Reviewer’s report

Title: Immunotoxicity of perfluorinated alkylates: Calculation of benchmark doses based on serum concentrations in children

Version: 1 Date: 12 February 2013

Reviewer: Dori R Germolec

Reviewer’s report:

This paper is well written and contains an important analysis on an environmentally relevant chemical and human health effects. As described below, some clarification of the BMD analysis would be useful. Also, an analysis with the maternal serum PFC levels or a better justification on why they did not perform the analysis (e.g., explain differences in LOEL) would be an informative addition to the manuscript.

Specific Points for the authors to consider:
1) Benchmark calculations section is well written but some questions remain on the methods.
   a. What software was used for calculations?
   b. Good to see that antibody concentration was transformed to achieve normal distribution
   c. Good to see that BMR of 10% and 5% were both used with explanations
   d. Why was BMR of 1 standard deviation (SD) not used? Recent methods suggest that BMR for continuous variables may be more appropriately set with 1 SD
   e. How does the minus two times log-maximum likelihood function compare to the #2 goodness-of-fit test (i.e., models with p < 0.1 failed to meet the goodness-of-fit criterion) and the Akaike’s Information Criterion (AIC) value (i.e., a measure of the deviance of the model fit that allows for comparison across models for a particular endpoint)?

2) The authors mention that they have maternal serum PFC levels measured during pregnancy but do not include them in the analyses or adequately explain why they did not include them. A comparison of LOELs may be useful to justify their choice of data rather than text on pages 7-8 “we chose to focus on the PFCs in the child’s serum at age 5 …. as these data represented the greatest sensitivity to PFC exposure so far documented.” The maternal data should be used develop a second LOEL / BMD calculation based on maternal level. The strength of the data (comparing the negative correlations between maternal PFC or 5-year old PFC and the antibody data) should be presented. Then the 2 BMD calculations to shown side by side. Biologically, it is an open question as to whether maternal or 5-year old PFC is more important for antibody response. These data can add to the scientific evidence for effects following exposures to
PFCs in that regard. Also, the use of maternal PFC as a co-variate could inform how the 2 exposure levels may be inter-related and it may not be possible to split the two (both mother an offspring eat essentially the same diet, etc.)

3) Results:

a. Text on page 10 is general and does not indicate whether the full scale fit or low dose fit is being used to select the BMDL.

b. Why state that the BMDL is “about”? Suggest identifying which values the author supports for tetanus and diphtheria and which model is selected, why, and how the full scale or low dose fit are applied.

c. The authors text on page 10 should clearly indicate which BMD and BMDL value they support as well as the range of values supported by alternate calculations. Table 2 is not adequately explained in the text.

4) Consistency between text and table

a. Page 10 lists BMDL as ug/L and table 2 lists serum concentration as ng/ml. suggest consistent use of units.

b. Table 3 – this would be much more clear if you place the data from table 1 in additional columns so that the data can be compared side by side for the affects you are comparing.

5) Editorial:

a. e.g., (page 5)

b. “is” should be “are” page 7 line 6

c. i.e., (page 9 line 10)

6) Discussion – the authors state that the BMDL results are of the same order of magnitude; this is true, but it is very close to 2 orders of magnitude (1.31 to 0.07 for PFOS tetanus) and 1.25 to 0.06 for PFOA and diphtheria). A more detailed discussion should be included as suggested above for results.

7) Discussion – also add discussion of the implications of the sensitivity analysis

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests