Geary Olsen/US-Corporate/3M/US
10/01/2007 04:19 PM

To William K. Reagen/US-Corporate/3M/US@3M-Corporate
cc
bcc
Subject Re: Fw: Request for comments

Bill,

Per his request, please forward these comments to Dr. Giesy. As the reviewer, Dr. Giesy has the sole decision to include, modify, and/or exclude any of these comments in his review and decision process.

Regards,
Geary


Comments re paper.doc

Geary Olsen
3M Corporate Occupational Medicine
Mail Stop 220-06-W-08
St. Paul, MN 55144
phone: 651-737-8569
fax: 651-733-9066
gwolsen@mmm.com

Exhibit
2177
State of Minnesota v. 3M Co.,
Court File No. 27-CV-10-28862

Summary of Comments. Although I believe the authors of this paper have a study database that eventually will be worthy of publication in a scientific journal, this manuscript, by its very content, is not suitable for *Toxicological Sciences*. The primary purpose of the paper, i.e., biomonitoring of 101 maternal/cord blood pairs, is not 'toxicological' but rather biomonitoring in purpose. Therefore, this paper should have been submitted to an environmental or public health journal such as *Environmental Research*, *Environmental Health Perspectives*, or *Environmental Science and Technology*. Prior to submission to one of these journals, however, this paper is in need of major revision. First, the authors must carefully review the published literature as the authors' manuscript is considerably out-of-date with the published literature, especially that which has occurred in the last 12 months. In particular, the authors are unaware of the two large studies that have examined perfluorochemical concentrations in maternal blood and cord blood. These studies are Apelberg et al. (Environ Health Perspect 2007), and Fei et al. (Environ Health Perspect 2007). The exact reference citations and details of these papers are discussed below. These studies, and Grice et al. (2007), also examined birth weight in relation to PFOS and PFOA biomonitoring data. The authors in their analysis of birth weight, failed to include critically important covariates, including maternal weight gain, parity, and smoking. These could have been easily abstracted from the medical record which the authors said they did. Also, the authors should delete their speculation about sex ratio alterations and devote much more attention to a reanalysis of their birth weight to include the above covariates. The authors are also out-of-date with published biomonitoring studies from the CDC that have shown perfluorochemical concentrations have declined in the general population by 35% (PFOS) and 25% (PFOA) between 1999-2000 and 2003-2004. Finally, the authors should address the reason why they continued to use the 'old' ion-pairing extraction procedures rather than the currently recommended methods of solid phase extraction.

Specific Comments.

Abstract. Second sentence. This sentence confuses "exposure" and biomonitoring data. Biomonitoring data have now been well-documented for both occupational and non-occupational (adult general populations). The specific exposures that have led to the ubiquitous serum concentrations found in the general population are not known although many sources have been shown to be possibilities.

Abstract, 15th line. The authors state that PFHS was quantifiable in 45.5% of the maternal and 20% of the UCB samples but do not state exactly what the concentrations were. This sentence, therefore, is uninformative and needs to be revised to add specific concentration-related data.

Introduction. First paragraph. 11th line. The authors cite serum half-lives as if they are highly precise estimates. They also cite an old reference (Olsen et al. 2005a) that was an abstract given at a conference. The authors need to cite the published paper by Olsen et al. See Environ Health Perspect 2007;115:1298-1305. In this paper, they will see that the estimates they should cite for an "average" value are the geometric means and they should also provide the 95% confidence intervals. These geometric means for PFOA, PFOS, and PFHS are 3.5 (95% 3.0-4.1), 4.8 (95% CI 4.0-5.8), and 7.3 (95% CI 5.8-9.2) years, respectively

Made Available by 3M for Inspection and Copying as Confidential Information:
Subject to Protective Order In Palmer v. 3M, No. C2-04-6309

Introduction. Second paragraph. 2nd line. What is "500 and 2000 ng/mL" in this sentence referring to? Is it the averages found?

Introduction. Second paragraph. Sixth line. The authors state that Gilliland and Mandel (1996) reported that PFOA may modulate the hepatic responses to obesity since hepatic enzymes (SGOT and SGPT) were increased in obese workers. Gilliland and Mandel did not analyze for PFOA rather they analyzed for total organic fluorine for which PFOA was likely the most prevalent compound. Also, this "modulation" effect was not replicated on several subsequent cross-sectional investigations of medical surveillance data from the same PFOA production facility when specific measurements of serum PFOA concentrations were used. See Olsen et al. Drug Chem Toxicology 2000; 603-620.

Introduction. Second paragraph, third sentence. The authors need to be much more specific when they cite fluorochemical concentrations throughout this document as to the geographical location and time period when the samples were collected. This third sentence is an example. The authors wrote, "In blood samples from a population without occupational exposure serum levels of POFS and PFOA were 34.7 ng/mL and 5.6 ng/mL, respectively (Olsen et al. 2003a; Olsen et al. 2005b). The first Olsen et al reference (2003a) is of an occupational study population and therefore is inappropriately cited. The 34.7 ng/mL and 5.6 ng/mL concentrations refer to measurements of blood samples collected in 1989. The Olsen et al. reference compares these data, cited by the authors, to blood samples collected in 1974 and 2001 from the same locality. The data, thus, are taken out-of-context.

