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SYSTEMATIC EVALUATION OF HEALTH EFFECTS FOR PERSISTENT ORGANIC POLLUTANTS: A CASE STUDY OF PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANE SULFONATE (PFOS)

L.S. Birnbaum[1], M.F. Miller[1], A.R. Rooney[1]

[1]*National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA;*

Introduction

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were widely used industrial and commercial surfactants and polymers having applications beginning as early as the 1950s.[1] They are used to make carpets, clothing, fabrics for furniture, paper packaging for food and cookware that are resistant to water, grease or stains. Additionally, they are used to fight fires at airports and in fluoropolymer manufacturing. In the early 2000s, in the United States, production of PFOS was phased out and eight major producers voluntarily agreed to phase out PFOA and PFOS from global production. That said, there are a number of ongoing uses and these chemicals are extremely persistent. They have substantial bioaccumulating and biomagnifying properties, although they do not follow the classic pattern of other persistent organic pollutants by partitioning into fatty tissues. Instead, they bind to proteins in the blood and the liver. These chemicals are listed as under the Stockholm Convention on Persistent Organic Pollutants as an Annex B chemical, requiring parties to take measures to restrict the production and use.[2] Despite declining emissions, there is continuing widespread exposure to both chemicals and these chemicals are commonly detected in the environment, wildlife, and humans.[1,3,4] The long half-lives of PFOA and PFOS and potential for bioaccumulation has driven the need for greater understanding of the human health impacts of long-term exposure to these chemicals

The potential for adverse health effects associated with PFOA and PFOS has driven the U.S. Environmental Protection Agency (EPA) to established health advisories for PFOA and PFOS based on the Agency's assessment of the latest peer-reviewed science.[5] In May 2016, the EPA published a health advisory to provide drinking water system operators, and state, tribal and local officials with information on health risks, so they can take the appropriate actions to protect their residents. The advisory indicates that "To provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS from drinking water, EPA established the health advisory levels at 70 parts per trillion." This advisory level is non-regulatory and non-enforceable so it is solely established to provide technical information.

The National Toxicology Program's (NTP) Office of Health Assessment and Translation (OHAT) initiated a systematic review to develop hazard identification conclusions with respect to the association between PFOA or PFOS exposures and immunotoxicity. Draft conclusions for each chemical were reached by integrating evidence from human and animal studies with consideration of relevant mechanistic data. The review focused on immunotoxicity because there are numerous studies reporting immune-related health effects of PFOA and PFOS in both humans and animals. For example, higher serum levels of PFOA and PFOS are associated with lower antibody responses to common vaccines in prospective and cross-sectional studies.[6-8] Adverse effects have also been reported in experimental animal studies of both innate and adaptive immunity (reviewed in DeWitt et al. 2012).[9] These reported effects, taken together with the observation that the general U.S. population has detectable blood levels of these chemicals[10] (CDC 2015) make PFOS and PFOA primary chemicals of concern for a systematic review of the health effect evidence.

The overall objective of the evaluation is to undertake a systematic review to develop NTP hazard identification conclusions on the association between exposure to PFOA or PFOS (or their salts) and immunotoxicity based on integrating levels of evidence from human and animal studies and consideration of the degree of support from mechanistic data. The scope of the NTP review includes the following Specific Aims:

- Identify literature reporting the effects of PFOA or PFOS exposure on immune endpoints in humans, animals (experimental and wildlife), or in vitro model systems.
- Extract data on immune health effects from relevant studies.
- Assess the internal validity (risk of bias) of individual studies.
- Summarize the extent of evidence available.

• Synthesize the evidence using a narrative approach or meta-analysis (if appropriate) considering limitations on data integration such as study design heterogeneity.
• Rate the confidence in the body of evidence for human and animal studies separately according to one of four statements: (1) High, (2) Moderate, (3) Low, or (4) Very Low/No Evidence Available.
• Translate confidence ratings into level of evidence of health effects for human and animal studies separately according to one of four statements: (1) High, (2) Moderate, (3) Low, or (4) Inadequate.
• Combine the level of evidence ratings for human and animal data and consider the degree of support from mechanistic data to reach one of five possible hazard identification conclusions: (1) Known, (2) Presumed, (3) Suspected, (4) Not classifiable, or (5) Not identified to be an immune hazard to humans.
• Describe limitations of the systematic review, limitations of the evidence base, identify data gaps and key research needs, and describe findings in the context of human exposure levels.

