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Subject 06/04/2010 Letter To EPA Docket Center

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June 4, 2010

EPA Docket Center, MC 2822T
U.S. Environmental Protection Agency
EPA West, Room 3334
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-0001Re: Submission to IRIS and AR-226 Database For PFOA/PFOS: EPA-HQ-ORD-2003-0016

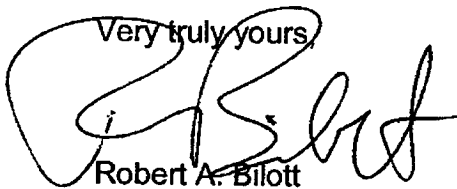
To IRIS Database for PFOA/PFOS:

In response to the Notice issued by USEPA on February 23, 2006, regarding USEPA's efforts to consider perfluorooctanoic acid ("PFOA") and perfluorooctane sulfonate ("PFOS") within the Integrated Risk Information System ("IRIS"), 71 Fed. Reg. 9333-9336 (Feb. 23, 2006), we are submitting the following additional information to USEPA for inclusion in that review, and for inclusion in the AR-226 database:

1. Comments of Perry Cohn, PhD, MPH, New Jersey Department of Health and Senior Services, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (June 1, 2010);
2. Comments of Gloria B. Post, PhD, DABT, New Jersey Department of Environmental Protection, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (June 1, 2010);
3. Comments of David Gray, PhD, MPH, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (May 31, 2010);
4. Comments of Olga V. Naidenko, PhD, Environmental Working Group, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (June 1, 2010);

June 4, 2010
Page 2

5. Comments of Jeff Ruch, Public Employees for Environmental Responsibility, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (June 1, 2010); and
6. Comments of Hope C. Taylor, MSPH, Clean Water for North Carolina, on North Carolina Science Advisory Board draft Maximum Allowable Concentration for PFOA in Groundwater (June 1, 2010).

Very truly yours,

Robert A. Bilott

RAB:mdm
Enclosure

cc: Gloria Post (NJDEP)(w/ encl.) (via U.S. Mail)
Helen Goeden (MDH)(w/ encl.) (via U.S. Mail)
Lora Werner (ATSDR)(w/ encl.) (via U.S. Mail)

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Acting Commissioner

Reginald C. Jordan, Ph.D., CIH
 NC Division of Air Quality
 Raleigh, NC 27699-1641

June 1, 2010

Dear Dr. Jordan,

As requested on the North Carolina Science Advisory Board (NCSAB) website, I am submitting comments on the scientific basis of the NCSAB Recommendation to the Division of Water Quality for a Maximum Allowable Concentration (MAC) for Perfluorooctanoic Acid (PFOA) in Groundwater.

I am an epidemiologist in the New Jersey Department of Health and Senior Services with responsibility for helping to develop the human health basis for New Jersey drinking water standards. Currently, the New Jersey Drinking Water Quality Institute (DWQI), an advisory body to the New Jersey Department of Environmental Protection, is developing a recommendation for a New Jersey Maximum Contaminant Level for PFOA.

Comments

My comments focus on two general areas. First, several relevant recent epidemiological studies were not included in the NC SAB review of the literature on PFOA. Second, the human serum levels that will result from chronic exposure to the groundwater concentrations proposed by the NC SAB should be considered in the context of the serum levels which have been associated which several effects in epidemiological studies.

Foremost among my concerns is the absence of any discussion of health effects found in community-based studies or studies based on data from the CDC National Health and Nutrition Evaluation Survey (NHANES), although some of these studies are listed in a table in an appendix. No rationale was given for not discussing them, while discussing only the results of cancer outcomes from occupational studies. Non-cancer occupational health analyses were also paid no attention.

One qualification about the results of the non-occupational studies is that causality has not been proven because the studies are cross-sectional. However, the occupational studies of blood/urine chemistry have essentially the same design and the longitudinal studies were based on volunteers with low rates of participation. In addition, the occupational studies had relatively few exposed female subjects and were largely based on death certificates, which tend to underestimate a number of chronic diseases, such as diabetes and prostate cancer.

The C8 Health Study examined approximately 70,000 people in 6 water districts in Ohio and West Virginia where drinking water was contaminated with PFOA. Serum PFOA and many clinical parameters were measured for each participant in this large study. The median serum level for participants in this study was 28 ug/L, but vary over a wide range (Steenland et al., 2009a). The median serum levels in the lower two deciles, 5.8 and 9.8 ug/L (0.0058 to 0.0098 ug/ml) (WVU, 2009), are similar to the 75th and 95th percentiles in the US general population (Calafat et al., 2007), while the median serum level in the top decile was 482 ug/L (0.482 ug/ml).

Several studies have been published by the C8 Science Panel on the findings in the C8 population. Several endpoints from those studies exhibited a steep dose-response curve in the lower deciles of PFOA serum concentrations, and plateau at the higher serum levels (approximately 40 ug/L (0.04 ug/ml) and above). Those include statistically significant associations between serum PFOA and certain serum lipids (especially total cholesterol) and uric acid (Steenland et al., 2009b; Steenland et al., 2009c). While the effects, as analyzed by regression methods, are not large, the percentage of individuals exceeding clinical reference levels increased with increasing serum PFOA. Higher cholesterol levels were also found among more exposed workers (reviewed by Steenland et al., 2010). A study of 4,747 workers (Sakr et al., 2009) found a marginally significant elevation in ischemic heart disease (IHD) mortality among workers in the two highest serum PFOA quartiles compared with the lowest quartile. Rate ratios analyzed with a 10-year lag were 40-60% elevated with marginal significance. The authors concluded that there was “no convincing evidence” to link PFOA exposure to IHD mortality, but there was a general trend, and the inability to adjust for important confounders could easily obscure a stronger association. While a 3M study (Lundin and Alexander, 2009) at its Cottage Grove, MN, facility did not observe an increase on IHD mortality with work exposure, their exposure analysis did not include serum PFOA levels. However, cerebrovascular disease mortality was associated with estimated exposure, and death from hypertension with and without heart disease (Lundin and Alexander, 2007) was marginally elevated.

No in-depth analysis has yet been published on the relationship between serum PFOA and the results of liver chemistry panels. However, the C8 Health Project (2009) has posted results of the unadjusted means of serum liver enzyme levels in each serum PFOA decile. The serum levels of several liver enzymes rise in relative monotonic fashion with increasing PFOA decile. Most occupational studies have also observed increased levels of serum liver enzymes among exposed workers.

The NHANES data provides a biennial survey of contaminants in blood and urine of a representative sample of individuals, along with results of clinical chemistry analysis of blood and urine, along with data on individual health status of each of the thousands of subjects across the U.S. Studies on data from the NHANES have also found an association of serum PFOA with serum total cholesterol (Nelson et al., 2009) and liver enzymes (Lin et al., 2009b).

(In addition, Sakr et al. (2007) reported that serum calcium, iron, potassium, and the enzyme lactate dehydrogenase were significantly associated with serum PFOA among workers at the DuPont Washington Works facility, though the direction of those associations was not given. No mention was made of those parameters in any other occupational study, but the C8 Health Project descriptive statistics revealed similar results with calcium iron, magnesium, and, among

women, potassium. It possible that these phenomena are related to affects on the kidneys that may be related to the observed elevations of serum uric acid.)

The crude data from the C8 Health Project (2009) and Fletcher et al. (2009) suggest immune system dysfunction with increased serum PFOA levels. The presence of antinuclear antibodies, a crude marker of increased risk, was higher among women in higher PFOA deciles, appearing to be significantly elevated (above the lowest decile) in the three highest deciles. The PFOA level in women with normal levels of antinuclear antibodies averaged 69 ug/L, while in women with high levels of antinuclear antibodies the average PFOA level was 98 ug/L. Self-reported Sjogren's syndrome and scleroderma displayed a dose-response relationship among 30-50 year old women, in which group the incidence is also higher among women.

A study of NHANES data (Melzer et al., 2010) show increased thyroid disease, especially among women, but also marginally significant among men. Analysis by quartile in adjusted logistic regression models showed that women in the top quartile of serum PFOA (≥ 5.7 ug/L) had greater prevalence than those in the combined bottom two quartiles (≤ 4 ug/L), resulting in an odds ratio of 2.24 (95% CI 1.38, 3.65). Notably, in the general population women develop thyroid and autoimmune diseases to a much greater degree than men.

An association with diabetes has not consistently been found in the C8 population and NHANES (Lin et al., 2009a; MacNeil et al., 2009; Nelson et al., 2009), but occupational studies have seen consistent increases in mortality or insurance claims due to diabetes (Olsen et al., 2004; Leonard et al., 2008; Lundin et al., 2009).

Additionally, associations with PFOA serum levels in the general population range (<20 ug/L) have been reported for decreased fetal growth, effects on sperm parameters, and decreased fertility as measured by time to pregnancy (Apelberg et al., 2007; Fei et al., 2007, 2008; Joensen et al., 2009). Other studies on fetal birth weight have also shown a negative effect, but not to statistical significance (Hamm et al., 2009; Monroy et al., 2009; Nolan et al., 2009; Washino et al., 2009). It has been noted that positive studies accounted for more potential confounding variables (Olsen et al., 2009). Maternally-reported low birth weight in the C8 Health Study was not associated with serum PFOA (Nolan et al., 2009; Stein et al., 2009).

In an unpublished study of cancer incidence the DuPont Cancer Registry surveillance report (Leonard, 2003) indicated that bladder and kidney cancer incidence among all male employees at the Washington Works was elevated during the 1959-2001 period. The Registry represents data on active employees and standardized incidence rates were calculated based on internal comparison (5-year time and age categories) with company-wide incidence rates. The respective standardized incidence ratios for bladder and kidney cancer were 1.9 (95% CI 1.2, 3.1) and 2.3 (95% CI 1.4, 3.6), based on 18 cases each. They point out that the incidence of both types of cancer was higher in West Virginia than in the U.S. or in neighboring Ohio. Nevertheless, elevated bladder cancer and kidney cancer is consistent with an unpublished analysis of 1959-2000 mortality among Washington Works employees (Leonard, 2003), as well as mortality from bladder cancer among workers at the 3M Decatur facility (Alexander et al., 2003). (A follow-up of the 3M study noted an elevated, though not statistically significant, mortality rate, but, if one included the 4 additional cases not included because of lack of consent to examine medical

records, bladder cancer would have been marginally significant, based on a total of 18 cases. Those who did not participate were younger, but tended to have spent more time in high exposure jobs.) The Leonard et al. (2008) mortality-based study of 1957-2002 deaths found an elevation of kidney, but not bladder cancer deaths. Unfortunately, there was no discussion of the unpublished results in the published article.

