TOX IMPACT STATEMENT

An Emerging Class of Global Environmental Pollutants:
The Perfluoroalkyl Substances
Approved by SOT Council, May 2018

The Problem

Perfluoroalkyl acids (PFAAs) are a class of surfactant compounds used for a wide variety of industrial (e.g., emulsifiers for polymer production and metal-electroplating) and consumer (e.g., fabric/carpet/food-packing paper coatings and fire-fighting foam) applications since the 1950s. These chemicals consist of a carbon-backbone (typically C4-C14) and a functional group (sulfonate or carboxylate) which confer their hydrophobic and oleophobic properties. The most useful and most highly produced PFAAs are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), the so-called "C8" chemicals. They are extremely stable in the environment and bioaccumulative in organisms.

PFAAs have been detected in all environmental media and a variety of wildlife. Importantly, a number of these PFAAs (highlighted by PFOS and PFOA) have been detected in production workers and populations worldwide, with higher serum levels reported in residents of contaminated areas. PFAAs are detectable in amniotic fluid, cord blood, and breast milk in humans.

In 2009, PFOS was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants, and PFOA was similarly nominated in 2016. Major production of PFOS and PFOA in the United States ceased in 2002 and 2015, respectively, but continues overseas. Significantly, more than 4,000 related chemicals consisting of poly- and perfluoroalkyl carbon-backbones with ether linkages have appeared to fill their market void. These new chemicals are termed poly- and perfluoroalkyl substances (PFASs), and some of them, such as GenX, have been detected recently in surface and drinking water.

Role of Toxicology

While environmental persistence, bioaccumulation, and human exposure to PFAAs are significant concerns, issuance of health advisories to the general public and regulatory actions for industry require credible evidence that these chemicals are capable of causing adverse health effects. Since the 1980s, toxicological studies have demonstrated the induction of hepatomegaly and hepatosteatosis by PFOA and other long-chain PFAAs in rats and mice, mediated by

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activation of the nuclear receptor peroxisome proliferator-activating receptor-alpha (PPARα). Subsequent toxicogenomic findings support these early histological and biochemical observations and implicate possible involvement of additional nuclear receptors—particularly the metabolic sensors—and their molecular signals. Indeed, the hepatic effects of PFAAs can be considered as a hallmark response of the entire class of chemicals, including their PFAS replacements, based on limited reports with GenX, ADONA, and F53-B.

At least seven categories of major toxicological effects have been described for PFAAs, predominantly PFOS and PFOA, though with varying degrees of certainty. Liver tumors are induced in the rat by PFOA, and more recently by GenX, along with pancreatic and Leydig cell tumors. Although the PPARα-mediated liver tumors in rat are unlikely to be relevant for human health risk, the relevance of pancreatic and Leydig cell tumors remains to be elucidated. Developmental effects of PFOS and PFOA include enlarged liver, increased neonatal mortality, growth deficits, and developmental delays. Immunotoxicity is another adverse effect associated with PFAA exposure. Suppression of acquired and innate immune responses by PFOS and PFOA has been demonstrated both *in vitro* and *in vivo*. PFAAs are known to produce hypothyroxinemia (reduction of serum T4 without compensatory elevation of TSH) in the rat, an effect likely associated with the propensity of the chemicals for protein binding (displacement of T4 from transthyretin). Other less-defined effects of PFAAs include weak estrogenic activity, neurotoxicity and altered neurobehavioral development, and the possibility of acting as an environmental obesogen. Further in-depth investigation will undoubtedly broaden the scope of their toxicological profile and bring clarity to their potential harmful effects on humans.

Activation of PPARα is the only extensively characterized mechanism for PFAA toxicity, but may not be the only mechanism involved. Other possible mechanisms related to PFAA toxicity include protein binding to displace endogenous ligands, interference of cell-cell communication, mitochondrial dysfunction, and oxidative stress. Toxicokinetics is a major factor in extrapolating PFAA toxicity data from animal studies to human risk assessment. There are substantial species differences in the rate of PFAA elimination between rodents (serum half-lives of days to weeks) and humans (months to years). Anion transporter activities are involved in the renal resorption of PFAAs, which, in part, lead to their differential clearance and body burden among chemicals. However, the mechanism(s) responsible for the species difference remains elusive.

Public Health Impact

PFAAs are a component of the National Health and Nutritional Examination Survey (NHANES), which started to track the presence of these chemicals in serum samples from the US general population from 1999 to the present. Five PFAAs (PFOS, PFOA, PFHxS, PFNA, and PFDA) were detected in approximately 99% of the population. Similar biomonitoring results were found

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in other developed countries. Human exposures and toxicity in animal studies spurred many epidemiological investigations, most notably the C8 Science Panel, which undertook a series of studies in the Mid-Ohio Valley of a large population of residents from a PFOA-contaminated locale. Toxicological studies played a key role in developing the endpoints for this study. Some concordance between epidemiological and laboratory results were noted, although the former also raised some interesting unique features (e.g., positive association between PFOA exposure and incidence of preeclampsia).

Importantly, since the cessation of PFOS and PFOA production in the United States, the levels of PFOS reported in NHANES have fallen by 84% and PFOA by 63% (estimated from the 1999 levels). The collective toxicological findings in the past two decades have played a significant role in the decision making by regulatory bodies and industry alike and have provided a sound basis to formulate health advisories for PFOS and PFOA, as well as other PFAAs. Governmental bodies, such as European Union member countries, and consumer advocates have proposed limiting the uses of PFAAs, prompt evaluation of their replacements to avoid "regrettable substitution," and development of safer and more environmentally friendly alternatives. Undoubtedly, toxicology will continue to play a significant role in these endeavors.

References and Resources

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