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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MEMORANDUM

SUBJECT: Preliminary Risk Assessment of the Developmental Toxicity Associated with PFOA (Perfluorooctanoic Acid) and its Salts

FROM: Kevin Y. Teichman
Director, Office of Science Policy (8104R)

TO: Charles M. Auer
Director, Office of Pollution Prevention and Toxics (7401M)

Thank you for the opportunity to review the Preliminary Risk Assessment of the Developmental Toxicity Associated with PFOA (Perfluorooctanoic Acid) and its Salts. In general, the document is well organized and informative. In addition, the document provides a comprehensive overview of the issues and a reasonable risk analysis based on the existing information. Our comments are provided in an attachment to this memorandum.

Attachment

cc: William Farland, 8101R
Karen Hammerstrom, 8601D
Jack Fowle, B305-02
Bob Hetes, B305-02

TAIN NO CBI

ORD Comments on the Preliminary Risk Assessment of the Developmental Toxicity Associated with PFOA (Perfluorooctanoic Acid) and its Salts

General Comments:

1. The use of the human and rat serum data is very reasonable for this preliminary assessment in calculating a range of MOEs for PFOA. This is especially true because of the gender differences in metabolism and half-life in the rat. Use of serum levels gives a truer picture of the internal doses and related outcomes in rats than would the external exposure levels, especially in this case where the relationship between internal doses and external exposure levels are not the same in male and female rats. There are many limitations in the data available for the assessment as noted in the text, but given the way in which a range of MOEs has been developed, the consideration of these as underestimating or overestimating the serum levels in F1 offspring is reasonable. There may be better animal models for the human, but a great deal of additional data would be needed to determine that. The way in which the assessment has been done uses the data available in an appropriate manner.

2. The discussion of the animal studies available could be aided by the use of tables with summaries in the text. Additionally, the provision of actual values would be helpful in considering the degree of effect in some cases. For example, the actual mean body and organ weights for different dose groups in F1 males and females from the York (2002) study would be helpful, as it is difficult to determine to what extent these are affected since only cases where there is statistical significance are provided. Were the statistical analyses on the two-generation study done using a nested design taking litter into account?

3. The document provides a thorough discussion of study results. However, there is a lack of clarity in some of the results reported. The document would greatly benefit from the use of more synthesis and conclusionary statements and tables.

Specific comments:

Page 1 - 3rd paragraph: Need to specify which serum PFOA values are specific to U.S. and Belgium plants.

Page 2 - Executive Summary: The authors note a weak association in the first occupational epidemiology study of prostrate cancer mortality and employment duration. While there may be limited overall evidence of an effect of PFOA (especially given findings from the latter study), an increased risk of more than 3-fold (SMR=3.3 for 10 years of employment) does not appear to be weak. This is a strong association, which appeared to prompt additional studies. More explanation is needed to understand why the document characterizes the relationship as weak.

Page 3 - There appears to be an inconsistency in the reported LOAEL and NOAEL for F1 males in the first paragraph as compared to the last sentence of the third paragraph.

Page 7 - The value of the molecular weight of PFOA free acid is missing.

Page 8 - In Table 1, the CAS number for the compound R-C(=0)F appears to be incorrect. Also for each compound in the table the "f" in "Rf" should be removed.

Page 17 - Line 5: in reference to ">1-fold," it would be helpful to provide the actual increase as a percentage.

Page 17 - The epidemiology section (3.3) is hard to follow, and it's difficult to determine the important findings. It is difficult to tell what is being modeled (presumably triglycerides and cholesterol) and if some of the other parameters were included in the models as potential confounders or risk factors of interest (i.e., an a priori hypothesis). It would be helpful to have additional background information on the epidemiology studies used in the assessment. For example, it is difficult to determine why specific endpoints are being studied epidemiologically (e.g., biologic basis/mechanism for evaluating serum triglyceride levels). Is there a concern about interaction between PFOA and fat levels? Similarly for alcohol consumption, is this an effect modification issue?

Page 29 - 3rd paragraph: Why isn't 5 mg/kg/day assigned as the LOAEL instead of 50 mg/kg/day when both dose groups produced similar increases in the incidence of defect (30% vs. 38%, over the 16% of control). The assessment points out that "A statistically significant increase in 13th ribs-spurred occurred in the mid-dose group of 5 mg/kg/day; however, the biological significance of this effect is uncertain since in both the high- and low-dose groups, this effect occurred at the same rate and was not statistically significantly different from controls." While the selection of the LOAEL is complicated by this inconsistency in the data, it could be argued that a more conservative or protective approach would be to use 5 mg/kg/day. Further explanation in choosing 50 over 5 is needed.

Page 31 - In the York study, did any of the neonatal mortality occur within the same litter? Because the litters were apparently not randomized and redistributed (within each dose group) at birth to maintain an equivalent litter size, litter should be used as a statistical unit. Was this taken into consideration when analysis was conducted to illustrate the statistical significance of the post-weaning losses?

Page 35 - In a recent presentation at the Society of Toxicology meeting, Kempet and Jepson indicated that the biphasic elimination of PFOA in the female rat *depends on the (administered) dose level* (Toxicologist 72:148). This may account for the apparent saturation kinetics reported (i.e., the highest administered doses yielded a serum level of PFOA similar to that with a lower dose, p. 35), and limits the possible effects of the "high" administered doses (due to an apparent body burden ceiling). The assessment should address this point.

Page 39 - Line 16: What does the denominator (28) of the ratios denote?

Page 46 - In section 5.0, in the 1st paragraph, the MOE should be defined as the ratio of the NOAEL, LOAEL or BMDL, not BMD, to the human exposure level, as the BMDL has come to be the standard for the point of departure.

Page 46 - Although accumulation of PFOA in the liver through enterohepatic circulation was suggested, the reported estimations of the chemical in the liver were surprisingly lower than those in the serum (in monkeys, p. 11, and in rat, p. 12). In fact, in humans, while low levels of PFOA were detected in serum, 90% of the liver levels were below detection (p. 46). This apparent discrepancy warrants further comment.

Page 54 - The assessment astutely points out the potential underestimation of the body burden of PFOA (using F0 female values) in the rat neonates due to the time required for maturation of the hormonally-driven clearance mechanism (p. 54). The developmental profile on organic anion transporters (OAT) is cited as evidence. An additional piece of information to bolster their argument is simply the relatively low levels of the sex hormones in circulation at early postnatal ages and their maturational increase in the first 3-4 weeks of postnatal life of the rat pups.

Page 55 - Section 5.5, 9th paragraph, last 2 sentences: It would seem likely that the accumulation of PFOA with continued exposure to F1 males could also contribute to the greater effect in offspring. That is, their exposure prior to weaning might be similar to that of the F0 females, but as they developed, they would begin to accumulate serum levels over and above what they were exposed to prenatally and early postnatally. We assume this is what is meant by the comment about the importance of developmental exposures, but it could be further clarified.

Page 55 - Section 5.5, 11th paragraph, 1st sentence: Strike the first "whether" (it's there twice) and substitute "i.e."