In general the epidemiological studies of PFOA exposure and health effects have too many limitations (Steenland et al., 2010) to use them directly as the quantitative basis for risk assessment in the development of regulatory water standards. However, these studies do have sufficient consistency to suggest that health effects of concern occur at exposure levels that occur even in the general population.

Therefore, the NC MCA was appropriately based on animal studies. However, I think that the serum levels that would result from chronic exposure at the proposed NC MCA should also be considered in the context of the serum levels at which associations have been observed in human studies and the serum levels at which toxicological effects in animals occur. (Although my comments are not directed at laboratory animal toxicology, it should be noted that there are several studies that found serious effects at levels much lower than those considered in this report. These include persistent effects on insulin and leptin homeostasis and mammary gland development (Hines et al., 2009; White et al., 2009).)

Based on the epidemiological literature, the relationship between serum PFOA concentrations and concurrent exposure from water strongly suggests a ratio of 100:1 or greater between serum PFOA (as ug/L) and drinking water (as ug/L) (Post et al., 2009a,b). Thus, chronic exposure to the lower end of the groundwater MAC proposed by the NC SAB, 0.9 ug/L, would be expected to result in serum levels of at least 90 ug/ml. The associations of PFOA with several health effects were seen between the first (median serum PFOA level of 5.8 ug/L) and second deciles (median serum PFOA level of 9.8 ug/L) of the C8 population, which suggests a level lower than 0.1 ug/L.

Thank you for the opportunity to provide comments on the NC SAB draft document. If you need further information, please feel free to contact me at (609) 826-4946 or perry.cohn@doh.state.nj.us.

Sincerely,

Perry Cohn, PhD MPH
Research Scientist

C: Jerald Fagliano, Program Manager

Citations

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State of New Jersey

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Reginald C. Jordan, Ph.D., CIH
NC Division of Air Quality
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June 1, 2010

Dear Dr. Jordan,

As requested on the North Carolina Science Advisory Board (NCSAB) website, I am submitting comments on the scientific basis of the NCSAB Recommendation to the Division of Water Quality for a Maximum Allowable Concentration for Perfluorooctanoic Acid (PFOA) in Groundwater.

I am a toxicologist with the New Jersey Department of Environmental Protection (NJDEP) with responsibility for developing the human health basis for New Jersey drinking water standards and guidance. I was responsible for the development of the current NJ health-based drinking water guidance for PFOA (NJDEP, 2007), the basis for which has been published in a peer-reviewed journal (Post et al., 2009). Currently, the New Jersey Drinking Water Quality Institute (DWQI), an advisory body to the Commissioner of NJDEP, is developing a recommendation for a New Jersey drinking water standard (MCL) for PFOA. I am one of the scientists involved with updating the 2007 guidance based on review of recent studies in order to develop a recommended human health basis for this MCL.

My comments focus on two general areas:

- First, the most scientifically appropriate studies and/or endpoints were not used as the basis for the NC SAB draft risk assessment, and the derivation of the Point of Departure for two of these endpoints is not scientifically justifiable. Information is provided on several relevant recent toxicological studies that should be considered in developing a MAC for groundwater.
- Second, the human serum PFOA levels that will result from chronic exposure to the lower end of the groundwater MAC concentrations proposed by the NC SAB are 22 to 30 fold higher than the median serum PFOA levels found in the US general population and 9 to 13 fold higher than the 95th percentile level in the US general population. These serum levels must be considered in the context of the serum levels that have been associated with several effects in human epidemiological studies and that have caused toxicological effects in animals. This is particularly true because PFOA is a persistent

bioaccumulative chemical whose health effects are not fully characterized, and because the serum PFOA levels that will result from chronic exposure at the proposed groundwater MAC level are associated with multiple endpoints in humans and experimental animals, including some considered clinically adverse. It is not scientifically defensible to set a groundwater MAC based on protection from health effects from chronic drinking water exposures at a level that will result in such increased serum levels.

- Finally, several factual points that should be clarified or corrected are noted.

Considerations related to toxicological studies and endpoints used as basis for proposed ground water MAC

Hepatic effects

There are several concerns with the use of increased liver-to-brain weight ratio data from the Butenhoff et al. (2002) subchronic cynomolgus monkey study as a critical study and endpoint for risk assessment. These concerns are related both to issues with the study itself and to the BMD modeling of the data. Little detail or discussion of this study is provided in the NC SAB document.

In this study as it was originally designed, male monkeys, age 3 to 9 years, were to be administered doses of 0, 3, 10, or 30 mg/kg/day by capsule, 7 days per week for 26 weeks. There were 6 animals per group, except in the 3 mg/kg/day dose group which had 4 animals.

Dosing of the 30 mg/kg/day group was stopped on Day 12 due to toxicity in first week, including low food consumption, weight loss, and few or no feces. The dosing of this group was restarted at 20 mg/kg/day on Day 22, after a 10-day break due to the toxicity in first week.

One high dose monkey was sacrificed on day 29 due to decreased body weight, lack of eating, hypoactivity, and coldness to touch. Dosing of three high dose monkeys stopped on days 43, 66, and 81 due to low or no food consumption, dramatic weight loss, and few or no feces. These three monkeys were monitored without dosing for the rest of the study. Additionally, one low dose monkey sacrificed on day 137 after exhibiting weight loss, low food consumption, few feces, hind-limb paralysis, ataxia, and lack of response to pain. Thus, **only three low dose and two high dose monkeys tolerated the administered dose well enough to complete the study.**

The LOAEL in this study is 3 mg/kg/day based on possible mortality (25%) and increased liver weight, and the NOAEL is unknown. It is important to note that 6 months represents less than 2% of the lifespan of this species of monkey, which is about 30 years. It is not known whether additional or more severe effects would have occurred with continued dosing of the few monkeys which were able to tolerate dosing for the full 6 months of the study. **Therefore, if this study is used as the basis for risk assessment, an uncertainty factor for less than chronic exposure duration should be included.**

In the study, serum PFOA levels were analyzed every 2 weeks, and it appeared that steady-state was reached after 2 to 4 weeks of dosing. Importantly, the serum levels were highly variable between animals within the same dose group and over time in the same animal, and did not increase proportionally with dose. The average serum levels in the 3, 10, 30/20 mg/kg/day groups, respectively, were: 81 ± 40 ug/ml, 99 ± 50 ug/ml, and 156 ± 103 ug/ml. The PFOA concentrations in liver also did not appear to increase with dose or time, and the highest concentration was in a high dose animal sacrificed at week 5.

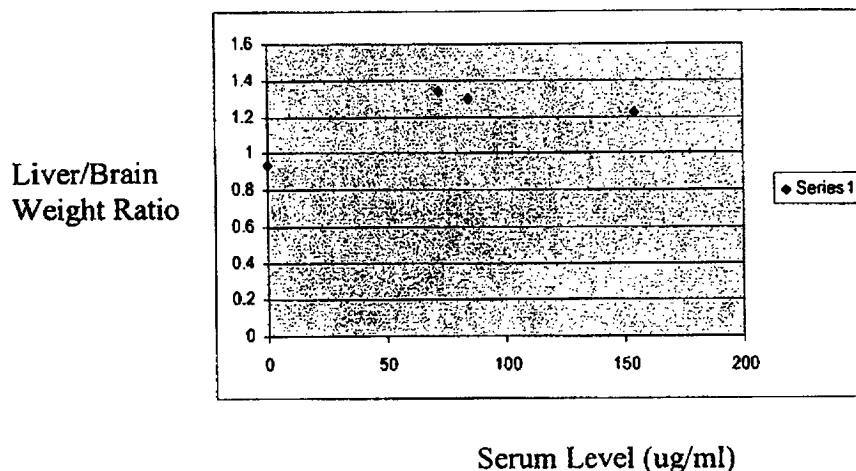
Butenhoff et al. (2004) reported benchmark dose modeling of the liver/brain weight ratio data from this study. A BMIC_{10} PFOA serum concentration of 40 ug/L and a LBMIC_{10} of 23 ug/ml were derived, and this BMIC_{10} is used as a POD in the draft NC SAB document. The data from this study on liver/brain weight ratio versus serum PFOA level are shown in the attached figure. As can be seen from the graph, the liver-to-brain weight ratio did not increase with increased PFOA serum level. The relationship is non-monotonic, and if anything, liver-to-brain weight ratio decreases with increased PFOA serum levels. Thus, these data do not support Benchmark Dose modeling, as was confirmed by Dr. A. Stern, NJDEP, who has extensive experience and expertise with BMD modeling.

Therefore, BMD modeling of these data is not appropriate for the following reasons: The dose-response relationship needed to support Benchmark Dose modeling does not exist since, as above, and stated by Butenhoff et al. (2002), liver/brain weight did not increase with dose. Additionally, there are an insufficient number of data points for BMD modeling. In the modeling conducted by Butenhoff, the highest dose group was dropped, leaving only two data points for dosed groups plus the control group. It should be noted that the reported LBMIC_{10} of 23 ug/L is in same range as the serum PFOA concentration in the low dose monkey that was sacrificed due to toxicity during the weeks before sacrifice.

Based on the above considerations, it is recommended that this study not be used as the basis for quantitative risk assessment. If this study is to be used in risk assessment in spite of its numerous limitations, it is suggested that the following POD and uncertainty factors be used: As discussed above, since the data do not support BMD modeling, the LOAEL serum level for both increased liver weight and increased mortality at 3 mg/kg/day should be used as the POD, and a LOAEL to NOAEL UF of 10 should be applied. Also as discussed above, an Uncertainty Factor for less than chronic study duration should be applied. In addition to the Uncertainty Factors for intraspecies (3) and interspecies (10) used in the NC SAB draft document, an additional uncertainty factor for database limitations should also be used due to the very small number of animals which completed the study and because mortality was seen in the low dose group.

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Cynomolgus Monkey PFOA Serum Levels vs. Liver/Brain Weight Ratio



Additionally, consideration should be given to several studies that have reported liver effects at lower administered doses and/or serum concentrations than at the Points of Departure (PODs) for hepatic effects used in developing the proposed groundwater MAC. The PODs used for hepatic effects in the draft document are BMIC₁₀s of 58 ug/L and 40 ug/L for increased liver-to-brain weight ratio in rats (Butenhoff et al., 2004) and monkeys (Butenhoff et al., 2006), respectively.

