 51 says Sakr 2007(b) confirmed the findings of elevated estradiol (positively associated with serum PFOA) reported by Olsen et al. 1998. Sakr et al. (2006, the cross sectional study) reported regression coefficients of 22.3 and 0.6 respectively for estradiol and testosterone in relation to PFOA. That study does not, however, provide specifics regarding units of measurement and relation to PFOA. It is assumed this refers to a 22.3 pg/dL change in PFOA and a 0.6 ng/dL change in testosterone for each 1000 ng/mL change in PFOA. These findings therefore do not necessarily confirm what was reported by Olsen et al. (1998). As stated in the published paper (Olsen et al. 1998), "Because a primary hypothesis of the present study was whether PFOA increased estradiol and decreased testosterone serum levels in a nonlinear fashion, we replicated these prior models with our 1993 and 1995 data. PFOA was not significantly associated with serum estradiol, free testosterone or bound testosterone."

Thyroid Hormones

The ATSDR document cites the Olsen et al. (1999) published paper with respect to thyroid hormones and PFOS. The ATSDR needs to also consider the 3M Final Report (Olsen et al. 1998 U.S. EPA docket AR226-0030) which provides additional supporting data from that study. There are three other papers that have examined thyroid hormone levels in general populations (Inoue et al. 2004; Bloom et al. 2009; Dallaire et al. 2009). Inoue et al. (2004) measured thyroid stimulating hormone (TSH) and free thyroxine in newborn samples from 15 Japanese women and reported no correlation between blood PFOS concentration and thyroid hormones.

Inoue et al. (2004) measured thyroid stimulating hormone (TSH) and free thyroxine in newborn samples from 15 Japanese women and reported no correlation with blood PFOS concentration.

Bloom et al. (2009) analyzed repository serum samples that were collected from thirty-one licensed anglers in New York State for TSH, free thyroxine and 8 perfluoroalkyls: PFOS, PFOA, PFNA, PFHpA, PFDA, PFUnDA, PFHS, and PFOSA. No statistically significant associations were detected for any perfluoroalkyl, or their sum, with TSH or free thyroxine.

Dallaire et al. (2009) measured TSH, free thyroxine, total triiodothyronine, and thyroxine-binding globulin in 623 Inuits along with 41 chemicals in their serum including PFOS. Dallaire et al. used linear regression to calculate the adjusted beta coefficient of these thyroid parameters with PFOA. Both explanatory and response variables were log transformed and adjusted for age, sex, BMI, plasma lipids, cigarettes/day, and education. Dallaire et al. (2009) reported statistically significant

($p < 0.05$) adjusted beta coefficients for TSH (-0.102), free thyroxine (0.014), triidothyronine (-0.030), and at $p < 0.01$ for thyroid-binding globulin (-0.034).

However, Dallaire et al. did not explain the magnitude of change that occurred for each thyroid parameter by unit of PFOS concentration, measured in parts per trillion (pg/mL). For example, to understand the clinically trivial change observed based on the statistically significant regression coefficients, the lowest (480 pg/mL = 0.480 ng/mL) and highest (470,000 pg/mL = 470 ng/mL) serum PFOS concentrations can be incorporated into the Dallaire et al. linear model. The adjusted absolute change in each thyroid parameter, based on the change from lowest to highest PFOS concentrations, can be estimated to be -0.27 mIU/L for TSH, 0.11 pmol/L for free thyroxine, and -0.017 nmol/L for triiodothyronine which are very small absolute changes within the reference ranges of these parameters as listed in the Dalliare et al. paper. Such a small absolute change could be expected given the fact that most subjects had thyroid measurements well within reference ranges (TSH 95%, free thyroxine 96.5%, and total triiodothyronine 99.2%, thyroid-biding globulin 86.3%).

## P. Diabetes

The ATSDR document does not cite the recent study by MacNeil et al. (2009) that analyzed the C8 Health Project database for type II diabetes and serum glucose concentrations. The analysis was restricted to adults $\geq$ 20 years of age (N = 54,468). A prevalence case-control study design was used to examine the relationship between serum PFOA decile exposure and type II diabetes. Cases were either self-reported or restricted to those with medical validation. Deciles were < 7.9 mg/dl (reference group), 8.0 – 11.6, 11.7 – 15.6, 15.7 – 20.8, 20.9-28.0, 28.1-39.4, 39.5-57.5, 57.6-89.7, 89.8-191.2, and >192 ng/mL. Odds ratios were adjusted for age, BMI, gender, family history, race, use of cholesterol-lowering medications, and use of blood-pressure-lowering medications.

Adjusted odds ratios for validated type II diabetes with no restriction on length of residence were for the deciles (95% CI in parenthesis): **1.00** (reference), **0.74** (0.62-0.88), **0.67** (0.56-0.80), **0.62** (0.52-0.74), **0.66** (0.56-0.79), **0.69** (0.58-0.82), **0.73** (0.61-0.86), **0.68** (0.58-0.81), **0.64** (0.54-0.76), **0.62** (0.53-0.74). These odds ratios were comparable to those calculated for validated type II diabetes among subjects residing in a water district of interest for at least 20 years.

The authors considered these adjusted odds ratios to show no clear trends of diabetes with increasing decile of serum PFOA. What the authors did not ask themselves (in the paper) is why did the lowest (first) decile have an approximate 30% increased risk of type II diabetes compared to the other deciles?

The authors also investigated the median fasting serum glucose levels in this population, excluding type II diabetics. There was no consistent pattern between fasting serum glucose serum PFOA concentrations with median levels by PFOA deciles at 94, 95, 95, 93, 94, 92, 92, 92, 92, and 93 mg/dL. The authors concluded that these cross-sectional data provide some information that argues against the hypothesis that PFOA is associated with type II diabetes.

The ATSDR should also be knowledgeable about the diabetes mortality results reported by Lundin et al. (2009) in their cohort mortality study of 3M Cottage Grove workers. Based on the job classifications of ever definite, ever probable/never definite, and nonexposed to PFOA production job categories, Lundin et al. reported SMR estimates for diabetes of 0.0 (95% CI 0.0 – 2.4), 2.0 (1.2 – 3.2), and 0.5 (0.2 – 1.1) based on 0 observed versus 1.5 expected, 18 versus 8.9 expected, and 5 versus 9.6 expected deaths, respectively. Using a time-dependent Cox regression analysis, hazard ratios based on exposure characterized by a weighted cumulative exposure years analysis, resulted in hazard ratios of < 1 year (reference), 1 – 4.9 years 1.3 (0.4 – 4.1), and $\geq$ 5 years 1.3 (95% CI 0.6 – 3.1).

**Q. Cancer - Animal Data**

At page 5, the discussion of animal tumors should address the fact that the tumors observed in both the PFOS and PFOA studies were benign. While the animal study results are properly referred to as "tumors," and not cancer, the next sentence refers to the possibility of cancer in humans. There is no evidence of an increase in malignant tumors in the animal studies. This discussion should also note that none of the tumors types seen in the animals have been observed in the human studies, including those with high exposure under occupational settings.

Page 21 refers to thyroid follicular cell adenoma in the PFOS dietary bioassay in rats. The apparent increase in those tumors occurred only in the males in the highest dietary dose group that were dosed for just one-year, not in the males dosed continuously for up to two years. (These males were given PFOS-containing diet for one year and then switched to control diet through termination of the study.) The study pathologists concluded that the increased incidence of thyroid follicular cell adenoma in these males dosed with 20 μg potassium PFOS/g diet for one year was a chance occurrence.

