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E-mail and Federal Express

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Re: Comments to the Sciences Advisory Board Perfluorooctanoic Acid Risk Assessment (PFOA) Review Panel

The purpose of this letter is to submit information for consideration by the USEPA's Science Advisory Board Perfluorooctanoic Acid Risk Assessment (PFOA) Review Panel (Panel) regarding its review the USEPA January 4, 2005, "Draft Risk Assessment of the Potential Human Health Effects Associated with Exposure to Perfluorooctanoic Acid and its Salts" (Draft Risk Assessment). We are an environmental consulting firm serving a variety of private and public sector clients, including USEPA, and have been involved in the assessment of PFOA human health risk for the past several years. We believe it would be useful to USEPA's deliberations regarding PFOA health risks if the Panel considered the issues described below.

I. Whether the human blood data used in calculating the MOEs is reflective of the US population.

The EPA Risk Assessment calculates margin of exposure (MOE) values by dividing either the serum PFOA concentration for the NOAEL or LOAEL in rats or monkeys by a human serum PFOA level. The human serum levels used for the calculation were taken from a study that measured PFOA levels in American Red Cross blood bank samples (ARC study). The results of this analysis for various demographic groups were stated in the Draft Risk Assessment to be representative of the US population. For example, the human serum level used for the prenatal MOE calculation is 4.2 ppb (8.4 ppb at the 90th percentile) from the ARC study for women aged 20 to 69 years. The MOE was then calculated to be 823 (412 90th percentile).

ARC study reports values are not consistent with those of the only other published study measuring PFOA blood levels in the US general population. A study of blood PFOA levels in the US and other countries was conducted at the New York State Health Department (Kannen et al., ES&T 2005) and involved investigators from nine countries. For US populations, the study reported the following mean values: New York City -- 27 ppb (both genders, n = 70); Kentucky -- 41.6 ppb (men, n = 19), 23 ppb (women, n =11); and Michigan -- 4.7 ppb (women, n = 46), 5.7 ppb (men, n = 29). Serum levels for other countries were highly variable with the highest averages of 88.1 and 35.5 ppb for Korean women (25) and men (25), respectively, while PFOA was not detectable in the blood of individuals from India, Malaysia, Italy, and Brazil.



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The variability in these blood data is greater than that suggested by the 90 percentile value (8.4 ppb) of the ARC database. The range of values from Kannan et al. (2005) for the 70 subjects from New York City is 14 to 56 ppb. The bottom of this range is substantially higher the 90 percentile value from the ARC database. This suggests the variability for U.S. serum PFOA levels may be much larger than that of the ARC study and the 90th percentile value may be much higher than 8.4 ppb. Roughly 27 million members of the US population have serum PFOA levels above the true 90th percentile value and 2.7 million above the 99th percentile. If the variability in US serum levels is greater than that of the ARC database, body burdens at the high end of the distribution may be at occupational PFOA levels or even experimental levels. MOEs for subpopulations at the high end of the distribution may then be much lower than that calculated by EPA from the ARC database.

Although these comments specifically address the prenatal MOE calculated by EPA, the human serum PFOA levels used in the other MOE calculations should also receive the attention of the Panel.

II. Whether the MOE for non-human primates should be calculated given that mortality occurred in the low-dose group of the subchronic cynomolgus monkey study.

MOEs should not calculated on severe endpoints if they are to be used to characterize the safety of chronically exposed human populations. Serum PFOA concentrations in the subchronic cynomolgus monkey study were not proportional to administered dose levels. The death of one of four monkeys in the low-dose group during week 20 is not surprising since the serum PFOA concentration of this monkey differed little from those of the high-dose group (143 versus 162, 111, 161, 154, and 137 ppm) at week 6. From week six to 12, three of high-dose monkeys had to be removed from dosing due to toxicity, suggesting the mortality seen in the low-dose group was treatment related. Treatment related mortality in the low-dose group indicates that serum or administered dose levels from this study should not be used to generate MOEs or RfDs for use in human health risk assessment.

III. Whether the statistically significant decrements in absolute and relative pituitary weight in the F1 female rats in the 2-generation York (2002) study be considered an legitimate endpoint.