- Loveless et al. (2006) reported that liver-to-body weight ratios were significantly increased in mice given 0.3 mg/kg/day PFOA (the lowest dose tested) for 14 days. The PFOA serum levels at this dose were 10-14 ug/ml. The increase at this dose was about 20%, so a BMIC₁₀ for increased liver-to-body weight based on these data would be expected to be below this 10-14 ug/ml range.

It should also be noted that Loveless et al. (2006) reported that the dose-response in mice and rats for peroxisomal beta-oxidation did not parallel the dose-response for increased liver weight, suggesting that liver weight increases in these species are not solely due to peroxisomal proliferation.

- The BMD₁₀ for increased maternal liver weight in the Lau et al. (2006) mouse developmental study was reported by EFSA (2008) as 0.52 mg/kg/day. This is the same study from which data on delayed ossification was used as a critical endpoint in developing the NC groundwater MAC. Assuming that the relationship between oral dose and serum PFOA level is linear in this range (as was done in the NC SAB document, p. 16), the BMIC₁₀ for increased liver weight would be 9 ug/ml.

It should be noted that the USEPA (2009) Short Term Provisional Drinking Water Health Advisory for PFOA of 0.4 ug/L, intended to protect for short term rather than chronic exposures, is based on increased maternal liver weight from Lau et al. (2006).

- **Abbott et al. (2007)** reported increased liver-to-body weight of >10% in wild type pups on PND22 (day of weaning) whose mothers were dosed with PFOA doses of 0.1 mg/kg/day or greater on GD 1-17. No NOAEL was found in this study. The serum level in the pups in the 0.1 mg/kg/day group at weaning was 0.8 ug/ml.

Developmental effects

The critical developmental endpoint used in the proposed NC SAB groundwater MAC is delayed ossification of fetal forelimb and hindlimb phalanges in mice exposed during gestation (Lau et al., 2006). There are several concerns with the use of this endpoint as the basis for quantitative risk assessment and with the BMD modeling used to determine the POD for this endpoint.

The LOAEL for this effect was 1 mg/kg/day, the lowest dose used in the study. Lau et al. (2006) reported a BMD₅ for delayed ossification of 0.90 mg/kg/day for forelimb and 0.96 mg for hindlimb ossification. In deriving the NC SAB groundwater MAC, the BMD₅ for forelimb ossification was doubled to estimate a BMD₁₀ of 1.8 mg/kg/day. Data provided by Lau et al. (2006) on serum levels at 1 mg/kg/day were then used to estimate the serum level at 1.8 mg/kg/day as 31 ug/ml. This serum level, 31 ug/ml, was used as the BMIC₁₀ (p. 16 of NC SAB document).

The data for delayed ossification are shown in Table 2 of Lau et al. (2006). It can be seen that the dose-response relationship for delayed ossification is non-monotonic for both forelimb and hindlimb proximal phalanges. The greatest effect (aside from the highest dose of 20 g/kg/day at which ossification was totally stopped) was at the lowest dose, 1 mg/kg/day, at which the number of sites ossified were 10% and 38% of the control value for hindlimb and forelimb, respectively. At 3, 5, and 10 mg/kg/day, delayed ossification rates were lower (e.g. ossification rates were greater) than at 1 mg/kg/day, with the lowest incidence of delayed ossification (the greatest ossification rate) at the intermediate dose of 5 mg/kg/day.

Delayed ossification is a dichotomous (quantal) endpoint, and the change from non-ossification to ossification occurs very rapidly. Thus, data on this endpoint are very dependent on time of observation and precise stage of pregnancy (Dr. C. Lau, personal communication). Without any corresponding overt digital defect noted, the observations of delayed ossification in the Lau et al. (2006) study are best viewed as a qualitative indicator of delayed development on a group basis (Dr. C. Lau, personal communication). The data identify a LOAEL of 1 mg/kg/day, with no NOAEL identified (Dr. C. Lau, personal communication). For these reasons, these data are not an appropriate basis for dose-response modeling.

Additionally, no information is presented in Lau et al. (2006) regarding the degree of fit of the data to the models used to estimate the BMD₅. However, the non-monotonic nature of the dose-response curve and the fact that ossification was reduced by 90% and 62% at 1 mg/kg/day

in hindlimb and forelimb, respectively, indicate that 1.8 mg/kg/day is not an appropriate value for the BMD₁₀. (Dr. C. Lau, personal communication). Furthermore, it is not appropriate to estimate a BMD₁₀ by simply doubling the value for BMD₅. In order to do this, the BMD model must be run and the value for BMD₁₀ obtained from the results (Dr. C. Lau, personal communication).

Other developmental studies and endpoints which should be considered by the NC SAB include:

- **Lau et al. (2006)** reported full litter resorptions, fetal death, decreased postnatal survival, decreased body weight gain, and accelerated sexual maturation in mice, in addition to delayed ossification. The LOAEL for significantly increased accelerated sexual maturation and decreased body weight gain, 1 mg/kg/day (the lowest dose given), was the same as the LOAEL for delayed ossification chosen as the critical developmental effect. For accelerated sexual maturation, the greatest effect occurred at the LOAEL, 1 mg/kg/day, and no dose-response is seen with increasing dose. Thus, BMD modeling is not appropriate, and a LOAEL to NOAEL approach should be used for this endpoint (USEPA, 2008).
- **White et al. (2009)** reported delayed mammary gland development in mice as early as postnatal day 1 from either gestational or lactational exposures. These mammary gland changes persisted in 18 months old females exposed only during gestation and/or lactation. The effects reported by White et al. (2009) on mammary gland development are similar to those reported by Macon et al. (2010). White et al. (2009) used higher administered doses than the more recent study of Macon et al. (2010). However, the peer reviewed paper of White et al (2009) reported delayed mammary gland development at serum concentrations of about **2 ug/ml**, more than an order of magnitude below the POD of 31 ug/ml for delayed ossification used in the NC SAB draft risk assessment.
- Delayed mammary gland development, effects on uterine anatomy and histology, and metabolic effects in adulthood have been reported from gestational exposure to doses as low as 0.01 mg/kg/day (**Hines et al., 2009a,b; Macon et al., 2010**), with no NOAEL identified. The mouse serum level at this dose is about **0.3 ug/ml** (Das et al., 2010; Macon et al., 2010; Dr. S. Fenton, personal communication). As discussed in the section below, this serum level is very close to the human serum level of **0.1 to 0.13 ug/ml** which is expected to result from chronic exposure to the proposed NC groundwater MAC of 0.9 ug/L, even without the application of the uncertainty factors used with animal data.

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

The effects on mammary gland development (Macon et al., 2010) follow a monotonic dose-response relationship. This study also evaluated liver weight, and the NOAEL for increased liver weight was 1 mg/kg/kg day, while, as stated above, mammary gland development was affected at 0.01 mg/kg/day and no NOAEL was seen for this effect. This indicates that mammary gland development is a more sensitive endpoint than increased liver weight in the mice used in this study.

- The NC SAB also reviewed the study of **Zhao et al. (2010)** which observed stimulation of mammary gland development in mice exposed to PFOA. It should be noted that these findings are **not** contradictory to the finding of Macon et al. (2010) discussed above for the following reasons: First, different strains of mice which were used in the two studies, and hormonal control of mammary development is known to differ in the C57Bl/6 mouse strain used by Zhao et al. (2010) compared to other mouse strains (Aupperlee et al., 2009). Second, the lifestage at which PFOA was administered differed in the two studies since PFOA was administered during gestation by Macon et al (2010) and during the peripubertal period by Zhao et al. (2010). Finally, the dose used by Zhao et al. (2010), 5 mg, was much higher than the doses used by Macon et al. (2010). At this dose, White et al., (2007) saw dramatic delays in milk protein production, functional lactation, and an apparent total lack of mammary gland development in offspring.

Neurobehavioral effects

The following two studies are included in a list of developmental studies in the NC SAB document (p. 10) but no discussion of them is provided. Although these studies are not appropriate for use as the quantitative basis for chronic risk assessment, the fact that a single low dose of PFOA during the neonatal period causes such permanent effects should be considered by the NC SAB in developing a groundwater MAC:

- **Johansson et al. (2008)** found permanent behavioral changes in mice after a single oral dose of 0.58 mg PFOA at age 10 days.
- **Johansson et al. (2009)** showed that a single oral dose of 8.7 mg of PFOA given to mice at age 10 days altered the levels of proteins important for brain development.

In summary, the concerns noted about the use of delayed ossification from Lau et al. (2006) and the additional studies and endpoints discussed above should be considered in developing the NC groundwater MAC for PFOA.

Consideration of the human serum levels which would result from chronic exposure at proposed groundwater MAC

As discussed in the NC SAB draft document (p. 6), kinetics of PFOA vary greatly between humans and experimental animals, and between genders of some animal species. Thus, it is generally agreed upon that comparisons of toxicological effects between humans and animals must be made on the basis of internal dose (serum level) rather than administered dose. The NC SAB's derivation of proposed groundwater MACs is appropriately based on internal dose, as measured by serum PFOA level.

The relationship between administered dose (or drinking water concentration) and human serum level in humans chronically exposed to PFOA has been evaluated both by Post et al. (2009a) and by Clewell et al. (2006). It is important to understand that the results of these two approaches are in close agreement (Post et al., 2009b). The approach of Clewell et al. (2006), used by the NC SAB in development of the proposed groundwater MAC, is based on a factor of 0.12 ug/kg ingested PFOA per ug/ml serum PFOA, while Post et al. (2009a) evaluated

PFOA serum levels in six communities with a range of PFOA drinking water concentrations to confirm a ratio of approximately 100:1 between serum levels and drinking water concentrations. Based on the USEPA (2004) mean estimate of daily water consumption of 17 ml/kg/day (equivalent to daily water consumption of 1.2 L for a 70 kg adult), the factor provided by Clewell et al. (2006) is equivalent to a serum:drinking water ratio of about 140:1. It should be noted that the factor provided by Clewell et al. (2006) which was used by the NC SAB was validated with the same data from Little Hocking, Ohio that are the original source of the 100:1 ratio (Emmett et al., 2006).