Results and Discussion
The human and animal immune data were sorted into major categories of immune response (i.e., immunosuppression, hypersensitivity, and autoimmunity). Tables 1 and 2 summarize the NTP OHAT systematic review evidence by health outcome, and hazard conclusions for PFOA and PFOS, respectively. They found that the majority of relevant animal studies assessed immunosuppression-related endpoints, particularly the antibody response, although there are some data on infectious disease resistance and natural killer (NK) cell activity. There were also several animal-based hypersensitivity studies, but there were no studies located that tested autoimmune endpoints in animal models. Human epidemiological studies also evaluated the antibody response and hypersensitivity-related outcomes, and infectious disease outcomes and autoimmunity.

Conclusions
PFOA and PFOS are persistent chemicals associated with changes in multiple immune outcomes in experimental animals and epidemiological studies.

The NTP's draft conclusions are that PFOA is presumed to be an immune hazard to humans based on two separate lines of evidence: (1) the high level of evidence that PFOA suppressed the antibody response from animal studies and the moderate level of evidence from studies in humans, and (2) high level of evidence that PFOA increased hypersensitivity-related outcomes from animal studies and low level of evidence from studies in humans. Although the strongest evidence for an effect of PFOA on the immune system is for suppression of the antibody response and increased hypersensitivity, there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance and increased autoimmune disease.

Further, the NTP's drafts conclusions are also that PFOS is presumed to be an immune hazard to humans based on a high level of evidence that PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans. Although the strongest evidence for an effect of PFOS on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from studies in experimental animals that PFOS suppresses disease resistance and NK cell activity.

For both chemicals, the evidence indicating that PFOA and PFOS affect multiple aspects of the immune system add to the overall confidence that these chemicals alter immune function in humans. The mechanism(s) of PFOA- and PFOS- associated immunotoxicity are unknown. For PFOA, the effects on diverse endpoints such as suppression of the antibody response and increased hypersensitivity may be unrelated. In contrast, for PFOS suppression of the antibody response and NK cell function are both potential mechanisms by which PFOS may reduce disease resistance.

References:

(1) Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, . Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag 2011;7:513–541.
(2) Stockholm Convention on Persistent Organic Pollutants. http://chm.pops.int/default.aspx

(3) Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Tully JS, Needham LL. Serum concentrations of 11 polyfluoroalkyl compounds in the U.S. population: Data from the National Health and Nutrition Examination Survey (NHANES). Environ Sci Technol 2007;41:2237–2242.
(4) Butenhoff JL, Olsen GW, Pfahles-Hutchens A. The applicability of biomonitoring data for perfluorooctanesulfonate to the environmental public health continuum. Environ Health Perspect 2006;114:1776–1782.
(5) US Environmental Protection Agency. Federal Register. Vol. 81, No. 101 / Wednesday, May 25, 2016.
(6) Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P, Heilmann C. 2012. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA : the journal of the American Medical Association 307(4): 391-397.
(7) Granum B, Haug LS, Namork E, Stolevik SB, Thomsen C, Aaberge IS, van Loveren H, Lovik M, Nygaard UC. 2013. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. J Immunotox 10(4): 373-379.
(8) Looker C, Luster MI, Calafat AM, Johnson VJ, Burleson GR, Burleson FG, Fletcher T. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. Toxicol Sci 138(1): 76-88.
(9) DeWitt JC, Peden-Adams MM, Keller JM, Germolec DR. 2012. Immunotoxicity of perfluorinated compounds: recent developments. Toxicol Pathol 40(2): 300-311.
(10) CDC (Centers for Disease Control and Prevention). 2015. Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables, February 2015. Atlanta, GA: U.S. Department of Health and Human Services. Available: http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Feb2015.pdf

Table 1:

PFOA Principal Immune Effects Summary Table						
Category of Immune Response	**Immune Outcomes**	**Confidence Ratings in the Body of Evidence**		**Level of Evidence in the Body of Evidence**		**Hazard Conclusion**
		Human	**Animal**	**Human**	**Animal**	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	**Presumed to be an Immune Hazard to Humans**
Hypersensitivity	Asthma and other hypersensitivity-related outcomes	Low	High	Low	High	**Presumed to be an Immune Hazard to Humans**
Overall Hazard Conclusion for PFOA Immunotoxicity: Presumed to be an immune hazard to humans						

Table 2:

PFOS Principal Immune Effects Summary Table						
Category of Immune Response	**Immune Outcomes**	**Confidence Ratings in the Body of Evidence**		**Level of Evidence in the Body of Evidence**		**Hazard Conclusion**
		Human	**Animal**	**Human**	**Animal**	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	**Presumed to be an Immune Hazard to Humans**
	Infectious disease resistance	Low	Moderate	Low	Moderate	Suspected to be a Hazard to Humans
	Natural killer (NK) cell activity	Inadequate	Moderate	Inadequate	Moderate	Suspected to be a Hazard to Humans
Overall Hazard Conclusion for PFOS Immunotoxicity: Presumed to be an immune hazard to humans						