Page 21 states that a mode of action has not been proposed for the PFOS tumors. That is incorrect. See the discussion in the mode of action comments below regarding PPARα activation by PFOS.

At page 21, the draft says EPA has encouraged a cancer risk assessment of each of the PFOA-induced tumors where data permit. However, ATSDR should appreciate that there is only one PFOA bioassay that used multiple doses (the 3M study), and that study found only testicular Leydig cell tumors, which rarely occur in humans. Benchmark doses have been calculated for the Leydig cell tumors (see Butenhoff et al. 2004), and it is clear that an increase in tumor incidence is not the most sensitive endpoint.

At pages 29-30 and 148, the draft document cites an increase in the incidence of mammary fibroadenoma in female rats in the 3M ammonium PFOA (Sibinski et al. 1983) bioassay. This is not correct based on either the discussion in the original study report or a Pathology Working Group review of the study. Page 29 should distinguish between statistically-significant findings and those that are biologically or toxicologically significant. The study director did not consider the increased incidence of fibroadenoma of the female mammary gland to be treatment-related in that is was within the range of control values when assessed historically for the strain,

and mammary gland carcinoma and adenoma was only found in controls. This study was subsequently reviewed by a Pathology Working Group which found no association of treatment with increased mammary tumor incidence among the female rats of the study. See Pathology Peer Review and Pathology Working Group Review of Mammary Glands from a Chronic Feeding Study in Rats with PFOA, Experimental Pathology Laboratories, sponsored by DuPont Haskell Laboratory, 2005, U.S. EPA Docket AR226-2723. The latter review is currently being drafted as a manuscript for publication.

Regarding page 136, Biegel et al. (2001) reported increased Leydig cell hyperplasia and adenoma in a 2-year PFOA bioassay, and this observation was consistent with the findings of the 3M (1983) study. The tubular hyperplasia of the ovaries was reviewed by Dr. Steven Frame (DuPont) and Dr. Peter Mann (EPL), and their report is on the EPA docket. FC-143: Two Year Oral Toxicity - Oncogenicity Study in Rats Peer Review of Ovaries, Peter C. Mann (Experimental Pathology Laboratories, Inc.) and Steven R. Frame (DuPont, Haskell Laboratory for Health and Environmental Science), 2004, U.S. EPA Docket AR226-1921. There were no statistically-significant increases in the incidences of gonadal stromal hyperplasia and adenoma in ammonium PFOA treated females as compared to controls when evaluated for total hyperplasia, adenoma, and hyperplasia and adenoma combined. Lesion grade scores were statistically-significantly higher in the highest dietary-dose group (300 μg/g diet), but more adenoma occurred in controls than in treated groups.

At page 115, regarding Seacat et al. (2003), the report notes that dosing with 1.3-1.6 mg/kg/day for 14 weeks resulted in a significant increase (45%) in segmented neutrophiles and states, "the biological significance of this finding was not discussed by the investigators". Although the investigators did not discuss the potential toxicological significance of the finding of a statistically-significant increase in segmented neutrophiles in male rats after 14 weeks of dosing at the highest dietary dose of potassium PFOS (20 μg/g diet), the difference between control males (1.1 x $10^3$ cells/μL) and treated males from the highest dose group (1.6 x $10^3$ cells/μL) could reflect increased stress or inflammation.

With regard to the discussion of the PFOS bioassay on page 149, the occurrence of a hepatocellular carcinoma in a high-dose female was considered an incidental finding that was within the bounds of historical control data.

At page 31, the document references the PFOS bioassay and the LOAEL for cystic hepatocellular degeneration. It is important to note that cystic degeneration observed in livers is of unlikely relevance to humans. See Karbe and Kirwin (2002) Toxicologic Pathology 30, 216-227: "The induction of cystic degeneration of the liver in laboratory rats by a test compound has no direct implication for the risk in humans, because such a lesion does not appear to exist in man: Human Ito cells do not seem capable of forming the lesion 'cystic degeneration' as observed in rats." Furthermore, there was a low incidence of cystic degeneration occurring in the PFOS bioassay: 1 out of 55 in the low dose female group; 1 out of 55 in the mid-dose female group; 2 out of 55 in the mid-high dose female group; and 4 out of 65 in the high dose female group.

On page 149, the draft document mentions a study in trout. We question the relevance of the trout as a model for evaluating human health and wonder why this study would be included in the review.

## R. Genotoxicity Testing

Regarding page 161, a number of mutagenicity studies appear missing for PFOA. These were reviewed in Kennedy et al. (2004).

At page 160, the draft refers to DNA strand breaks in HepG2 cells caused by PFOA, likely caused via reactive oxygen species. Bjork and Wallace (2009) have shown that primary (normal) human liver show damage at 200 μM PFOA, while HepG2 cells seem to tolerate that exposure. If ATSDR is going to refer to such HepG2 studies, the document should also note that the concentrations employed in the HepG2 studies have been quite high relative to what would be expected to occur in the environment, and these concentrations reflect cell-culture conditions.

## S. Grouping of Substances in Table

The draft document discusses all of the substances together. While there is some benefit to that, 3M suggests ATSDR add cautionary language that given the stark differences in databases and the properties of the various compounds, one cannot generalize between compounds. In particular, Table 3.5 and Figure 3.5 group together the tabulations of LOAELs and NOAELs for multiple compounds. The Table and Figure would be more useful disaggregated given the dissimilarities of the compounds.

## T. Non-Adverse Liver Effects

With regard to the discussion of Seacat et al. (2003) at page 120, ATSDR should be aware of the U.S. EPA Health Effects Division guidance document, which states that it is common with hepatocellular hypertrophy to get some increase in ALT or AST with no evidence of hepatic injury, therefore increases should not be considered adverse until they are at least 2-fold to 3-fold greater than control levels. (U.S. EPA HED 2002) and more than one marker enzyme shows elevation.

The discussion of the PFOA 3M bioassay at the bottom of page 29 refers to serum tranaminases, lumping together ALT and AST. The increases in AST were not consistent across time points and were not clinically significant. Details are provided on page 119, but the text still does not address the magnitude of the change.

## U. Acute Effects

There is an acute inhalation study with PFOS that should be added to pages 15 and 30. See An Acute Inhalation Toxicity Study of T-2306 CoC in the Rat, Bio/dynamics, Inc., 1979, U.S. EPA Docket AR226-0954.

On page 27, the discussion regarding PFOA inhalation is missing the bridging inhalation study by Hinderliter et al. (2006).

At page 150, the draft omits PFOS dermal data that has been submitted to the EPA docket. See:

- Final Report, Primary Dermal Irritation/Corrosion Study of T-5898 in Rabbits (lithium perfluorooctane sulfonate), Hazelton Wisconsin, U.S. EPA Docket AR226-0325;

- Primary Dermal Irritation / Corrosion Study of T-6684 in Rabbits (OECD Guidelines), Corning Hazleton, Inc. (didecyldimethylammonium salt of perfluorooctanesulfonate), U.S. EPA Docket AR226-0321;

- Dermal Absorption and Intravenous Pharmacokinetic Studies in Rabbits, U.S. EPA Docket AR226-0009;

- Single-Dose Dermal Absorption/Toxicity Study of T-6049 in Rabbits, 3M Environmental Laboratory, U.S. EPA Docket AR226-0011;

- Final Report - Analytical Study, Single-Dose Dermal Absorption / Toxicity Study of T-6053 in Rabbits, 3M Environmental Laboratory, U.S. EPA Docket AR226-0158;

- Draft Report, 5-Daily Dose Dermal Absorption / Toxicity Study of T-6684 in Rabbits, Covance Labs, Bibliography only, U.S. EPA Docket AR226-0327;

- Final Report, 5-Daily Dose Dermal Absorption/Toxicity Pharmacokinetic Study of T-6684 in Rabbits, Covance Laboratory (didecyldimethyl ammonium salt of PFOS), U.S. EPA Docket AR226-0655.