The PFOA serum levels which would result from chronic exposure to drinking water at the proposed groundwater MACs are not discussed in the draft NC SAB document. Based on the approaches of Clewell et al. (2006) and Post et al. (2009a), respectively, exposure to the lower range for the proposed groundwater MAC, 0.9 ug/L, is predicted to result in median serum concentrations of about **130 ug/L (0.13 ug/ml) and 90 ug/L (0.1 ug/ml)**. **These serum levels are 22 to 33-fold higher than the U.S. population mean serum level of 4 ug/L (0.004 ug/ml) and 9 to 13-fold higher than the 95% serum concentration in the U.S. general population of about 10 ug/L (0.01 ug/ml) reported by Calafat et al. (2007).**

As discussed in detail below, the serum PFOA levels associated with numerous effects in human epidemiological studies are well below the serum levels (**90 to 130 ug/L, equivalent to 0.09 to 0.13 ug/ml**) which are expected to result from chronic exposure to the proposed groundwater MAC of 0.9 ug/L or higher. Although causality has not been proven for these effects, it is not scientifically defensible to set a ground water MAC that will lead to serum levels that are associated with multiple effects in humans in a dose-related fashion, and that are very close to the serum levels at which toxicological effects in animals occur (see section on mammary gland effects above). This is particularly true for a contaminant such as PFOA that is persistent (human half-life of several years) and bioaccumulative in humans, and for which the nature and threshold, if any, for toxicological effects are not yet fully characterized.

It should be noted that the drinking water concentration in the contamination situation in Germany (Holzer et al., 2009) discussed in the NC SAB draft document were 0.5 to 0.6 ug/L, well below the proposed groundwater MAC range of 0.9 ug/L and above. Additionally, PFOA drinking water concentrations in four of the six water districts included in the C8 Health Study in Ohio and W. Virginia (Anderson-Mahoney et al., 2008) were below 0.4 ug/L. As discussed in the draft NC SAB document, in both of these localities, measures (bottled water and/or drinking water treatment) were taken to end the exposure in the affected communities, and studies were undertaken to determine the rate of decline of the elevated PFOA serum levels in exposed individuals.

The C8 Health Study is an epidemiological study of about 70,000 people residing in six water districts in Ohio and West Virginia whose drinking water was contaminated with PFOA at 0.05 ug/L (0.05 ppb) or above. Data on serum PFOA levels and many clinical parameters have been obtained from the participants in this large study. The median PFOA serum level for participants in this study is 28 ug/L and the serum PFOA levels in this study vary over a wide range (Steenland et al., 2009a). The median PFOA serum levels in the lower two deciles, 5.8 and 9.8 ug/L (0.0058 to 0.0098 ug/ml) (WVU, 2008) coincide with the 75th and 95th percentiles

in the US general population (Calafat et al., 2007), and the median PFOA serum level in the top decile is 482 ug/L (0.428 ug/ml).

A dose-related association with serum PFOA concentration has been reported for several clinical endpoints in this study, although causality has not been proven. The effects associated with serum PFOA in this study include elevated risk of clinically elevated cholesterol in adults (Steenland et al., 2009b) and children (Steenland et al., 2009c), increased risk of clinically elevated uric acid (Steenland et al., 2010a), and immune system changes (Fletcher et al., 2009). Several of these endpoints exhibit a steep dose-response curve in the lower deciles of PFOA serum concentrations, and appear to plateau at the higher serum levels (approximately 40 ug/L (0.04 ug/ml) and above).

Additionally, associations with PFOA serum levels in the general population range (<20 ug/L or <0.02 ug/ml)) have been reported for increased cholesterol levels (Nelson et al., 2010), decreased fetal growth (Apelberg et al., 2007), increased incidence of thyroid disease (Melzer et al., 2010), effects on sperm parameters (Joensen et al., 2009), and decreased fertility as measured by time to pregnancy (Fei et al., 2009).

Steenland et al. (2010b) reviewed the current epidemiological evidence on health effects of PFOA. They note that a positive association of PFOA with cholesterol was observed in cross sectional studies including six occupational studies, three studies of a community highly exposed through drinking water, and one general population (NHANES data) study. The association in six of these studies was significant at the $p < 0.05$ level. The risk of high cholesterol (≥ 240 mg/dl) was also increased with PFOA exposure in some studies. Many studies also showed positive relationships of PFOA with other lipids (i.e., LDL cholesterol and triglycerides), with the exception of HDL cholesterol, which was consistently not found to be associated with PFOA.

Steenland et al. (2010b) also reviewed a study in which individuals who had taken statins, associated with a large decrease in cholesterol, had similar PFOA levels to those who had not taken statins. They state that these results provide some evidence against reverse causality (increased cholesterol causing increased retention of PFOA). They also state that three longitudinal studies indicating that cholesterol and PFOA were related over time in subjects with repeated measurements strengthen the case for, but do not definitively prove, a causal relationship.

Steenland et al. (2010b) state that, in general, the slope of the PFOA exposure vs. cholesterol relationship increases with lower PFOA exposures. The slopes varied by 2-3 orders of magnitude among studies, with the steeper slopes in studies of community populations than the occupational studies that have higher exposures. They state that this finding might be explained if the slope of the exposure-response relationship is steep at low PFOA levels and then flattens out, such as if some biological pathways are saturated. There is a suggestion of such flattening in some studies for which the exposure-response curve was evaluated in detail, while most studies did not examine the exposure-response curve in detail.

In summary, the serum levels that would result from chronic exposure to the proposed NC MCA should be considered in the context of the serum levels at which associations have been observed in human studies and the serum levels at which toxicological effects in animals occur. As above, it is not scientifically defensible that a groundwater MAC based on chronic drinking water exposure will result in such elevations of PFOA serum levels. This is particularly true since PFOA is a persistent bioaccumulative chemical whose health effects are not fully characterized, and because the serum levels that would result from continued exposure to the proposed groundwater MAC have been associated with multiple endpoints, including some considered clinically adverse.

Other specific comments on the scientific basis of the proposed groundwater MACs

Background information (p. 1) – It is relevant to include the fact that PFOA does not degrade in the environment.

Sources of Human Exposure (p. 3) – The mean PFOA levels reported by Emmett et al. (2006) in the vicinity of a production plant in West Virginia were 3.55 ug/L, not 0.035 ug/L as stated.

p. 4-5 – The rate of decline of serum PFOA concentrations in communities after exposure to drinking water contaminated with PFOA in Germany and Ohio/W. Virginia is discussed. In addition to the discussion of the rate of decline in serum levels in this situations, it is relevant to discuss the relationship between the drinking water concentrations to which the communities were exposed and the resulting PFOA serum concentrations (Emmett et al., 2006, Holzer et al., 2008, Post et al., 2009a).

Subchronic studies – In the discussion of the potential involvement of PPAR alpha in PFOA's hepatic effects, it is important to note that several studies indicate that the effects of PFOA on the liver are not totally mediated by PPAR alpha.

Effects of PFOA seen in PPAR alpha null mice include increased liver weight (Yang et al., 2002, Wolf et al., 2008) and histological changes and increased cell proliferation (Wolf et al., 2008), while the prototype PPAR alpha agonist Wyeth 14, 643 did not increase liver weight in PPAR alpha null mice in these studies. PFOA also activated genes not associated with PPAR alpha, including genes associated with other nuclear receptors such as CAR in livers of adult mice (Rosen et al., 2008a, 2008b) and newborn mice (Rosen et al., 2007). Additionally, PFOA caused fatty liver in mice, an effect not associated with PPAR alpha (Kudo and Kawashima, 1997).

A recent study (Minata et al., 2010) showed that PFOA induced hepatocyte and bile duct injuries in PPAR alpha null mice that differed from the effects seen in wild type mice. In the PPAR alpha null mice, PFOA produced fat accumulation, severe cholangiopathy, hepatocellular damage, and apoptotic cells, especially in bile ducts, and several biochemical parameters were affected more than in wild type mice. The authors hypothesized that PPAR alpha is protective against the bile duct injury produced by PFOA.

In regard to PPAR alpha's role in hepatic effects seen in monkeys, the USEPA SAB (2006) review of the USEPA (2005a) draft PFOA risk assessment noted that the same early effects associated with PPAR alpha activation in liver "actually occur in monkeys exposed to PFOA. These effects include the induction of peroxisomal β -oxidation activity (2.6 fold), significant increases and positive dose-response trends for absolute and relative liver weights (1.6 fold), and the return of relative liver weight to control levels after a 13-week recovery period."

Finally, most PPAR alpha activators lower cholesterol and lipids in both humans and experimental animals. Similarly, PFOA lowers lipid levels in experimental animals (e.g. Loveless et al. 2006). However, statistically significant elevations of cholesterol, as well as of the risk of hypercholesterolemia defined as greater than or equal to 240 mg/dl, are associated with serum PFOA in a dose-related fashion in humans exposed through drinking water (Steenland et al., 2009b), in the general population (Nelson et al., 2009) and are also seen in occupationally exposed individuals, as summarized in Steenland et al. (2009b, 2010b). As discussed by Steenland et al. (2009b), the findings on human serum cholesterol indicate that PFOA does not have the same effects as other PPAR alpha activators on lipid metabolism in humans.

Chronic/cancer studies - It is stated on p. 10 of the NC SAB document that, "Both the Biegel and Sibinski studies showed that PFOA induced liver adenomas, Leydig cell adenomas, and PACT in male S-D rats." Only Leydig cell adenomas were found in the Sibinski study, not liver or PACT tumors. Also, no mention of the tumor findings is included in the description of the Sibinski study.

Animal Studies – Developmental/Reproductive (p. 10) – It should be discussed that PFOA is excreted very quickly in female rats, but not in female mice or humans. It should be stated that, because of this kinetic difference, the rat is not a good model for human developmental effects.

Animal Studies – Immunotoxicity (p. 12) – It is unclear why the authors of the NC SAB document do not consider any of the effects seen in the immune system to be adverse. This conclusion should be reconsidered, or a rationale for this conclusion should be provided. Also, DeWitt et al. (2009) concluded from the studies in adrenalectomized mice, which are discussed in the NC SAB document, that the immune effects of PFOA are not secondary to stress.

Human Studies (p. 13) – The discussion should be expanded to include the many studies of workers, communities exposed through drinking water, and the general population which have evaluated endpoints in addition to cancer.

Selection of Key Studies and Critical Endpoints (p. 13) – The rationale for selection of the three key studies from the many toxicological studies in the literature, including many showing effects at lower doses and serum levels, should be provided. It is unclear why these three studies and endpoints were chosen.

