NTP Studies of Per- and Poly-fluoroalkyl Substances: Understanding Human Translation

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Overview

The National Toxicology Program (NTP) has a large research program[1] evaluating the per- and poly- fluorinated alkyl substances (PFAS) class. These chemicals represent a large group of manufactured compounds widely used to make everyday products more resistant to stains, grease, and water. We have evaluated multiple PFAS in in vitro model systems, examined the toxicokinetics of seven PFAS, evaluated the toxicity of seven PFAS in 28-day toxicity studies (TOX-96[2] and TOX-97[3]), conducted a two-year carcinogenicity study on perfluorooctanoic acid (PFOA), conducted rodent and cell-based immune toxicity studies, and carried out a literature-based systematic review of PFOA and perfluorooctane sulfonate (PFOS) and immunotoxicity. Furthermore, as the PFAS class has expanded, NTP has developed the Responsive Evaluation and Assessment of Chemical Toxicity (REACT) initiative, working with the US Environmental Protection Agency to evaluate new PFAS in various in silico, in vitro, and in vivo models. Each of these efforts has focused on strengthening the science base for the PFAS class to inform decision making.

NTP's systematic review evaluated the immunotoxicity associated with exposure to PFOA and PFOS. Based upon the available scientific evidence and using a 4-point scale (known, presumed, suspected, not classifiable), NTP concluded that PFOA and PFOS were *presumed immune hazards to humans* (NTP Monograph[4]).

The 28-day in vivo studies in rats identified potential toxicity and related these findings to internal dose measurements, which is important as the toxicokinetics vary across the chemicals and species. We learned that long- and short-chain PFAS affected the same organ systems—the liver and thyroid hormone. Our studies also found that higher doses of short-chain PFAS were needed to have similar effects on liver and thyroid hormone when compared with long-chain PFAS.

NTP completed two-year chronic toxicity and carcinogenicity studies of PFOA (TR-598[5]) and the draft report was peer reviewed[6] at a public meeting in December 2019. These studies examined the contribution of PFOA perinatal exposure (gestation and lactation) to chronic toxicity and carcinogenic activity by comparing rats with perinatal plus post-weaning exposure to rats with only post-weaning exposure. The study found *clear evidence of carcinogenic activity* in male

[1] https://ntp.niehs.nih.gov/go/PFAS
[2] https://ntp.niehs.nih.gov/go/tox096abs
[3] https://ntp.niehs.nih.gov/go/tox097abs
[4] https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf
[5] https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2019/december/tr598draft.pdf
[6] https://ntp.niehs.nih.gov/events/past/index.html?type=&&date=2019-12-12

rats based on neoplasms in the pancreas and liver, *some evidence of carcinogenic activity* in female rats based on neoplasms of the pancreas, and *equivocal evidence of carcinogenic activity* in the uterus and liver of female rats. The additional effect of perinatal exposure in combination with postnatal exposure was considered to be uncertain by the peer-review panel and limited to the observation of hepatocellular carcinomas in male rats.

A challenge in sharing data from NTP's studies on PFAS is providing context for understanding the potential human health impact. For example, research suggests that the mechanism for many of the two-year study findings could be related to PPARα activation, which has questionable relevance for human health. In other cases, the human health impact of NTP's findings may not be known. With this in mind, we are interested in understanding the human translation of NTP's study outcomes and would like to explore how best to communicate the interpretation and application of our work.