At page 160, the draft seems to omit a number of IP dosing studies. (Alsarra et al., 2006; Austin et al., 2003; Cheng and Klaassen, 2008; Goecke-Flora and Reo, 1996; Goecke et al., 1992; Harrison et al., 1988; Ikeda et al., 1985; Kudo et al., 1998; Kudo et al., 2001; Liu et al., 2008; Powers and Aust, 1986; Reo and Adinehzadeh, 2000; Reo et al., 1994; Takagi et al., 1991; Taylor et al., 2002; Van Rafelghem et al., 1987; Van Rafelghem et al., 1988; Ylinen and Auriola, 1990; Ylinen et al., 1989)

## V. Monkey Studies

On page 16, the last sentence of the first full paragraph should say that the effect was believed to be associated *in part* with significant mitochondrial proliferation. The publication does not say that it was due entirely to mitochondrial proliferation. Similarly, with respect to the end of the first paragraph on page 29, Butenhoff et al. (2002) did not fully attribute increased liver weight in monkeys to mitochondrial proliferation, but they did suggest that this may contribute, at least in part, to the increased liver weight.

Also on page 29, the Butenhoff et al. (2004) paper on PK in cynomolgus monkeys states that steady state serum PFOA concentrations were attained within 4

weeks, although Butenhoff et al. (2002) indicated that steady state was achieved by 6 weeks. The 2004 paper represents a more complete analysis of the pharmacokinetic data. (Butenhoff et al., 2002; Butenhoff et al., 2004).

On page 20, the bottom paragraph should note that serum was also analyzed for estrone and estriol with no effect in the cynomolgus monkey study for PFOA. (Butenhoff et al., 2002).

On page 55, Seacat et al. (2002) should be added.

On page 119, the top paragraph contains an error in stating the effects of PFOA treatment on triglycerides in monkeys from the Butenhoff et al. (2002) study. Triglycerides were NOT increased in the high-dose group on days 31, 63, and 91. There is an error in the first sentence of the results section for "Clinical Pathology" in the Butenhoff et al. (2002) paper. The increased triglycerides for the 10 mg/kg dose group are ascribed to the 30/20 mg/kg dose group instead of the 10 mg/kg dose group. The third paragraph correctly describes the triglycerides data for the 30/20 mg/kg dose group. They were increased in this group relative to time-matched controls on days 31 and 182, but were increased only on day 31 based on the pre-study baseline within-group mean value. Mean triglycerides in the mid-dose group (10 mg/kg/d) were increased on days 31, 63, and 91 relative to the within-group pre-treatment mean, and levels were also increased relative to time-matched controls on day 91. The mid-dose group had a statistically-significantly higher within-group mean than the control group when measured pre-treatment. Considering inter-individual variability and the lack of a consistent dose-dependent effect, these triglyceride changes were not convincingly treatment-related.

On page 121, baseline HDL levels were not obtained for the PFOS monkey study described in the first paragraph. The decrease in mean group HDL levels in mid-dose females resulted in values for two female monkeys being slightly below the reference range. These studies must be assessed by looking at within group changes over time as well as comparison to the control group. Because of the diversity of the monkeys with respect to individual values, within-group changes are most meaningful.

On page 137, regarding the study described in the first paragraph, cholesterol was significantly reduced in monkeys given 0.75 mg/kg. That is likely the reason that estradiol was reduced as well. In other words, this effect on estradiol is an overall effect on steroid synthesis.

## W. Immune Effects

On page 131, the description of the Yang et al. study needs to note the strain and mode of administration, as both strain and mode of administration may affect immunological response.

On pages 131-133, the discussion is missing PFOS papers on immune effects, which have shown suppression of adaptive immunity in mice and enhancement of innate immunity in mice. Both of these outcomes were attenuated by knocking out PPARα, and the studies showed species and strain differences. The question remains

as to whether the effects noted are secondary to other changes, for example, PPARα-mediated liver effects. The following chart describes all eight studies on immune effects:

Immune Effect Studies on PFOS

| **Study** | **Species strain** | **Sex** | **Duration** | **Admin.** | **Dose µg/g** diet | **Dose mg/kg** body weight | **Serum PFOS µg/mL** | **Outcomes** | **NOAEL mg/kg** | **NOAEL µg/mL** |
|---|---|---|---|---|---|---|---|---|---|---|
| Lefebvre (2008) | Rat/SD | M & F | 28 d | Diet | 2 - 100 | 0.14 - 7.58 | 0.95 - 43 | Changes in immune parameters did not manifest as functional alterations in response to immune challenge with Keyhole Limpet Hemocyanin and may be secondary to hepatic-mediated effects | <0.15 liver weight; | <1.5 liver weight; |
| Kiel (2008) | Mouse B6C3F1 | Pups | GD 1 - 17 | Gavage | | 0.1 - 5.0 | | Decreased NK-cell activity, IgM production, and lymphocyte subpopulations in offspring at 8 weeks postnatal. Liver weight increased in males at 4 weeks. | 0.1 | |
| Peden-Adams (2008) | Mouse B6C3F1 | M & F | 28 d | Gavage | | 0.000166 - 0.166 | 0.018 - 0.666 | Increased NK-cell activity and plasma lysozyme activity; changes in thymic and/or splenic lymphocyte subpopulations; decreased SRBC-specific IgM at lowest dose. | 0.000166 | 0.018 |
| Qazi (2009a) | Mouse C57BL/6 | M | 10 d | Diet | 10 & 200 | 1.6 - 32 | | Lymphopenia; decreased macrophages in bone marrow but not spleen and peritoneum; increased release of TNFα and IL-6 from bone marrow and peritoneal macrophages (not splenic macrophages); enhanced innate immunity | 1.6 | |
| Qazi (2009b) | Mouse C57BL/6; Sv/129 | M | 10d | Diet | 10 - 200 | 1.6 - 32 | 51 -340 | Liver hypertrophy as most sensitive endpoint. Decreased cellularity of thymus and spleen. Histological alterations in thymus. PPARα plays a role, although extent of this remains to be determined. | <1.6 liver; 8 immune | <51 liver; 97 immune |
| Zheng (2009) | Mouse C57BL/6 | M | 7 d | Gavage | | 5 - 40 | 110 - 338 | Stress (increased corticosterone) at ≥20. Decreased body weight, spleen weight, thymus weight, splenic and thymic cellularity, B-cell proliferation, and NK activity at ≥20. Increased liver weight at ≥5. Decreased SRBC-specific IgM and proliferation of T cells in spleen at ≥5. | <5 | <110 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dong (2009) | Mouse C57BL/6 | M | 60 d | Gavage | | 0.0083 - 2.08 | 0.674 - 121 | Decreased Body weight, thymus weight, spleen weight, splenic and thymic cellularity at ≥0.42. Decreased kidney weight, increased corticosterone (stress), NK-cell activity, and decreased T-cell proliferation in spleen at ≥0.83. Increased liver weight and decreased SRBC-specific IgM at ≥0.083 (7.1 ppm in serum) | 0.0083 | 0.674 |
| Qazi (2009c) | Mouse B6C3F1 | M | 28 d | Diet | 1.56 | 0.25 | 11 | Increased liver weight and decreased body weight at 0.25 (11 ppm in serum). No effect on splenic and thymic weights, in vivo SRBC-specific IgM and IgG, total plasma cells in spleen and thymus, total circulating plasma leukocytes, PFC assay, and hemoagglutination assay. | <0.25 LW & BW; 0.25 immune | <11 LW & BW; 11 immune |

## X. Mode of Action

On page 15, in the first full paragraph, the events initiated by activation of PPARα in rodents include suppression of apoptosis and increased hyperplasia. (Klaunig et al. 2003).

On page 16, the first full paragraph appears to refer to a study by Yang et al. (2002) (we assume this is the study referred to using PPARα-null mice) used C57Bl/6 mice as their "control" for Sv/129 PPAR-alpha-null mice. This raises questions as to the significance of the observation relative to liver weight in PPAR-alpha-null mice given PFOA in their diet. (Yang et al., 2002). Thus, we question the conclusion also reported on pages 116 and 117. The Yang study is also discussed on page 28, in the first paragraph on PFOA oral exposure.

Regarding the bottom paragraph on page 16 and the discussion on pages 120 and 121: Note that eosinophilic granules were observed in the liver of rats given PFOS in their diet for one year or longer in the two-year PFOS bioassay (as indicated on page 121 of the draft document). This observation provides reasonable microscopic evidence of an increase in peroxisomes. The statement on page 121 that PFOS did not induce peroxisome proliferation thus may not be completely accurate.

Other dietary studies with PFOS have also shown evidence for a PPARα mode of action. For example, ATSDR should reference Shipley et al., 2004; Sohlenius et al., 1993; Takacs and Abbott, 2007; Vanden Heuvel et al., 2006; and Wolf et al., 2008, showing PPARα activation with PFOS. Curran et al. 2008 showed PPARα activation in rodents in a 28-day dietary exposure to PFOS. See also Final Report, 104-week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS: T-6295) in Rats, Covance Laboratories Inc., 2002, U.S. EPA Docket AR226-1051a. Additional unpublished studies by Dr. Cliff Elcombe at CXR addressing this issue are available on the EPA docket. See 3M's Submission to U.S. EPA Docket AR-226, dated February 20, 2008.

On page 195, regarding the statement in the top paragraph that "The effects on peroxisome fatty acid [beta]-oxidation did not seem to be receptor-mediated since PPAR[alpha] mRNA expression was not affected." This statement does not make sense. PPAR-alpha agonists activate the receptor which turns on the peroxisome proliferator response element (PPRE), a set of genes responsive to activation of PPAR-alpha. The activation is the binding of activator ligand to the receptor, recruitment of cofactors and formation of the heterodimer with the RXR nuclear receptor. Induction of mRNA for PPAR-alpha nuclear receptor is not required.

Also, the next sentence on page 195 refers to a "typical" peroxisome proliferators. The meaning of "typical" peroxisome proliferator is not clear. There is cross-talk between nuclear receptors, and, with the exclusion a few "pure" PPAR-alpha agonists, such as WY-14643, many peroxisome proliferators may also activate, directly or indirectly, other nuclear receptors. ATSDR should evaluate all the evidence for a PPAR-alpha mode of action for PFOS, not simply the Hu paper. See also 3M's comment on page 16 of the draft ATSDR document. Based on several lines of evidence, PFOS is a "peroxisome proliferator." The Hu paper looked at a very limited sample from a specific time point.

On page 17, the draft document notes that increases in peroxisome activity are related not to carbon chain *per se* but to differential accumulation in the liver as carbon length increases. However, *in vitro* studies show differences in potency of the different chain lengths. See Bjork and Wallace (2009) study of primary rat and human hepatocytes; and Wolf et al. 2008 Toxicol Sci 106, 162-171.

On page 122, regarding the discussion in the second full paragraph, there is a 90-day study report with PFBA that provides evidence for PPARα mode of action. See the study appendices. Van Otterdijk, F.M., Repeated Dose 90-Day Oral toxicity study with MTDID 8391 [PFBA] by Daily Gavage in the Rat Followed by a 3-week Recovery Period. NOTOX BV Laboratory, December 21, 2007, in 3M's Submission of Perfluorobutane Carboxylate studies to U.S. EPA Docket AR-226, dated July 8, 2008.

On page 129, regarding the first paragraph of the body weight effects discussion: The pair-feeding control data suggest that reduced feed consumption is responsible, at least in part, for body-weight decrease in the Pastoor et al. (1987) study. Because PPARα activation upregulates burning of fat, decreased fat and weight would be expected.

On page 195, regarding the bottom of the top paragraph, relative to Starkov and Wallace (2002), PFOS and PFOA were non-specific, non-protonophoric, and weak uncouplers of oxidative phosphorylation in isolated mitochondria. Uncoupling was due to a surfactant effect on mitochondrial membranes.

## Y. Developmental Effects in Animals

At page 12, the paragraph at the top should include a discussion of what the study found relative to birth weight and gestational age.

With respect to the discussion on pages 18 and 19, 136 and 142-143, please note that the dose used in the study which the authors are referring to relative to mammary gland differentiation was 5 mg/kg. (White et al. 2007; White et al. 2009). This dose level actually affected viability of the offspring in a study by Lau et al. (2006). Thus, this finding may have little real-world relevance.

On page 19, the draft states that serum PFHxS levels were not available. Those data appear in Butenhoff et al. (2009a).

On page 19, the middle paragraph should take the Loveless, et al. paper into account.

At page 18, the first full paragraph omits the developmental neurotoxicity study conducted with PFOS. (Butenhoff et al. 2009b). Page 133, the bottom of the page under neurological effects, also omits the PFOS developmental neurotoxicity study (Butenhoff et al. 2009b), as well as the functional observation batteries done with PFBA in the 28-day and 90-day studies (docket), PFHxS in the published study (Butenhoff et al. 2009a), and PFBS in the published 90-day study (Lieder et al. 2009). (Butenhoff et al., 2009a; Butenhoff et al., 2009b; Lieder et al., 2009a).

On page 26, the 28-d and 90-d studies with PFBA included a functional observational battery (FOB) and also included such a battery of functional tests for PFOA-exposed animals.

Also on page 26, in giving the NOAEL for the PFBA 90-day study, it would be useful to give the corresponding serum level in males (14,000 ng/mL serum; 3,000 ng/mL liver).

On page 28, there is reference to a "serious" LOAEL. This term has not been explained at this point in the document.

At page 30, the second paragraph discussing PFOS incorrectly states that "two 2-generation" studies were performed. Only one 2-generation study was conducted with PFOS, the others were 1-generation studies. (Luebker et al. 2005a; Luebker et al. 2005b). Similarly, on page 127, the study mentioned in the first paragraph by Luebker et al. (2005b) was a one-generation study, not a two-generation study.

At the top of page 31, the draft states that maternal serum levels were not available for Lau et al. (2003) study. Thibodeaux et al. (2003), Figure 3, presented maternal serum levels of PFOS for the pups evaluated in the Lau et al. study.

On page 113, the discussion misses the observation of enlarged right atrium was observed in fetal rats and mice by Thibodeaux et al. (2003).

At page 144, the teratology discussion omits studies by Case et al., 2001; Lau et al., 2004; Staples, 1985; Staples et al., 1984.

At page 145, regarding the paragraph at the top: The eye-opening delay was slight and could have been related to body weight.

At page 145, regarding the middle of the last full paragraph from the bottom: the cross-foster study has demonstrated that *in utero* exposure alone was sufficient to produce effects observed in neonates, lactational and *in utero* exposure augmented effect on weight gain.