Selection of Key Studies and Critical Endpoints – Cancer Effects (p. 14) and Quantitative Assessment (p. 16) – *Sibinski, 1987*- Low dose extrapolation is the default USEPA (2005b) approach for cancer risk assessment when the MOA is not definitively known. It is not clear why a NOAEL/uncertainty factor approach instead of low dose extrapolation from a POD is discussed as the basis for assessment of the cancer endpoints.

Uncertainty Factors (p. 16) – As discussed above, the delayed ossification data from this study may not be an appropriate basis for quantitative risk assessment, and the BMD₁₀ derived for this effect is not supportable. An approach based on a LOAEL, with an uncertainty factor for NOAEL to LOAEL extrapolation, is appropriate if these data are used. Other endpoints reported in this study may be a more appropriate basis for quantitative risk assessment.

Other Assessments of PFOA in Water – New Jersey

Post et al. (2009a) evaluated the ratio of serum:drinking water PFOA concentrations in five communities with lower drinking water concentrations than the community where the 100:1 ratio was first observed by Emmett et al. (2006). It should be clarified that Post et al. (2009a) confirmed that the 100:1 ratio is valid over the range of drinking water concentrations in these communities, rather than stating that they “assumed” the 100:1 ratio of Emmett et al. (2006).

Thank you for the opportunity to provide comments on the NC SAB draft document. If you need further information, please feel free to contact me at (609) 292-8497 or gloria.post@dep.state.nj.us.

Sincerely,

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

CC: Gary Buchanan, Ph.D., Manager, Office of Science

Citations:

Abbott, B. D.; Wolf, C. J.; Schmid, J. E.; Das, K. P.; Zehr, R. D.; Helfant, L.; Nakayama, S.; Lindstrom, A. B.; Strynar, M. J.; Lau, C. (2007). Perfluorooctanoic acid induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator activated receptor- α . *Toxicol. Sci.* **98**, 571–581.

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May 31, 2010

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1641 Mail Service Center

Dear Dr. Jordan:

Thank you for the opportunity to comment upon the North Carolina Science Advisory Board (NCSAB) document titled "Recommendation to the Division of Water Quality for a Maximum Allowable Concentration for Perfluorooctanoic Acid (PFOA) in Groundwater, Draft for Public Comment." I have worked as state scientist and manager in toxicology and risk assessment for many years. More recently for the last eight years I have served as expert toxicology witness in litigations involving perfluorooctanoate (PFOA) for private clients and for the U.S. Environmental Protection Agency (USEPA). I have also extensively supported USEPA, US Food and Drug Administration (FDA), and the U.S. Agency for Toxic Substance and Disease Registry (ATSDR) in the assessment of human health risk of exposure to toxic agents and in the development of risk assessment methods such as USEPA's Benchmark Dose approach to dose response analysis.

I am not being compensated for my review and comment on the NCSAB document and no one has reviewed my comments prior to your receiving them. My perspective is somewhat unique in that I have likely had access to more information on perfluorinated chemicals than any other non-industry scientist due to my litigation work involving these compounds. My comments are less extensive than I would like given the very short comment period I have had to develop them, but I hope they will be useful. In my review I make the assumption that the NCSAB document is a risk assessment and that it is NCSAB's intent that this risk assessment is intended to be generally consistent with EPA's risk assessment framework. Other state risk assessment programs with which I am familiar are generally consistent with EPA's risk assessment framework, but may add detail in areas of specific interest to the state.

Abbreviations used in these comments in the following: milligrams per kilogram per day (mkd), a unit of dose in studies using experimental animals; microgram per liter of PFOA in blood or water is shown as parts per billion (ppb); no-observed-adverse-effect-level (NOAEL), the highest dose in an animal study with no statistically significant adverse effect for a given endpoint; lowest-observed-adverse-effect-level (LOAEL), the lowest dose in an animal study with a statistically significant adverse effect for a given endpoint.

My comments are as follows.

1. Benchmark Dose Calculations (Table 10)

The benchmark dose calculations used to calculate the proposed Maximum Allowable Concentrations (MAC) use the Benchmark Dose (BMD) and not the lower 95th percentile confidence limit on dose of the Benchmark Dose (BMDL) as the Point of Departure (POD). When expressed as internal dose, as is commonly the case for PFOA, these become the Benchmark Internal Concentration (BMIC) and the lower 95th percentile confidence limit on the Benchmark Internal Concentration (LBMIC). It is USEPA policy and all state risk assessment policy of which I am aware that it is the lower 95th percentile confidence limit on dose of the Benchmark Dose, not the Benchmark Dose itself, that is used as the POD in the Benchmark Dose approach. The use of the Benchmark Dose itself as the POD underestimates risk and is not consistent with EPA policy or any state guidance of which I am aware.

The following illustrates EPA's risk assessment framework relating to development of a POD. The material below is taken from EPA's Water Quality Standards Academy online course on the development of human health Ambient Water Quality Criteria (AWQC). The information including the chart was accessed from EPA's web site on May 31, 2010 and is a simple description of the relationship between the BMD, BMDL, LOAEL, and NOAEL. These relationships would be the same in the case of a risk assessment using serum levels, as is usually done for PFOA, substituting the BMIC and LBMIC for the BMD and BMDL, respectively.

Most recent EPA assessments for noncarcinogens use a Benchmark Dose (BMD) assessment procedure to describe the experimental data. This approach has an advantage over the NOAEL/LOAEL approach in that it considers all of the dose-response data and models the dose-response curve following a procedure very similar to that used for cancer.

Depending on the exposed population as well as the size and quality of the data set, the BMD methodology can determine a BMD for 10% (BMD₁₀), 5% (BMD₅), or 1% (BMD₁) of the study group. It can also model continuous data such as a change in average group body weight or the average serum levels of an enzyme that is a biomarker for cellular damage. The BMD in the case of continuous data is usually a 1 standard deviation or 0.5 standard deviation change from the control population.

The BMD modeling programs for noncarcinogens include several curve fitting options. Generally several models are applied and the one with the best fit to the dose response is selected. A 95% confidence limit on the BMD is determined (BMDL) and that value is used as the Point of Departure (POD) for the RfD analysis. The RfD is derived by dividing the BMDL by a composite UF.

The figure below illustrates the use of the BMD approach to quantify an estimated safe dose for a noncancer effect.

therefore, be considered a LOAEL as it is greater than the LOAEL reported by Lau et al. (2006). Because the POD is a LOAEL for this endpoint, an uncertainty factor other than one must be included in Table 11 for the LOAEL-to-NOAEL uncertainty. The value chosen for this uncertainty factor would normally be 3 or 10 or some other number calculated from data reflecting the difference between this LOAEL and a likely NOAEL for this endpoint and should be discussed in the NCSAB document. The only discussion currently in the document is "BMIC₁₀ used to estimate a NOAEL," which is a contradiction in terms.

On page 15 of the NCSAB document there is a discussion of the rat reproduction study (Butenhoff, 2004). The NCSAB authors state that "since the NCSAB uses a central estimate value for a chronic endpoint, the lesser of the two central estimates, BMIC₁₀ = 58 µg/mL, was selected as a conservative Point of Departure (POD)." Since the LBMIC₁₀ of 48 µg/mL for this rat study was not used from Table 7, I assume the authors are relying on a NCSAB policy of using central estimates for chronic endpoints to justify using BMIC values rather than LBMIC values. I have not read a description of this NCSAB policy regarding this issue, but I assume it is similar to policies relating to the use of population averages to characterize long-term risk to the general public. Such a policy would have no logical application to the Benchmark Dose calculations on toxicology data, or the use of no-effect-levels for PODs as required by the EPA risk assessment framework. Also, the use of the term "conservative Point of Departure" is inappropriate since the use of a BMIC by NCSAB results in an underestimation of health risk. Invoking a policy relating to chronicity is also strange since none of the three studies chosen by NCSAB as potential critical studies are chronic studies (monkey studies of 6 months duration are not considered chronic by EPA, see IRIS monkey studies for PCB Aroclors 1016, 1248, and 1254).

2. Uncertainty Factors (Table 11)

The selection of uncertainty factors by NCSAB is, in some cases, inappropriate or poorly described and results in an underestimation of risk. For the interspecies (animal-to-human) uncertainty factor, a value of 3 is listed with the following rationale, "PFOA is not metabolized in humans. Half-life in humans is much greater than for rodents. Humans are likely to be less sensitive to toxic properties of PFOA than rodents." While I don't disagree with the value of 3 for this factor (1 for the pharmacokinetic subfactor since serum levels are being used and 3 for pharmacodynamics since PFOA mechanisms are unclear at this point), the supporting rationale is misleading. The statement that PFOA is not metabolized in humans implies that PFOA is metabolized in some other species—it is not. The fact that the half-life in humans is much longer than in rodents has nothing to do with PFOA not being metabolized. Also, the statement that "humans are likely to be less sensitive to toxic properties of PFOA than rodents" is totally unsupported by and greatly conflicts with the available data which show associations between adverse outcomes in human populations and PFOA serum levels at much lower levels than in experimental animals exhibiting similar effects. The standard rationale for using a value of 3 in such a case is that it is common practice to use an interspecies factor of 3 when the dose metric is serum level and serum level is considered to reflect tissue concentration at the target organ.

For the Study Type (subchronic-to-long term) uncertainty factor the rationale states "There is little discernable difference in serum levels at which effects have been reported in subchronic and chronic studies." There are only two chronic PFOA toxicology studies, Biegel et al. (2001) and Sibinski (1987). The Biegel study was a rat study at a single high dose of about 14 mkd without time-series measurements of endpoints. The Sibinski study in male and female rats, however, was at two PFOA doses of 1.3 and 14.2 mkd in males and included blood chemistry values for liver enzymes and other parameters at 3, 6, 12, 18, and 24 months. Alanine aminotransferase (ALT), the liver enzyme reflecting fresh damage to hepatocytes, was elevated relative to controls at all time points for both doses. There is also a trend indicating greater elevation with longer dosing periods from 3 months to 6 and 12 months for both dose groups. At 24 months ALT levels are still elevated but fall off somewhat which may reflect the loss the more susceptible rats from the study or the loss of liver tissue from which ALT could originate in these older rats. These data indicate that liver damage gets worse with dosing durations longer than subchronic (90 days) and it happened at both the high and low dose. The low dose of 1.3 mkd is a LOAEL for this study even though it was not reported as such by 3M in 1987 and demonstrates that these low-dose effects are exacerbated with long-term dosing.

