

The NTP Rapid Evaluation and Assessment of Chemical Toxicity (REACT) of Polyfluorinated Alky Substances (PFAS) Project

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PFAS are industrial chemicals used for a variety of products including, non-stick cookware, stain resistant fabrics, food packaging and firefighting foams. PFAS were originally nominated to the program by USEPA/OPPTS. In response to the nomination the NTP designed an *in vivo* testing program around seven PFAS that included three sulfonates and four carboxylates. A fluorotelomer alcohol was also included in toxicokinetic studies. In addition, *in vitro* studies evaluated 16 PFAS. The prototype PFAS are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Due to their toxicity, persistence and bioaccumulation, PFOA and PFOS have been replaced by other PFAS. It is estimated that there are hundreds of PFAS released into the environment as either the products, their impurities, or breakdown products. Little is known about the toxicity of these PFAS substitutes, impurities and breakdown products. Because of the large number of new PFAS chemicals entering the environment, the USEPA, Department of Defense, NCEH/ATSDR and other federal agency partners have expressed interest in an expanded evaluation of PFAS to include as many as 75 individual compounds plus mixtures and novel firefighting foams.

To address these needs, the NTP has developed the REACT PFAS project. This is a collaborative program with the USEPA's National Center for Computational Toxicology. Because of the intent to generate information up to 75 chemicals, the project incorporates *in silico* and *in vitro* screening efforts followed up by select *in vivo* studies. *In silico* screening of test articles was performed using structure activity relationships and existing high throughput data to prioritize compounds for targeted testing in select *in vitro* systems. Initial *in vitro* efforts are evaluating the effects of PFAS on cell viability and mitochondrial toxicity in human liver, placenta and mammary gland derived cells. In addition, we are examining the adipogenic and lipogenic responses of PFAS in mouse pre-adipocyte cells. To broaden the biological effects under evaluation we will also evaluate transcriptional profiles of PFAS using high throughput transcriptomics in human liver derived cells. The *in vitro* work will be accompanied by *in vitro* to *in vivo* extrapolation approaches to aid in prioritization of these chemicals for *in vivo* screening and toxicity studies. These screening efforts will complement the *in vivo* PFAS studies at the NTP and will aid in identifying those compounds for further *in vivo* testing.