At page 145, the draft combines a discussion of pre-natal and post-natal development. The draft would be clearer if pre-natal and post-natal development were discussed as separate topics.

At page 147, regarding the discussion in the second paragraph: Because of the rapid elimination of PFBA in mice (Chang et al., 2008a), the maternal serum PFBA reported is at a point after significant elimination. AUC would be a better measure. (Chang et al., 2008a)

On page 171, the discussion at the top omits several studies, including Monroy et al. (2008), Luebker et al. (2005a,b), Lau et al. (2003; 2006), Thibodeaux et al. (2003), Das et al. (2008), and Butenhoff et al. (2009a,b).

At page 172, the discussion at the top omits a study by Kuklenyik, which analyzed milk samples related to Luebker et al. studies. In addition, Luebker et al. provides indirect evidence for transfer through milk from the cross-foster study. (Kuklenyik et al., 2004; Luebker et al., 2005a).

## Z. Thyroid Hormones in Animal Studies

Also at line 6 of page 127, a reduction in "FT4" is noted from the study by Thibodeaux et al. (2003). However, it should be noted that Thibodeaux et al. (2003) employed an analog method for the measurement of FT4. Chang et al. (2007) have since shown that this method results in negative bias and that a method based on equilibrium dialysis of serum should be used. In fact, this equilibrium dialysis method was also used by Seacat et al., (2002) and Luebker et al. (2005a).

Chang et al. (2008b) also explored thyroid hormone status in rats. The end of this paragraph notes "the clinical relevance of the lowered TT3 values was not apparent." There probably is no clinical relevance; however, T3 would be expected to be displaced more readily than T4 due to decreased binding affinity for TTR and TBG, and this observation may relate to binding competition with PFOS. (Chang et al., 2008b; Chang et al., 2007; Luebker et al., 2005b; Seacat et al., 2002).

Also, the reduction in FT4 is mentioned on page 145. Chang et al. have shown that this would have given an artificially low reading and that a method based on equilibrium dialysis should be used. (Chang et al., 2007).

## AA. Pharmacokinetics

At pages 23 and 25, the draft incorrectly indicates that no pharmacokinetic models for humans have been developed. Dr. Harvey Clewell of the Hamner Institutes is developing such a human model under an EPA STAR grant, and this model has been used to develop a drinking water exposure level for PFOA (Tardiff et al. (2009).

At page 23, the paragraph at the bottom makes assumptions about the time to reach steady state that are based on a simple compartmental model. In fact, modeling suggests that a simple compartmental model is not adequate. Therefore, these assumptions are not especially valid or useful. This is illustrated on page 24, where steady state serum PFOA concentrations were reached in monkeys within 4 weeks in all treated groups as opposed to 90 days, as estimated by assumptions in this paragraph (Butenhoff et al., 2004). Also the draft should note that human general population blood levels are falling, not increasing, for PFOS, PFHxS and PFOA.

On page 25, contrary to what is stated at the top of the page, structure activity relationships for elimination rates in humans have been explored for PFBA, PFOA, PFBS, PFHxS, and PFOS. See Chang et al., 2008a; Olsen et al., 2007; Olsen et al., 2009).

At page 164, the first paragraph under 3.4.2.2 should note that Ehresman et al. demonstrated that PFBS, PFHxS, PFOS, and PFOA do not associate with red blood cells by washing cells before processing for analysis. (Ehresman et al., 2007).

Also at page 164, regarding the bottom paragraph, the findings of Vanden Heuvel et al. (1992) are questionable because it is difficult to envision how covalent binding would occur without metabolic activation. See also Kuslikis et al. (1992) Kuslikis, B.I., Vanden Heuvel, J.P. and Peterson, R.E. (1992) Lack of evidence for perfluorodecanoyl- or perfluorooctanoyl-coenzyme A formation in male and female rats. J Biochem Toxicol 7, 25-29.

Regarding the discussion at the top of page 165, PFBS was found only to bind to albumin, whereas PFHxS, PFOS, and PFOA were found to have the potential to bind to other human serum binding proteins, in isolation. See Kerstner-Wood, Protein Binding of Perfluorohexane Sulfonate, Perfluorooctane Sulfonate and Perfluorooctanoate to Plasma (Human, Rat, and Monkey), and Various Human-Derived Plasma Protein Fractions, SRI, U.S. EPA docket AR226-1354.

At page 166, the draft uses PFOA female rat data without discussing the time of measurement or any averaging such as an AUC calculation. Any use of the female rat data for PFOA must bear in mind the rapid clearance and consider when serum concentrations were measured.

Regarding the middle paragraph on page 167: There are data on relative distribution of PFHxS, PFBS, and PFBA between serum and liver. Also, the draft omits early radio-labeled absorption and distribution studies for PFOS that have been submitted to the EPA docket, including a study that looked at tissue distribution of PFOS 89 days after dosing. Johnson, JD, and Gibson, SJ, Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Rats after a Single Intravenous Dose of FC-95-14C, Riker Laboratories, Inc., 1979, U.S. EPA Docket AR226-0006; Absorption of FC-95-14C in Rats after a Single Oral Dose, Riker Laboratories, Inc., AR-226-0007.

At page 173, discussion in the last paragraph should specifically identify compounds and not use generalizations such as "Perfluoroalkyls are secreted in bile…" This incorrectly assumes data exist for all "perfluoroalkyls" to demonstrate this. Also, the discussion omits studies by Chang et al. (2008), Olsen et l. (2009) (Chang et al., 2008a; Johnson et al., 1984; Olsen et al., 2009).

Also at the bottom of page 173, as well as on page 192, the draft document omits transporter papers published by Katakura et al., 2007; Kobayashi et al., 2002; Kudo and Kawashima, 2003; Nakagawa et al., 2008; Nakagawa et al., 2009; and Yang et al., 2009. In addition, a paper by Weaver et al. has recently been accepted by Toxicological Sciences and characterizes the renal transport of a series of perfluorinated carboxylates.

At page 174, the middle of the page states "…they are based on evaluations of populations of limited size in relatively few studies." The human worker studies involved a larger number of subjects (26, 24 male and 2 female**)** than the published lab animal studies (3 to 6 subjects have been used for mouse, rat, and monkey pharmacokinetic studies).

Table 3.8 starting on page 175 refers to IV studies and lists them as having a duration of 1 day. It does not appear accurate to suggest a 1-day exposure duration for an IV study; the IV studies involve a single injection, and then the animals are followed for some period of time certain after injection.

The bottom of page 192 notes the biliary secretion rates of PFOA are similar in male and female rats when renal excretion is blocked by ligation of the kidneys. The same is true for PFOS as well. Also, the discussion omits Johnson et al. (1984).

**BB. PFHxS Data**

At the bottom of page 18 to the top of page 19, the draft states that PFHxS serum levels were not available in a study. The PFHxS OECD 422 study includes serum concentration data for PFHxS. (Butenhoff et al., 2009a)

On page 26, in the paragraph discussing PFHxS, the correct current citation for the study is Butenhoff et al. (2009a).

At pages 162-163, the draft omits data on oral dosing for PFHxS, which is available (see Butenhoff et al. 2009a).

The following study is available in the EPA Docket AR-226, and should be cited as additional references for PFHS data (see pages 25-26, 122):

- A Pharmacokinetic Study of Potassium Perfluorohexanesulfonate in the Cynomolgus Monkey, SRI, U.S. EPA Docket AR226-1361

**CC. PFBS Data**

On page 26, bottom paragraph, to the top paragraph of page 27, the discussion is incomplete and omits 90-day and 2-generation studies on PFBS. (Lieder et al., 2009a; Lieder et al., 2009b).