The statement by NCSAB that there is "little discernable difference in serum levels at which effects have been reported in subchronic and chronic studies" is problematic for several reasons. First, there has not been serum PFOA levels reported for either of the two chronic PFOA studies so a direct comparison of subchronic and chronic studies is not possible. An estimate based only on serum PFOA levels in subchronically dosed rats would involve an assumption that young and old rats would have the same serum PFOA level for a given dose level. We know there are substantial age-related differences in humans consuming the same PFOA level in drinking water. Some of these differences in humans are likely due to age-related physiological changes and similar changes may also occur in aging rodents. Secondly, I am not aware of any PFOA rat study that reports significantly elevated liver enzymes at PFOA doses around 1 mkd other than the chronic Sibinski (1987) study. For these reasons, the rationale provided by NCSAB appears to be unsupported for effects on the liver, possibly the most sensitive endpoint for adult rodents. Also, the critical study used by NCSAB is a developmental study and the NCSAB report should contain some discussion of the issue of chronicity relating to use of a 17 day study, such as EPA guidance on such use.

The uncertainty factor for LOAEL-to-NOAEL is given as one in Table 12 of the NCSAB document. I have discussed this above and reiterate that a BMIC₁₀ that is greater than the critical study LOAEL cannot be used as a NOAEL under any guidance I have seen. I believe NCSAB should include an uncertainty factor for the use of a LOAEL and should generate a LBMIC₁₀ as an estimate of the LOAEL.

3. The Sibinski (1987) Study

The NCSAB document contains a fairly extensive description of the Sibinski study. However, there is no discussion of why NCSAB chose to characterize the low dose as a NOAEL while observing that "statistically significant increases in clinical chemistry were observed in both treated male groups from

3-18 months.” The document refers to these changes as slight which they are not. At 12 and 18 months ALT values are 2-3 fold those of controls. The fact that these values are somewhat lower at sacrifice is likely due to the loss of susceptible rats or loss of liver tissue and does not change the fact that the ALT values at 12 and 18 months make this a legitimate chronic endpoint.

The NCSAB evaluation of this study is important because this study was the basis of the New Jersey PFOA guideline, one of the few in the U.S. It is also the only multidose chronic toxicology study of PFOA. If noncancer human health risk assessment is to be done on animal studies, chronic multidose studies are generally considered most appropriate. NCSAB should provide some detail on their decision to not use this study for risk assessment. A BMDL for the Sibinski study liver effects would, in my opinion, be lower than those reported by Lau et al. (2006), so it cannot be dismissed based on the sensitivity requirement in the EPA risk assessment framework.

4. Use of Animal Instead of Human Data

There is no discussion in the NCSAB document of why human data were not used in the risk assessment other than the statement that “because human studies have not demonstrated a quantifiable dose-response relationship between PFOA exposure and health effects, the NCSAB elected to rely on animal studies.” Human data is preferable to studies in experimental animals for use in risk assessment if the data are of high quality and demonstrate a dose response. High quality PFOA dose response data on the general population has been published in the scientific literature by the C8 Science Panel and these data do demonstrate a quantifiable dose response relationship. These data suggest that effects may be occurring due to PFOA exposure to the general population at much lower PFOA serum concentrations than those at the NOAEL in animal studies. There is a very large difference between the PFOA serum levels associated with adverse outcomes in human general populations and the much higher animal PFOA serum levels in toxicology studies. This large difference suggests that humans may be much more sensitive to the effects of PFOA than experimental animals. This large difference has implications for the risk assessment of PFOA and should be discussed in the NCSAB document. A credible risk assessment for this chemical needs to recognize this issue, especially since there is much more human data on the way in the near future.

Current estimates of the ratio between drinking water PFOA levels and serum PFOA resulting from exposure to this drinking water range from 100 to 220. The PFOA MAC proposed by the NCSAB risk assessment (0.9–1.6 ppb) could accordingly result in general population serum levels of about 100-300 ppb on top of the general background level for the U.S. of about 4 ppb. Such levels are substantially higher than the median PFOA serum level (28 ppb) in the C8 Health Project population. The C8 Science Panel has reported serum PFOA to be associated with a number of adverse outcomes in this population with the results of more detailed studies coming soon. The upper end of the serum PFOA range resulting from long-term consumption of drinking water at the proposed MAC, 300 ppb, would be near median values for occupationally exposed individuals (Dupont Washington Works, WV, 400–500 ppb).

Even if the NCSAB chooses not to use the human dose response data, it should recognize in its risk assessment that there are about one dozen adverse outcomes that have been associated with PFOA serum levels in human populations. The human PFOA serum levels associated with these outcomes are thousands of times lower than that reported by Lau et al. (2006) for the mouse LOAEL (21.9 µg/mL or 21,900 ppb) that is shown in Table 9 of the NCSAB document. For the risk assessment to consistent with EPA risk assessment guidance there should be a rationale provided for using animal data given the large amount of human data showing adverse associations.

5. Low-dose Animal Studies

The critical study chosen for the NCSAB risk assessment was the Lau et al. (2006) developmental study in mice with a LOAEL at the lowest dose of 1 mkd. There are a number of PFOA mouse studies with LOAELs below 1 mkd. These studies include the following:

Macon, M.B. et al. 2010 (USEPA Poster at Society of Toxicology 2010 Annual Meeting)

Delayed mammary development in mice—gestational dosing days 10-17;

LOAEL = 0.01 mkd.

Hines, E.P. et al. 2009 (USEPA) Mol Cell Endocrin 304:97-105.

Gestational dosing days 1-17; Increased body weight, increased serum insulin and leptin;

LOAEL = 0.01 mkd

Hines, E.P. et al. 2009 (USEPA Poster at Society of Toxicology 2009 Annual Meeting)

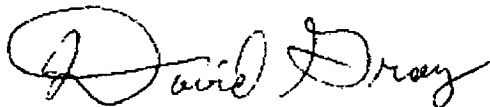
Postnatal dosing days 18-20; increased uterus weight;

LOAEL = 0.01 mkd

The NCSAB risk assessment should provide a discussion of how the selection of a study with a LOAEL of 1 mkd meets the requirement to select most sensitive study (the study showing effects at the lowest dose) as the critical study.

Thank you very much for considering my comments regarding the NCSAB risk assessment.

Sincerely,



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June 1, 2010

EWG urges North Carolina Science Advisory Board to develop a health-protective standard for PFOA in groundwater

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Regarding: NCSAB recommendations for perfluorooctanoic acid (PFOA) Maximum Allowable Concentration in groundwater

Dear Dr. Jordan,

Environmental Working Group (EWG) is a non-profit public health and environmental research and advocacy organization based in Washington, DC. We focus much of our research on human and environmental health risks from chemical contamination. With this letter, we urge the North Carolina Science Advisory Board on Toxic Air Pollutants (NCSAB) to reconsider their recommendation setting a Maximum Allowable Concentration (MAC) for highly toxic and persistent contaminant perfluorooctanoic acid (PFOA) in groundwater in the range of 0.9 – 1.6 parts per billion (micrograms per liter, or $\mu\text{g/L}$) and to rely on the latest scientific information for developing a PFOA water standard that would provide a sufficient margin of safety for the citizens of North Carolina.

Due to PFOA's widespread use in commerce and in manufacturing of everyday consumer products from cookware and food packaging to clothing as well as the extraordinary persistence and toxicity of this chemical, PFOA is now known as a pervasive global contaminant (EPA 2010a). It has been slated for removal from emissions and products by 2015, under an agreement between the U.S. Environmental Protection Agency and eight major manufacturers (EPA 2006).

This regulatory scrutiny and phase-out of PFOA could not be timelier. As demonstrated by an extensive body of research, PFOA is linked to developmental toxicity, immunotoxicity, alterations in the hormonal levels, metabolic disturbances and an elevated risk of cancer. It is laudable that, in the absence of the federal standard for PFOA in drinking water, state environmental health agencies have embarked on the process of developing their own standard for this toxic contaminant. Yet, long-term exposure to PFOA in drinking water in the concentration range proposed by the draft NCSAB recommendations would result in the pollutant building up in the body to levels at which adverse health effects are observed in human epidemiological studies.

The current draft developed by the NCSAB has three key shortcomings that undermine the scientific validity of the current MAC recommendation and that could put public health at risk:

1. If the MAC were finalized at the proposed level, North Carolinians drinking water polluted to this extent would have far higher body burdens of PFOA than other Americans. Drinking water polluted with PFOA at the level proposed as the MAC would

result in PFOA building up in the body to levels 20-40 fold higher than the current average in the general population, 90-160 ppb as compared to the general average of 4 ppb PFOA in the American population (Calafat 2008). This amount in the body would be higher than levels associated with reproductive and developmental effects, as well as effects on the immune system, hormone levels, and metabolism in human epidemiology studies. The NCSAB draft does not take into account the fact that PFOA concentrates in the body to 100 times the amount in drinking water (Emmett 2006).

2. The NCSAB draft does not take into account the extensive body of human epidemiological data on PFOA toxicity that reports a risk for reproductive and developmental effects at current levels of exposure in the general population. The MAC proposed by NCSAB could result in exposures far above those found to be potentially harmful in epidemiology studies.
3. The MAC proposed by the NCSAB is more than 30 times higher than that which would be established using standard U.S. EPA protocols for accounting for uncertainties in understanding the full range of health risks from exposures to this toxic, persistent compound. In particular, the NCSAB's unwarranted choice of inappropriately low uncertainty factors for interspecies (animal-to-human) and study type (subchronic-to-long term) conversions results in a MAC far above what is normally considered to be adequately protective of human health.

EWG strongly disagrees with the draft's assumption that "humans are likely to be less sensitive to toxic properties of PFOA than rodents" (draft recommendations, p. 16). This assumption is not supported by the available data; instead, studies are finding evidence of human health effects of PFOA at the levels found in the general population (Apelberg 2007; Fei 2009; Joensen 2009).

Below we provide to you details and specific suggestions on the steps to remedy the shortcomings of the current draft as well as EWG estimates of appropriate PFOA MAC in the range of 0.03-0.05 µg/L that is based on the latest research and U.S. EPA regulatory procedures for developing drinking water contaminant standards.