Introduction. Second paragraph, fifth sentence. The authors discuss pooled-serum data reported by the U.S. Centers for Disease Control and Prevention but failed to cite several very important studies that have been published subsequently from the CDC involving the NHANES database. These readily available published papers include the 1999-2000 NHANES data (Calafat et al. Environ Sci Technol 2007;41:2237-2242), the 2003-2004 NHANES data (Calafat et al. Environ Health Perspect 2007; doi:10.1289/ehp.10598) and a preliminary assessment of American Red Cross blood donor data collected in 2005 (Olsen et al. Chemosphere 2007;68:105-111). The latter two studies clearly indicate that PFOS and PFOA concentrations are declining in the U.S. general population since 2000. According to the 2003-2004 data by Calafat, these are 35% and 25% declines of PFOS and PFOA, respectively, since the NHANES 1999-2000 data were collected. Olsen et al. indicate the declines approach 50% by 2005 although their sample size is quite small as it was only a preliminary study.

Introduction. Third paragraph. First sentence. PFCs are not reproductive hazards. If they are, the authors need to cite which study suggests they are reproductive hazards. Clearly, they are developmental hazards. Indeed, the authors come to this conclusion in their third to last sentence of the fourth paragraph of their Introduction when they write, "Taken together the animal data raises concern for potential developmental effects in the human population and thus highlight the need to measure exposure during fetal development." The authors do not surmise that the data suggest reproductive problems and neither do the collective toxicological data published in the literature.

Made Available by 3M for Inspection and Copying as Confidential Information:
Subject to Protective Order In Palmer v. 3M, No. C2-04-6309

Introduction. Fourth paragraph. Given the great length that many developmental toxicologists measured internal concentrations of PFOS and PFOA, it is disappointing to see these authors only cite dose levels (mg/kg) and not internal concentrations in their Introduction, let alone discuss the benchmark dose internal concentrations (5%) that have been provided in the literature. If these authors desire to publish in *Toxicological Sciences*, they need to cite toxicological data critical to the interpretation of their biomonitoring data. For example, Lau et al. has reported (see Toxicol Sci 2007:99:366-394) that the $BMDL_5$ for the effects reported by Thibodeaux et al. and Luebker et al. for PFOS provide a range between 25 ppm and 67 ppm. This equates to 25,000 ng/mL and 67,000 ng/mL, four orders of magnitude higher than the concentrations the authors have measured. The authors also need to keep the same unit comparisons, i.e., in ng/mL, when comparing animal toxicology data to human data since the latter are reported in low ng/mL concentrations.

Materials and Methods. First paragraph. There is no discussion on the inclusion criteria by which a subset of 101 study subjects were enrolled in this particular study from the 1058 subjects who agreed to be contacted. How were these 101 study subjects chosen? Were there refusals? If so, how many? What their demographic characteristics were like compared to the responder? Were other chemical compounds measured in the blood besides those listed by the authors?

Materials and Methods. First paragraph. Last sentence. Given the respiratory difficulties that the rat pups demonstrated at birth, did these authors collect Apgar scores from the medical charts? If not, why not?

Materials and Methods. Third paragraph. Analytical methods. Why did the authors use the much older "ion-pairing" method for extraction when solid-phase extraction techniques are much more readily accepted now?

Materials and Methods . Statistical Analysis (pages 11 – 12). The authors desired to determine the effect of "PFC" exposure on birth weight using multiple stepwise regression analysis Given the fact that the authors had access to the Apelberg et al. paper (Environ Health Perspect doi:10.1289/ehp.10334) prior to their manuscript's submission to *Toxicological Sciences*, a critical question is why did the authors not adjust for many of the potential covariates that can affect birth weight. For example, Apelberg et al. included as covariates in their birth weight models the following: maternal age, current smoking status, ethnicity, previous preterm birth, underweight status, overweight status, obesity, hypertension, and diabetes. Since the authors of this manuscript had access to the medical record of their 101 subjects, it is confusing why they did not abstract from the record some of these covariates that need to be adjusted for when examining birth weight. For the authors to state that looking at birth weight was not the primary purpose of the paper is not an acceptable answer. The authors clearly intended to look for an effect with birth weight. To discount their 'lack of an association' because it was not a primary purpose is simply an inappropriate explanation. Yet somehow, the authors (discussed below) speculate about sex ratios?