At page 163, the draft omits oral data on PFBS (see Olsen et al. paper).

At pages 113, 114, 115, and 155, the draft omits the 90-day PFBS study. (Lieder et al., 2009a)

At page 137, the draft omits mention of the published two-generation study. (Lieder et al. 2009)

**DD. PFBA Data**

On page 20, the first paragraph discusses thyroid observations with PFBA. TSH was measured in the 90-day study of PFBA (see study appendix 7) and showed no effect. Histomorphometric data on thyroids of male rats is also available. See Van Otterdijk, F.M., Repeated Dose 90-Day Oral toxicity study with MTDID 8391 [PFBA] by Daily Gavage in the Rat Followed by a 3-week Recovery Period. NOTOX BV Laboratory, December 21, 2007, in 3M's Submission of Perfluorobutane Carboxylate studies to U.S. EPA Docket AR-226, dated July 8, 2008.

On page 127, the hyperplasia discussed in the paragraph at the bottom should be described as minimal to slight. The effect on thyroid follicles noted was also minimal to slight and was not apparent when histomorphometric analyses were conducted (see AR-226 docket for histomorphometric analyses reports from NOTOX). Also, three lines up from bottom, it is not clear why the word "lesion" is used.

At page 127, the last line states that none of the studies measured TSH in serum. TSH was measured in both studies and was included as an appendix to the 90-day study report.

Histomorphometric analysis was done on the high-dose males and the control animals in both the 28-day and 90-day studies. See Van Otterdijk, F.M., Repeated Dose 28-Day Oral Toxicity Study with MTDID-8391 [PFBA] by Daily Gavage in the Rat, Followed by a 21-Day Recovery Period, Final Report, NOTOX B.V. Laboratory, December 2006, in 3M's Submission to U.S. EPA Docket AR-226, dated July 8, 2008; Lieder, et al., Twenty-Eight Day Oral Toxicity Study of Perfluorobutyrate in Rats, abstract and poster presented at 2007 annual meeting of the Society of Toxicology ("SOT") (SOT abstracts are published as a supplement to the journal *Toxicological Sciences* titled the *Toxicologist* and are available at www.toxicology.org), in 3M's Submission to U.S. EPA Docket AR-226, dated July 8, 2008; Van Otterdijk, F.M., Repeated Dose 90-Day Oral toxicity study with MTDID 8391 [PFBA] by Daily Gavage in the Rat Followed by a 3-week Recovery Period. NOTOX BV Laboratory, December 21, 2007, in 3M's Submission of Perfluorobutane Carboxylate studies to U.S. EPA Docket AR-226, dated July 8, 2008.

There are also genotox studies on PFBA that have been submitted to the AR226 docket. See 3M's Submission to U.S. EPA Docket AR-226, dated July 8, 2008.

**EE. PFDeA Data**

On pages 27 and 123, the draft omits PFDA data that has been submitted to the EPA docket. Peterson, R.E., B.I. Kuslikis, and J.P. Vanden Heuvel. Protein acylation by the peroxisome proliferators perfluorodecanoic acid (PFDA) and perfluorooctanoic acid (PFOA) in rats. See 3M's Submission to U.S. EPA Docket AR-226, dated May 25, 2000.

On page 128, the second paragraph cites a publication by Harris et al. for an increase in T3 and T4 associated with PFDA dose. However, Langley and Pilcher et al. have found that PFDA *decreases* T3 and T4. This was further explored by Gutshall et al. in two papers. (Gutshall et al., 1988, 1989; Langley and Pilcher, 1985).

**FF. PFDoA Data**

At page 138, top, the relevance of the discussion on the effects of PFDoA is unclear because the study did not evaluate reproductive function in rats. The discussion purports to describe a mechanism of a reproductive effect in the absence of any data that suggests there is a reproductive effect.

## GG. Other Missing Data

As a general observation, we note that Chapters 1 and 2 would benefit greatly from the inclusion of references.

At the top of page 12, the draft document discusses studies by Emmett and Nolan. The results of these studies should also be included.

At page 19, the first full paragraph, ATSDR should consider additional citations. (Dewitt et al., 2009; Loveless et al., 2008).

On page 171, the last line at the bottom of the pages omits Tao et al. (2008a) and von Ehrenstein et al. (2009). The discussion is also missing Volkel et al. (2008) and additional research by Tao et al. (2008b).

At page 163, the draft is missing oral dosing information on PFOS by Seacat et al. (2002) and Curran et al. (2003). Page 163 is also missing oral dosing information on PFOA in monkeys by Butenhoff et al. (2004).

The draft references Austin at page 200-201. First of all, Austin et al. used a highly unusual method of dosing, repeated intraperitoneal injections, that is not at all relevant to typical human exposure. Secondly, data from the high-dose group should not even be considered due to the substantial reduction in mean body weight and food consumption as well as the substantial increase in serum corticosterone, indicative of stress in these females. Details of the evaluation criteria are not given, and it is difficult to know how these compare to accepted methodology. The two-week time period seems short compared to standard methods, which usually include three weeks of evaluation to obtain 4-5 cycles. The analytical results may be questionable based on the recent publication of Reagen et al. (2008).

## HH. MRL

### 1. Human Data

3M agrees with ATSDR's conclusion not to derive MRLs for perfluoroalkyl compounds, for the reasons described in the profile, including the conclusion that there are no effects in humans.

We also agree that none of the birth weight studies establish a cause-and-effect relationship between PFOA/PFOS serum levels and birth weight and that there is a question whether the magnitude of the correlation seen in some studies is adverse (as stated on page 22).

While we also agree that "it is difficult to define points of departure for MRL derivation with any degree of confidence based on the human data available at this time", we disagree with ATSDR's reasoning. It is difficult to define points of departure because there are no proven consistent health effects in humans caused by perfluoroalkyls. 3M does not agree that "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." While it may be true that not every nuance of pharmacokinetics is known, there have been several studies recently published on the issue. Moreover, a human pharmacokinetic model developed by Dr. Harvey Clewell under an EPA grant is now available.

German authorities, in collaboration with industry partners, have issued a "Chemical Safety Report" for PFOA that used REACH methodology to develop a "Biological Derived No Effect Level" (Biological DNEL) for PFOA for Man via the Environment. The Biological DNEL is expressed in terms of serum PFOA concentration and is 800 ng/mL. This is based on an observed human no adverse effect serum PFOA concentration level of 5,000 ng/mL.

**2. Animal Data - PFOA**

At page 30, the draft document states that the developmental study in mice by Abbott et al. would preclude use of the cancer bioassay as a basis for deriving the chronic duration oral MRL. 3M agrees that the cancer bioassay does not drive the risk assessment. The Abbott et al. study showed that the birth weight effects referenced by ATSDR's draft were PPARα mediated, as acknowledged in the draft document. Thus, this effect is not likely relevant to humans and is not an appropriate choice for an MRL.

We urge ATSDR to consider use of the monkey data when it does address the MRL, as the Minnesota Department of Health has done in setting its Health Risk Limits for PFOS and PFOA. Given the very significant challenges in addressing the species differences observed with PFOA, we believe it is most scientifically justifiable to use the species most relevant to humans in establishing the MRL.