1. If the MAC were finalized at the proposed level, North Carolinians drinking water polluted to this extent would have far higher body burdens of PFOA than other Americans.

As demonstrated by the seminal study from the University of Pennsylvania, PFOA ingested with drinking water builds up in the human body to levels 100-fold higher than found in the contaminated water source (Emmett 2006). Due to this tendency of PFOA to accumulate and persist in the body, at the drinking water levels of PFOA proposed in the current draft, body burden levels in exposed residents of North Carolina may end up as high as 90-160 ppb, 20-40 times above the average levels in the general American population (Calafat 2008). As described below, these levels of PFOA have been associated with adverse health effects in human epidemiological studies. Thus, proposed MAC would place the health of the North Carolina citizens at risk from this toxic chemical.

2. For the development of MAC, NCSAB should take into account the extensive body of human data on PFOA toxicity at the levels observed in the general population.

The most recent research findings have found evidence of adverse health effects at the levels of PFOA that are found in the general population and so far scientists do not know what internal concentration of PFOA may be safe.

Key studies are listed below:

- A recent study found an association between PFOA levels in the blood and delayed time to pregnancy, a well-established indicator of fertility problems. Analyzing data from a cohort of 1,240 women enrolled in a Danish longitudinal study, a team of scientists based at the University of California-Los Angeles found that women with elevated blood levels of PFOA experienced more difficulties in conceiving and were twice as likely to be diagnosed with infertility as women with lower PFOA body burdens. For women with more than 3.9 parts per billion (ppb) of PFOA in their bodies the risk of infertility increased by 60 to 150 % (Fei 2009). This PFOA concentration is 20-40 fold lower than the levels that could build up in exposed people due to the proposed MAC.
- Study by Danish scientists associated PFOA with lower sperm quality in otherwise healthy young men (Joensen 2009). This study included 105 Danish men (median age 19 years) from the general population; the median levels of PFOA in this population were 4.9 ppb. Researchers observed that men with high levels of perfluoroalkyl acids (PFAAs) had a median of 6.2 million normal spermatozoa in their ejaculate compared to 15.5 million normal spermatozoa counts among men with low PFAA levels. The authors of the study suggested that “high levels of PFAAs may contribute to the otherwise unexplained low semen quality seen in many young men” (Joensen 2009). PFOA concentration in this study population was 18-32 fold lower than the levels that could build up in exposed people due to the proposed MAC.
- An association of the PFOA with serum lipids was reported in a multi-year study of 69,000 West Virginians and Ohioans whose drinking water was contaminated by a fluorochemical manufacturing plant in Washington, W.Va., along the Ohio River (Steenland, Tinker, Frisbee 2009; West Virginia University School of Medicine 2008). These findings of elevated cholesterol and other lipids in people exposed to PFOA in drinking water are in agreement with the increased lipid levels in PFOA-exposed workers in fluorochemical plants (Costa 2009; Sakr, Kreckmann 2007; Sakr, Leonard 2007). The authors of the study concluded: “If a causal relation between perfluorinated compound levels and cholesterol exists, there could be potentially serious consequences in the form of increased risk of cardiovascular disease” (Steenland, Tinker, Frisbee 2009).
- In the same study, known as the C8 Health Project, greatly decreased concentrations of estradiol were observed in women and in girls with higher serum levels of PFOA (West Virginia University School of Medicine 2008). Adverse effects on the immune system have also been noted (Frisbee 2008). The immune system changes included a significant decrease in serum levels of two immune defense proteins, immunoglobulins IgA and IgE, which correlated with increasing PFOA serum levels (C8 Science Panel 2009). The levels

of PFOA that could build up in the bodies of North Carolina citizens due to the proposed MAC would be in the range where changes in key biological markers are observed in the C8 Health Project study population.

- The latest publication from the C8 Health Project found that PFOA is significantly associated with elevated levels of uric acid in serum (Steenland, Tinker, Shankar 2009); similar results have been reported in cross-sectional studies of PFOA-exposed workers (Costa 2009; Sakr, Kreckmann 2007). Increased uric acid is a risk factor for hypertension; it may also be associated with stroke and diabetes (Heinig 2006; Steenland, Tinker, Shankar 2009).

These studies are only the latest addition to the rapidly growing body of data indicating that the levels of PFOA in the general population pose a risk to human health. We agree with the NCSAB opinion that currently published human studies cannot be used to derive a quantifiable dose-response relationship (draft recommendations, p. 13). Yet, we strongly disagree with the draft's decision to rely exclusively on animal studies for estimating MACs without taking human data into consideration.

Additionally, human PFOA toxicity studies outlined above clearly demonstrate that the assumption about lower sensitivity of humans to PFOA compared to animals is unwarranted. They also demonstrate that chronic PFOA exposure is associated with the type of health effects that may be easily missed in short-term (subchronic) animal studies, such as the effects on the immune system, metabolism, and fertility, as well as increased risk of cancer. In people these effects would lead to long-term, chronic health problems that carry a heavy burden of suffering as well as high financial costs.

3. NCSAB should incorporate uncertainty factors into the PFOA standard development that will result in a MAC that protects public health, using a total uncertainty factor of 1000 and deriving a Maximum Allowable Concentration estimate of PFOA in groundwater in the range of 0.03-0.05 µg/L. The uncertainty factor used in the current draft is 33 times less protective than what EPA advises for the development of drinking water standards.

The current draft identified three studies for selection of critical endpoints and the points of departure for the development of MAC. These studies are:

- A reproductive toxicity study in rats where animals were orally dosed with PFOA for 2 months (males) to 4 months (females) (Butenhoff 2004).
- A small scale study in male cynomolgus monkeys which involved only 4 animals in the lowest exposure group and lasted 6 months (Butenhoff 2002)
- A developmental toxicity study in mice where female mice were dosed with PFOA during pregnancy (gestational day 1 through 17) and critical developmental endpoints were examined in newborn pups (Lau 2006).

These three studies selected by NCSAB for quantitative assessment and derivation of the benchmark internal concentration dose are an important contribution in the PFOA research field. However, none of these studies was developed with the specific goal of determining the safe drinking water concentration of PFOA. Thus, data from these studies need to be treated with appropriate consideration of their limitations as well as their strengths.

Assessment of public health risks from drinking water contaminants relies on an inherently difficult extrapolation from animal studies to humans which is the reason why the U.S. Environmental Protection Agency (EPA) has developed a series of guidelines for conducting animal studies that are suitable for regulatory purposes (National Research Council 2006; U.S. EPA 2010). For a life-time exposure, chronic animal studies “conducted for a period of at least 12 months” serve as a key source of data (U.S. EPA 1998).

A subchronic (less than a year) toxicity study can be used for deriving short-term drinking water health advisories (Donohue 2002; U.S. EPA 2002, 2009). If a chronic toxicity study is not available, data from subchronic exposure study can be used with the application of appropriate uncertainty factors to derive safe drinking water concentrations from experimental animal data. As described by EPA guidance document, uncertainty factors are generally 10-fold and are intended to account for, among several consideration, “the uncertainty in extrapolating animal data to humans (i.e., interspecies variability)” and “the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure)” (U.S. EPA 2002).

The draft NCSAB assessment chose an uncertainty factor of 3 for account for interspecies extrapolation, on an unfounded assumption that “humans are likely to be less sensitive to toxic properties of PFOA than rodents.” Nowhere in the draft document did NCSAB provide a scientific rationale and support for this statement. In fact, as demonstrated by a growing body of science, we are now finding health effects at the PFOA levels found in the general populations (average of 4 ppb in the American population, as determined by the researchers at the Centers for Disease Control and Prevention (Calafat 2007)). No animal studies have been even conducted at the PFOA levels so low. This human data, combined with the fact that PFOA has a much longer half-life in people compared to rodents (Olsen 2007) requires an application of a 10-fold safety factor, not an unjustifiable 3-fold factor that was chosen by the draft.

The study type uncertainty factor was selected by the draft to be at 1, which is inappropriate since the three studies used for the selection of the points of departure are not chronic studies. In Butenhoff (2004) study, rats were dosed with PFOA for no longer than 40 days. Butenhoff (2002) study suffered from the small group size, with only 4 animals in the group exposed to the lowest concentration (3 mg/kg/day) of PFOA and the study lasted 6 months. Finally, in Lau (2006) study, the duration of exposure was only 17 days of gestation, a far cry from the guideline 1-year study.

Another shortcoming of all three studies is that the true LOAEL (lowest observed adverse effects level) was not, in fact, identified in any of the publications because of the study design limitations. In each case, adverse health effects were noted at the lowest dose tested (1 mg/kg in

Butenhoff 2003; 3 mg/kg in Butenhoff 2002 and 1 mg/kg in Lau 2006). The current draft incorrectly classifies these lowest tested doses as LOAEL without noting the limitation that the true LOAEL could have been significantly lower but was simply not tested in those studies. Although the available data can be utilized for calculation of the benchmark dose, it is important to remember that these datasets likely underestimate the full extent of PFOA toxicity because of the high dose range tested.

Furthermore, human studies outlined in point 2 above demonstrate that PFOA accumulation and persistence in the body places humans at a type of long-term risks that mice and rats, with much faster PFOA elimination, might not experience. These data demonstrate that a 1-fold uncertainty factor for extrapolation from subchronic animal studies to a safe dose for human life-long exposure is inappropriate. Combined, all of these factors mean that a full, 10-fold uncertainty factor should be applied for study type extrapolation since the draft aims to start from a subchronic animal study and estimate a PFOA drinking water concentration for life-time exposure.

In sum, with the correctly updated uncertainty factors (10 for interspecies, as demonstrated above; 10 for intraspecies, as used in the draft; and 10 for study type, as demonstrated above), the total uncertainty factor should be 1000, not 30 as used in the current draft. Therefore, starting from the range of points of departure calculated in the draft with the benchmark dose methodology (31-58 µg/ml, p. 17 of the draft recommendations), the final Maximum Allowable Concentration estimate of PFOA in groundwater would be in the range of 0.03-0.05 µg/L.

In conclusion, EWG urges NCSAB to remedy the severe gaps in the current draft that, should the currently proposed standard be accepted, would pose a significant health risk for the citizens of North Carolina. We strongly advise the Board to incorporate the appropriately protective uncertainty factor of 1000 into the MAC estimates and to develop new guidelines for Maximum Allowable Concentration of PFOA in groundwater that would be in line with the latest scientific research. We will be pleased to continue working with NCSAB on the issues of PFOA safety for humans and the environment and provide our feedback on the future steps in this important process.