In the York (2002) study, doses of 0, 1, 3, 10, and 30 mg/kg/day were administered orally to the parental, F1, and F2 generations. Absolute and relative pituitary weight statistically significantly decreased 12--15% for the 3, 10, and 30 mg/kg/day groups. The study authors interpret these changes as not treatment related and state that "the pituitary weights for individual animals in the higher dosage groups were within the range of values for study controls; a similar pattern of pituitary weight changes was not observed in the P-generation female rats; a similar pattern of pituitary weight changes was not observed in either generation of male rats, which are typically more sensitive than females to APFO-induced effects; and no microscopic changes were seen in the pituitary in either sex of either generation; the statistics are based on a change in the mean weight value of control of 2 mg (17 versus 15 mg) with standard deviations of 2-4 mg."

The reasons given by the study authors relate to the magnitude of the changes, the sex or life-stage specificity of the changes, or the lack of histopathological findings. The EPA



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guidance on reproductive toxicology which provides recommendations on two-generation studies such as the York study clearly states that statistically significant pituitary weight changes are to be considered adverse effects. The guidance also clearly envisions sex and life-stage specific effects as meaningful endpoints since seeking such effects are among the primary reasons for conducting a multigenerational study in the first place. Also, histopathological changes are not a prerequisite for considering an organ weight change an adverse effect according to EPA guidance.

Additional considerations regarding pituitary weight include the following;

- PFOA has been shown to affect endocrine function in rodents that involve disrupted feedback to the hypothalamic-pituitary axis. Testosterone, thyroxine, and triiodothyronine levels in male rats are decreased while estradiol is increased (Cook 1992, Logan et. al. 2004). In these studies, lutenizing hormone and thyroid stimulating hormone were not elevated as would be expected in response to diminished sex and thyroid hormone levels.

- PFOA has produced effects on the male pituitary in other studies. The 3M 2-year rat study showed a 43% reduction in pituitary weight at the one-year interim sacrifice. The Goldenthal (1978) study reported absolute but not relative decreased pituitary weights in male rats and a dose-related increase in histopathological findings (focal cytoplasmic vacuolation of basophils) in 100% of high-dose males and none in any female dose groups.

[The above two bullets describe pituitary changes in male rats that were not seen in females. The reason for the absence of these effects in the female rat is very likely the great difference in serum PFOA levels for a given administered dose level. Female rats excrete PFOA much more efficiently than the male rat and average female serum levels are generally less than 5% that of the male rat for a given administered dose.]

- Moderate changes in relative pituitary weight have been reported as toxicological endpoints for other chemicals. Ethanol is a chemical that alters endocrine function in prenatally exposed rats. Decreased pituitary weight relative to body weight (15%) has been reported in adult female rats prenatally exposed to ethanol. These rats demonstrated altered pituitary sensitivity to growth hormone releasing factors that may be related to the growth retardation observed in these rats (Conway and Garbouzova 1996; relative pituitary weight percentage taken from bar charts in this paper). Also, tolualdehyde has been reported to decrease relative pituitary weight 28 to 14% with no histopathological findings in a 13 week rat study (Brantom et al. 1972). These reported decreases in relative pituitary weight are similar in magnitude to those observed for PFOA.

<u>IV. Whether the statements contained in the EPA risk assessment at 3.9.3.2 entitled "Human Relevance of the Rat PPARα-agonist Induced Liver Toxicity and Liver Adenomas" adequately consider the findings of the Scientific Advisory Panel (FIFRA SAP, 2004) convened by EPA to consider PPARα-related tumors.</u>

The EPA risk assessment describes the SAP findings as concurring "with the premise that when liver tumors are observed in long term studies in rats and mice, and 1) the data are sufficient to establish that the liver tumors are a result of a PPARα agonist MOA [mode of


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action] and 2) other potential MOAs have been evaluated and found not to be operative, the evidence of liver tumor formation in rodents should not be used to characterize potential human hepatocarcinogenic hazard." The EPA risk assessment neglects to point out that the Panel did not agree with the proposed EPA policy for all life stages. The SAP's "Summary of Panel Discussion and Recommendations" contains the following statement: "The Panel does not support the OPPTS conclusions that the PPAR-α agonist MOA in adult rodents would also apply to young rodents, and similarly any conclusions regarding the relevance of the MOA for human hepatocarcinogenesis would apply to the young, as well as the adults." The SAB Panel should consider whether the proposed PPARα agonist MOA policy is really relevant to human populations if developing life stages are not included. The stated lack of such relevance is an important factor in developing EPA's cancer descriptor of "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential."

Sincerely,

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