Results. The write-up regarding the concentrations of the different perfluorochemicals could be condensed as it seems repetitious. Table III is an adequate description of what these authors found in maternal serum concentrations at 24-28 weeks, at delivery, and in the umbilical cord

Made Available by 3M for Inspection and Copying as Confidential Information:
Subject to Protective Order In Palmer v. 3M, No. C2-04-6309

blood. The text could easily be condensed given the data provided in Table III. Note: PFNA is not perfluorononanoic but perfluorononanoate. See footnote in Table III. Same for PFHpA and PFdeA. The Figures displayed are graphed on the wrong axis. The response variable is birth weight. The explanatory variable is the fluorochemical. Therefore, birth weight needs to be on the y-axis and the fluorochemical needs to be on the x-axis. See Apelberg et al. as an example.

Discussion. First paragraph. The authors write there are "no reports of human developmental toxicity following exposure to PFCs." The authors have, unfortunately, failed to review the recent literature for their paper. There are three major studies that have examined human developmental toxicity endpoints, in particular, low birth weight. These include the following: 1) Apelberg et al. Environ Health Perspect doi:10.1289/ehp.10334; 2) Fei et al. Environ Health Perspect doi:10.1289/ehp.10506; and 3) Grice et al. J Occup Environ Med 2007;49:722-729. These three studies provide highly conflicting data. Whereas Apelberg et al. suggested there was an inverse association between birth weight and PFOA and PFOS cord blood concentrations at general population concentrations measured comparable to what these authors measured, such findings were not replicated in a much larger study using 1400 maternal serum samples in Denmark for PFOS and a much weaker association was observed for PFOA. Grice et al. did not find an association between PFOS or PFOA occupational concentrations that were approximately 250 times higher than the general population, with self-reported birth weight recalled by female production workers. None of this literature is discussed by the authors and undoubtedly needs to be included in this paper. The authors are to be credited, however, in recognizing the critical fact that any analysis of birth weight must consider plasma volume expansion that occurs during pregnancy. Yet, the authors, without comment, then do not adjust for proxy variables of plasma volume expansion, such as maternal weight gain, when they analyze for birth weight.

Discussion. First paragraph. The authors place too much emphasis on the Inoue et al. 2004 paper. This analysis included only 15 individuals. The studies by Apelberg et al., Fei et al., and Grice et al. are much more relevant.

Discussion. First paragraph. The authors infer that their pregnant women in their study had maternal serum levels of PFOS that were lower compared with non-pregnant adults with non-occupational exposure. The authors, unfortunately, have not kept their collection time periods in mind. The data they cite to substantiate their statement were collected in the 2000 time period yet their samples for their study were collected in 2004-2005. The correct reference group to use is the data reported by Calafat et al. from NHANES 2003-2004 (see reference above) which showed average PFOS concentrations at 21 ng/mL in the representative sample of the general United States population. This level is very comparable to the authors' study subjects blood concentrations that were at 18 ng/mL. It is important for these authors to recognize that PFOS (and PFOA) concentrations are not constant since the phase-out of the primary manufacturer's production in 2000.

Discussion. Fourth paragraph. In the first sentence, multiple regression is an inanimate object. It does not "fail" anything. This first sentence, therefore, needs to be re-written. The next several sentences also make no sense. The authors state the primary focus of their study was to characterize developmental exposure to PFC, and then imply the lack of birth weight association

Made Available by 3M for Inspection and Copying as Confidential Information: 3MA02540637
Subject to Protective Order In Palmer v. 3M, No. C2-04-6309

should be minimized. Yet they then devote 11 lines on the non-statistically significant sex ratio as if it may be a biological plausibility. The references by James refer to this particular researcher's lifelong quest to prove sex ratios are altered by a variety of chemicals. There are many critics of the work that James has done besides that of Marcus et al. (1998). If the authors believe sex ratio is affected, they should devote the time necessary to examine sex ratios of the pup data published in the developmental studies rather than refer to totally unrelated work done by James.

Discussion. Fifth paragraph. Second sentence. The authors write that *in utero* exposure to PFOS resulted in an increased number of birth defects such as cleft palate, anasarca, ventricular septal defect and enlargement of the right atrium. Although true, this is clearly related to maternal toxicity and as Lau et al write in their review of the perfluoroalkyl acids in *Toxicol Sciences* (2007:99:366-394), these findings are generally unremarkable when maternal toxicity is taken into account.

Discussion. Fifth paragraph. Third sentence. It is not correct to state that PFOS compromised fetal lung maturation during late gestation causing the observed respiratory distress syndrome. The findings of respiratory distress, as studied and discussed by Grasty et al. (2005), involved investigating the effects of pulmonary surfactant abnormalities, phosolipid composition, gene profile expression, and the effect of co-administration of dexamethasone or retinyl palmitate (lung maturation promotion compounds). Grasty et al. concluded that the respiratory distress of PFOS-exposed newborns is likely not to be related to immaturity of the lung. Lehmler et al. (Colloids Surf B Biointerfaces 2006:51:25-29) has now shown it is more likely due to the effect of PFOS (i.e., PFOS is a surfactant) to interact with pulmonary surfactants. In their study they examined how PFOS interacted with dipalmitoylphosphatidylcholine.

Made Available by 3M for Inspection and Copying as Confidential Information:
Subject to Protective Order In Palmer v. 3M, No. C2-04-6309