With best regards,

Olga V. Naidenko, Ph.D.
Senior Scientist
Environmental Working Group

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June 1, 2010

Reginald C. Jordan, Ph.D., CIH
NC Division of Air Quality
North Carolina Dept of Environment and Natural Resources
Raleigh, NC 27699-1641

Dear Dr. Jordan:

I am writing on behalf of Public Employees for Environmental Responsibility (PEER) to urge the North Carolina Science Advisory Board (SAB) to recommend a Maximum Allowable Concentration (MAC) for Perfluorooctanoic acid (PFOA) in groundwater that is protective of public health.

Regardless of the final MAC recommended, due to serious public health concerns and demonstrated technical feasibility and efficacy of activated carbon treatment, we urge the SAB to include a recommendation for treatment upon detection. This recommendation is supported by the experience cited in Arnsburg, Germany, where charcoal filtration was installed soon after detection (at levels of 0.5 to 0.64 ppb). Treatment successfully brought PFOA levels below detection and reduced residents' blood plasma levels by approximately 20% (draft, Table 1, @ page 4). We note that **the SAB's draft recommended health based MAC of 0.9 – 1.6 ppb is in excess of the levels that triggered treatment requirements in Germany**

Similar reductions in serum PFOA were achieved by treatment systems installed in several communities in West Virginia and in Ohio (draft, Table 2, @ page 5). In this vicinity, residents were eligible to be included in a health study and bottled water and/or treatment were begun if the PFOA concentration exceeded 0.05 ppb, almost 20 times lower than the lowest MAC recommended by the NC SAB.

Moreover, the U.S. Environmental Protection Agency has issued a Provisional Drinking Water Health Advisory for PFOA which is intended for short term (not chronic or lifetime) exposure of 0.4 ppb, which is less than the North Carolina proposed MAC which is intended for lifetime exposure
(See http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA_PFOS.pdf).

PEER does not believe that the SAB requires mechanistic data or proof of causality in humans to establish a precautionary MAC standard that is protective of the most sensitive effects associated with PFOA, which are serious adverse fetal growth and developmental effects (see sources cited in Cooper letter, below).

We suggest that the SAB draft recommended range of 0.9 – 1.6 ppb may not be adequately protective due to:

- 1) Over-reliance on the work of Dr. Tardiff of “The Sapphire Group” which is well known (see <http://www.thesapphiregroup.com/>) for its representation of industrial clients; and
- 2) Application of uncertainty factors.

I) Over-reliance on the work of Dr. Tardiff

We are concerned about the use of the paper authored by Dr. R.G. Tardiff and others from the Sapphire group as the primary basis for the SAB deliberations and recommendations.

Dr. Tardiff and his Sapphire group colleagues were funded to develop the risk assessment presented in the paper by DuPont and 3M, two companies who are responsible for contaminating the environment with PFOA (see <http://www.thesapphiregroup.com/pdf%20documents/PFOA%20Press%20Release.pdf>). In that capacity, Dr. Tardiff has incentives to select studies, interpret data, and resolve uncertainty to the benefit of his clients, DuPont and 3M.

The financial connections create an appearance that Dr. Tardiff’s work on PFOA may not be independent and objective. Dr. Tardiff’s apparent bias conflicts with the SAB’s mission to conduct independent objective science. The SAB mission is to promote protection of public health by exercising sound, unbiased scientific judgment in making conservative and protective assumptions, data interpretations, and resolving uncertainty. At a minimum, transparency and scientific integrity require that Dr. Tardiff’s financial conflicts be disclosed to the public.

Our concerns were heightened by a letter to the editor of the journal Food and Chemical Toxicology (April 19, 2010), in which Dr. Keith R. Cooper of Rutgers University raises serious concerns about Tardiff’s analysis (see: http://sz0045.wc.mail.comcast.net/service/home/~/-cooper%20letter%20on%20Tardiff%20FCT%20paper.pdf?auth=co&loc=en_US&id=200961&part=3).

“...The journal’s length limit for letters to the editor allows for discussion herein of only some of the most important of the **numerous errors, omissions, misrepresentations, and deviations from established risk assessment approaches in this [Tardiff et al] paper.**[...] It is my opinion that the authors (Tardiff et al) selectively chose the studies and endpoints considered in their analysis and used unconventional application of uncertainty factors in order to inflate their recommended health based drinking water levels. The concentrations given as safe for chronic exposure, 0.88 – 7.7 ug/L are not supported by either animal data or current epidemiological studies. Chronic exposure to these levels in drinking water would cause elevation of serum concentrations to levels associated with dose-related effects in humans and with permanent developmental

effects in rodents. **Thus, chronic exposure to these levels cannot be considered to be protective of public health.** (emphasis added)

We strongly urge the SAB to review Cooper's full analysis, consider the sources cited by Cooper on developmental effects, and re-assess and more closely scrutinize the work of Dr. Tardiff.

Dr. Tardiff's work was reviewed by the SAB on August 26, 2009: <http://daq.state.nc.us/toxics/risk/sab/proceed/143.pdf> The October 21 and November 18, 2009 SAB minutes indicate that the SAB reviewed the risk assessment work of New Jersey and Minnesota, and discussed seeking New Jersey and Minnesota scientific reviews of the draft Risk Assessment. That apparently was not done. However, review of the minutes suggests that Dr. Tardiff was relied on as the source to critique the use of some uncertainty factors in the NJ risk assessment. We are concerned with this apparent asymmetrical situation.

SAB meeting minutes also show discussion and concern by Dr. Kenneth Rudo, North Carolina State Toxicologist, about Dr. Tardiff's inappropriate use of uncertainty factors in his risk assessment. Dr. Rudo supported the use of uncertainty factors of 10 for each component in order to be more protective.

II) Use of uncertainty factors

According to NCSAB Policy and Practices guidelines:

<http://daq.state.nc.us/toxics/risk/sab/sabpolicy.shtml>

"Following deliberation, the NCSAB develops a recommendation including a 'range of risks' for the compound being reviewed. NCSAB recommendations are part of a narrative (see model outline below) prepared by the NCSAB Liaison and approved by NCSAB members. The narrative is not an in-depth examination of the toxicology of the compound. Rather, it is a document that is intended to discuss the NCSAB recommendation, **with adequate explanation of all safety factors used, points of uncertainty or disagreement, a discussion on alternate recommendations and the resulting risks to the public health**, and a mathematical representation of the final risk assessment methodology." (emphasis added)

While the draft MAC recommendation does provide a narrative overview of the scientific literature, we do not believe there is full transparency and adequate explanation of all safety factors used and full discussion of points of uncertainty or disagreement.

This discussion is particularly warranted, as we sense that there is a high degree of scientific controversy regarding health risk of PFOA; because the SAB recommended MAC range deviates significantly from other state health based levels; and because the recommended range appears to be sensitive to study selection, target health endpoints, assumptions, data interpretations, and uncertainty factors used.

A more thorough discussion of these issues is warranted in order to adequately inform and meaningfully involve the public in the SAB recommendation. Complete transparency and robust discussion are especially warranted, given Cooper's critique, a reasonable perception of Tardiff's bias, and DuPont's potentially inappropriate influence.

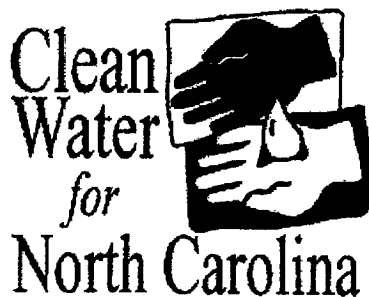
We urge the SAB to reconsider the draft MAC in light of the studies on developmental effects cited by Cooper and Cooper's analysis of Dr. Tardiff's risk assessment

PEER appreciates the opportunity to submit these comments and urges your favorable consideration.

Sincerely,

Jeff Ruch
Executive Director

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2009 Chapel Hill Rd. Durham, NC 27707

June 1, 2010

Reginald C. Jordan, Ph.D., CIH
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 1641 Mail Service Center

COMMENTS ON RECOMMENDED MAC FOR PFOA

Dear Dr. Jordan:

Clean Water for NC is a science-based environmental justice organization working with communities to protect their right to safe, affordable water and environmental health. From 2004, we have been concerned with groundwater and air contamination by DuPont's Fayetteville manufacturing facility as well as other manufacturing plants that may be using PFOA in their processes. Our organization has met with the local community around the Fayetteville plant, has collaborated with organizations who have taken samples from the Cape Fear River and wells in the vicinity of the plant.

As an organization that advocates for the safe use of NC's groundwater as affordable rural water supply, we must object to the recommended standard, as it is:

- 1) could result in a substantial overall increase in body burden of PFOA in those drinking PFOA contaminated water with unknown health effects and no regulatory consequences for producers or users of PFOA, a public health experiment that is unconscionable.
- 2) Is significantly above the levels reported in the Cape Fear River and at sites very close to the point of production, thus reducing regulatory leverage and monitoring to protect the public from contaminated surface water that may be a drinking water source with no PFOA contaminant removal requirements, or groundwater migrating off site to potential public or private wells or small impoundments used for fishing or swimming.

We are deeply concerned by the proposed groundwater standard of 0.9 to 1.6 ppb on several grounds, and the studies on which it was based. We believe that a reasonable level of precaution would have called for a standard ten to 30 fold lower than this range.

- 1) the long-reported differences in metabolism between humans and other studied animals and apparent highly efficient renal reabsorption in humans, as well as the greater than ten fold variation in individual retention and sensitivity of organ systems should have driven a more cautionary uncertainty factor than the 30 fold that was applied

- 2) the assumptions about the volume of water consumed (2liters) and source contribution of 0.2 are significantly less conservative than is appropriate for a recommendation for groundwater levels of a persistent anthropogenic toxin.
- 3) I was present when DuPont scientific staff presented to the SAB and was startled by the lack of incisive questions for the presenter, indicating passive acceptance of the risk assessment approach and studies the industry had been using as the basis for seeking weak standards. This lack of a critical analysis is reflected in the final recommendation to the Division of Water Quality.

In summary, the recommended MAC of 0.9 to 1.6 ppb falls short of a protective standard that would allow conscientious regulation in the public interest. We ask that DWQ take a more precautionary approach, apply more conservative uncertainty factors and implement a standard at least 10 fold lower, in order to protect the public's water and long-term health.

Yours sincerely,

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