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July 5, 2016

Dear Xie,

This letter is in regards to draft document "Systematic Review of Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS)" that has been published in the Federal Register for public comment. I have been asked to review and evaluate the data from ecological/wildlife studies that have been used in evaluating the potential immunotoxic hazard PFOA and PFOS may pose to humans and animals. Thus, my comments are specific to only those studies that were cited within the text of the document.

Overall, this report does an excellent job at summarizing and utilizing the relevant ecotoxicological studies in support of human and traditional mammalian toxicity studies and the conclusions derived from those data. My greatest concerns regarding the representation of the ecotoxicological studies fall into two general categories, the issue of exposure characterization and route of exposure.

Several of the ecotoxicological studies utilized by the NTP committee were field based studies that measured a variety of immune-related responses and correlated these responses to PFOS and PFOA concentrations measured in several tissue, principally blood and liver. In several of these studies, significant correlations were observed between PFOS and PFOA and altered immune-related endpoints. One is study with sea otters (Kannan et al. 2006) that was cited in several sections of the NTP report and that was deemed to be highly biased due to problems with exposure characterization. While this determination was appropriate based on the experimental design, the reasons underlying this bias were not sufficiently explained. In most field-based correlative studies, the greatest uncertainty revolves around the relationships between an effect and chemical exposure and/or dose in that most organisms in terrestrial and aquatic ecosystems are typically exposed to a large number of chemicals of which only a few are actually accounted in these chemical mixtures. To date, measured PFOA and PFOS concentrations in wildlife typically have been found in areas that are also highly contaminated with other chemical classes including heavy metals (arsenic, cadmium), polychlorinated biphenyls, dioxins and furans, industrial chemicals and pesticides. Without taking the other chemical classes into account, determining the significance of PFOS and PFOA on altering immune responses is uncertain and could overestimate the influence on these compounds on altering immune systems. This issue is relevant for all other field base studies that were used in the NTP report including:

Fair PA et al. 2013 (dolphins)
Kannan K et al. 2006 (sea otters)
Kannan K et al. 2010 (brown bats)
Houde Q et al. 2015 (medaka)
Sletten S. et al. 2016 (eagles)
Wirth JR et al. 2014 (dolphins)

As such, while the NTP report has properly defined the bias associated with these paper, the definition of what "exposure characterization" should be more explicitly defined in the text relative to the influence of confounding factors, especially that of other chemicals that these organisms are exposed.

The second issue is with the representation of the result of a study with chickens (page 61) published by Peden-Adams MM et al. (2009). This study supports the findings found in several mammalian studies that showed a

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relationship between PFOS and its effect on the antibody response as determined by antigen-specific IgM antibody production (SRBC). While the results from this study are properly described in the report, the route of exposure is not mentioned in the text. This was an egg injection study but reading the last sentence of this paragraph makes it appear that it's route of exposure was dietary study given the oral dose range at end of the paragraph. The route of exposure should be properly denoted in section as well as in other sections in the NTP report.

I hope that these comments are useful in the final version of this document and thank you for taking time to hear my concerns.

Thank you for your time and considerations.

Sincerely,

John Newsted
Senior Scientist
Natural Resource Technology, Inc.