We disagree with the statement on page 198 that the lack of human health effects precludes identifying the most appropriate animal model for risk assessment. While it is of course correct that you cannot identify effects similar to those in humans if there are no effects in humans, our assessment of the available human and animal data leads us to conclude that it is most appropriate to base risk assessment on the species most similar to humans or on no observed adverse effect levels in humans.

A large body of human data is available that is associated with serum concentrations of PFOS and PFOA, and these can be evaluated in conjunction with the data from toxicological studies, many of which have generated data on serum concentrations of the perfluoroalkyl. In addition, the six-month study of ammonium PFOA in cynomolgus monkeys resulted in the monkeys being at steady state through a majority of the study. In the six-month study with PFOS in cynomolgus monkeys, steady state was evident at the highest study dose (0.75 mg/kg/d) at about 4 months. Repeated measures of clinical parameters allow for identification of change in clinical parameter in association with serum concentration of perfluoroalkyl in these studies. Current modeling efforts allow estimation of the impact on daily exposure at a given level on serum perfluoroalkyl concentration level. Differences between rodents and primates in the response to PPARα agonists argue for the preferential use of human and non-human-primate data.

## II. ATSDR's Summary Section

On page 5, the discussion of laboratory animal data at page 5 refers to irritation studies at high levels of PFOA and to liver damage and weight loss at "lower levels" in rats. Those relative terms may leave a misimpression. It would be helpful to clarify dose or exposure levels and that the rat studies that show effects in laboratory experiments are at levels that are high vis-à-vis human exposure.

Under Laboratory Animals, at page 6, the draft document refers to birth defects in mice born to females exposed to relatively high amounts of PFOS during pregnancy. The study referenced is the Thibodeaux et al. study, which saw similar findings in the rat. It is important to note that structural alterations occurring in these laboratory animals in response to maternal dosing occur at doses producing high body burdens relative to what is expected in the environment. The highest observed PFOS concentration in a human was 13,000 ng/mL and occurred in a production worker. It is evident from the Thibodeaux study that the effects noted occurred at serum PFOS concentrations generally in excess of 100,000 ng/mL, and clear no effect levels were established at lower doses. In addition, maternal toxicity or stress may have been a factor in the rat outcomes based on body weight, food consumption, and relative liver weight. Also, relative liver weight was affected in mice at lower doses than in rats (5 mg/kg/d in mice versus 10 mg/kg/d in rats). ATSDR should be careful not to imply that humans may experience similar body burdens of PFOS due to environmental exposure.

With respect to the recommendation on drinking water at page 6, ATSDR should take care not to appear to be suggesting bottled water or filtration is necessary if low levels of perfluoroalkyls are found in drinking water sources. Part per trillion levels of some perfluoroalkyls have been found in a number of water supplies and pose no concern. Although the discussion on page 6 does refer to a choice to adopt exposure reduction measures, it is appropriate to point out the existence of the EPA Provisional Health Guidelines in order to assist consumers in evaluating whether perfluoroalkyls are a concern. In addition, it would be useful to mention the state of Minnestota's Health-Based Value for PFBS and its Health Risk Limit for PFBA. See http://www.health.state.mn.us/divs/eh/risk/guidance/gw/index.html.

Under Measuring Exposure at page 7, the draft states that the "presence of perfluoroalkyl compounds in your blood does not necessarily mean that you will suffer adverse health effects. Additional studies are needed to help determine the health effects associated with exposure to perfluoroalkyls." While we agree with the first sentence, the latter statement seems to imply there *will* be health effects and it has simply not yet been determined what they are. This drafting oversight should be fixed, as clearly ATSDR does not intend to be making such a prediction. Indeed, 3M has been monitoring its perfluoroalkyl production workers -- the most highly-exposed humans -- for over thirty years now, and as ATSDR notes in a number of places in the draft document, no adverse health effects have been observed to be causally related to perfluoroalkyl exposure in humans. Thus, while further research is always helpful, the possibility of effects being found in humans, particularly as exposure levels continue to decline, would seem unlikely.

Page 7 states "you should, however, see a physician if you believe that you have been exposed to high levels of perfluoroalkyls." While there is no harm in conducting a physical and performing blood analysis, the most important step one can take is to reduce or eliminate exposure. There are no other preventative steps available to reduce body burden, and no conditions to monitor. Workers with the highest exposures to perfluoroalkyls have been monitored for over 30 years without any consistent or demonstrated health effect.

At page 11, the fourth paragraph, omits discussion of cholesterol results from Steenland et al. (2009) and MacNeil et al. (2009).

Also, the draft omits any discussion of the Minnesota Department of Health's cancer incidence study of Washington County communities.

At page 12, the second paragraph cites hepatic enzyme results from regression analyses published in papers by Sakr et al. This discussion may be misleading because it suggests the researches observed a clinically important increase. Also, the draft omits discussion of results published by Lundin et al. paper results (noncancer).

At page 13, the fourth sentence of the second paragraph alludes to a paper by Apelberg et al. as a "recent study of the general population in the United States." This paper, however, was not a study of the general United States population but primarily a hospital based population of inner city Baltimore. Also, this discussion states that "no significant associations were observed between either PFOS or PFOA concentrations and newborn length or gestational age." For consistency, the assessment should point out that although a negative association was observed between cord blood concentration and birth weight, that negative association also was not 'significant' from a statistical sense.

Also at page 13, the discussion of birth outcomes reported by 14,000 Danish women (Fei et al.) should also state that no birth parameters (including birth weight) were significantly associated with PFOS. The discussion also omits other important observations reported by Fei et al., including that newborns' Apgar scores were normal and that there were no associations between PFOS and PFOS and any developmental milestones from age 0 to 18 months. The discussion of birth outcomes reported by 428 Japanese women (Washino et al. (2009)) only showed a significant birth weight association with PFOS among female births. No association with PFOS was seen with male births. Unlike Apelberg et al. and Fei et al., Washino et al. did not observe any association with PFOA. Additionally, the highest concentrations in community studies have not seen an association with birth weight for PFOA (Nolan and Stine). The draft also omits research by Grice which did not observe an association between exposure and birth weight in an occupational setting.

At page 14, the second paragraph contains incorrect and incomplete statements. The draft omits research on prostate cancer (Lundin et al.) and bladder cancer (Alexander and Olsen) (see comments to Section 3). Also, in discussing the study by Leonard et al., the draft mentions specific sites evaluated but does not discuss the findings. The draft document would benefit by including comparisons across Alexander et al. (and Grice et al.) with Lundin et al. and Leonard et al. for liver, pancreatic, bladder, and prostate cancer.

The discussion of human data on page 21-22 is missing references for Sakr (2006 (cross-sectoinal and longitudinal), Olsen et al. 2000, Costa et al. 2009, Steenland et al. (2009) and MacNeil et al. (2009). As noted above, it is more than a 'small number' of studies that examined developmental outcomes in relation to perfluoralkyl body burdens. The document should state that Fei did not find PFOS to be associated. Washino only found birth weight to be associated with female births. This section of the document makes no mention of Monroy et al., Nolan et al. or Stine et al., or of Grice, even though the occupationally exposed population clearly had the highest potential for exposures.

The discussion of PFBA on page 25 should include data on the serum elimination half-life in human. The discussion of PFBS on page 26 should include discussion of serum elimination half-lives in rats, monkeys, and humans (Olsen et al. 2009).

**JJ. Physical/Chemical Properties and Environmental Fate**

Although acknowledging declines in industrial releases, the second paragraph at page 9 states that "large amounts" of perfluoroalkyls have been released to the environment in and around fluorochemical facilities. This is not correct, at least with respect to 3M's facilities.

The paragraph also refers to "companies" phasing out of production and use of some perfluoroalkyls in the early 2000s. To our knowledge, 3M was the only company to do so at that time.

The third paragraph on page 9 generalizes with respect to the physical and chemical properties of perfluoroalkyls. The draft needs to acknowledge the wide variability in properties among different compounds.

Similarly, the discussion of biomagnification in the food chain at page 9 cannot be generalized to all perfluoroalkyl compounds.

Regarding page 10, the second sentence of the second paragraph: increasing bioaccumulation potential occurs only within a range of chain lengths. It increases as chain length increases from four to eight carbons. It then declines with further increases in chain length. Conder et al., 2008.

The draft report recommends a number of steps that 3M has already initiated.

On page 10, and later in the profile at page 249, ATSDR states that "The highest concentrations of perfluoroalkyls in animals are measured in apex predators, such as polar bears, which indicates that these substances biomagnify in food webs." We find the quote about biomagnification overly broad. This statement may be true for PFOS, some longer chained perfluoroalkyl sulfonates, and for perfluorocarboxylic acids longer than 8 carbons, but it is not true for PFOA, shorter perfluorocarboxylates, and perfluoroalkyl sulfonates with a chain length less than 8 carbons.

Page 305 again refers to biomagnification through food webs. While that may be true for some perfluoroalkyls, it is not true for all 13 perfluoroalkyls covered by this draft profile. Some specificity of substance or specific support for biomagnification should be included here.

A potential major source of human exposure, the perfluorinated phosphonic acids (D'Eon et al. 2009a; 2009b), are not discussed in this ATSDR draft document. The polyfluoroalkyl phosphoric acid diesters have been shown to degrade to perfluorocarboxylates *in vivo* and may be a source of human concentrations (D'Eon et al. 2009a).

## KK. Typographical Errors

Finally, we wish to point out the following instances where there appear to be typographical errors:

- On page 141 in the sentence: "Another small study of 19 women from China found no statistical significant correlation between concentrations of PFOS (0.045-0.36 ng/mL) and PFOS (0.047-0.21 ng/mL) in breast milk and infant weight (So et al. 2006b)." One of the references presumably needs to be to PFOA.
- The following sentence at page 142 appears to be internally redundant, and accordingly may contain a typographical error: "The study did find, however, that decreasing gestational age and maternal age 20-24 years were associated with an increased likelihood of low birth weight, while maternal age < 24 years, female sex, and decreasing gestational age were associated with lowered mean birth weight."
- On page 173, the second full sentence in the paragraph continued from the prior page reads "...slower elimination of PFOA in male rats resulted in steady state plasma concentrations within 3 weeks days of repeated exposures"; it should be either "3 weeks" or "3 days", but not "3 weeks days".
- On page 198, there appears to be a typographical error in the first sentence under Lack of Reported Effects in Humans; there is an extra word, "have," in the third line.
- On page 217 "severily" should be revised to "severely"
- On page 247, second paragraph, 3M also ceased production of PFOA in 2002.

## LL. Production, Import/Export, Use, and Disposal

In describing the uses of perfluoroalkyls at page 2, the text provides production volumes of PFOS and PFOA for 2002. 3M completed its phaseout of perfluorooctanyl chemistry in 2002, and thus these figures are not representative of subsequent years. While other parties entered production or import of PFOA after 3M's phaseout, there has been no further U.S. production of PFOS or PFOS precursors by 3M or others in the U.S. since 2002. This fact should be clarified.

Page 245 states that "information regarding the import and export of perfluoroalkyl compounds were not located." The third paragraph on page 304 states

something similar. Yet, on page 251, the draft profile states that some PFBA is "reportedly imported for commercial use," citing 3M 2008a and ATSDR 2008. Pages 245 and 304 ought to mention that there is data that PFBA is imported for some commercial use.

**MM. Chapter 7: Analytical Methods**

We commend ATSDR for the comprehensive discussion of Analytical Methods covered in Chapter 7. The chapter captures the data accuracy concerns for perfluorochemical analytical methods published in the PERFORCE studies.

However, the Chapter omits two key publications on this topic, and we believe the discussion needs to be updated to include both of the following publications:

1. Jahnke A., Berger U.: "Trace Analysis of Per-and Polyfluorinated Alkyl Substances In Various Matrices - How Do Current Methods Perform?" Journal of Chromatography A, 1216, 2009, 410-421.

2. EPA Method 537: Determination of Selected Perfluorinated Alkyl Acids in Drinking Water by Solid Phase Extraction and Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS), version 1.0, September 2008, National Exposure Research Laboratory Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, Ohio.

The Jahnke review paper contains an exhaustive and thorough review of analytical methods, and while ATSDR accurately captures the concerns expressed in Section 7.3.1, the review paper does a more comprehensive job.

The ATSDR draft states at page 309 that "No methods approved by federal agencies and organizations were located for perfluoroalkyl compounds." This is no longer accurate. EPA Method 537 should be included in the draft profile, as it was published in September 2008.

We note also that ISO published a method on water in February 2009, but the EPA Method supersedes the ISO method, even though published slightly earlier. (See ISO/DIS 25101; Published February 2009 "Water quality – Determination of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) – Method for unfiltered samples using solid phase extraction and liquid chromatography/mass spectrometry".)

**NN. Chapter 8: Regulations, Advisories, and Guidance**

The document states at page 315 that EPA has not derived a reference dose for perfluoroalkyls. Although there is no IRIS entry yet, EPA did indeed derive reference doses in order to arrive at Provisional Health Advisories (PHAs) for PFOA and PFOS, which ATSDR cites on the next page of the draft document. The PHAs can be accessed via EPA's web site by visiting http://www.epa.gov/waterscience/criteria/drinking/ and locating the link to the PHA for PFOA and PFOS.

Table 8-1, starting at page 316, incorrectly indicates there is no ACGIH TLV data applicable to perfluoroalkyls. ACGIH has, in fact, established a TLV-TWA for ammonium perfluorooctanoate (APFO) of 0.01 mg/m³. On the same page, the table indicates there is no ACGIH carcinogenicity classification applicable to perfluoroalkyls. This also is inaccurate. ACGIH's cancer classification for APFO is A3.

Table 8-1, continuing on page 317, lists only Minnesota and New Jersey as states having regulations, advisories, or guidelines applicable to perfluoroalkyls. ATSDR should add that North Carolina is currently working on a permanent standard, and has an existing interim drinking water guidance level of 2 10µg/L.

ATSDR should add the United Kingdom's drinking water standards and reference dose to the table, as well. The UK Drinking Water Inspectorate set a drinking water guidance level for PFOA of >10µg/L or >10 ppb, and for PFOS of >1ppb. See Guidance on the Water Supply (Water Quality) Regulations 2000/01 specific to PFOS and PFOA Concentrations in Drinking Water, UK Drinking Water Inspectorate, June 1, 2007.

Finally, the table includes relevant information from Minnesota, but needs to be updated to include the most current regulatory guidance issued by the Minnesota Department of Health (MDH). MDH has issued guidance in the form of Health Based Values (HBVs) for PFBA and PFBS. The HBV for PFBA is 7 ppb, the sub-chronic HBV for PFBS is 9 ppb, and the chronic HBV for PFBS is 7 ppb.

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We hope the foregoing comments are helpful in improving the scientific accuracy of the draft Toxicological Profile. If you deem it appropriate, we would appreciate your forwarding a copy of these comments to interested parties such as ATSDR and local authorities.

3M would be pleased to provide any additional information that would be helpful to ATSDR.

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