PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
5100 Wisconsin Ave. NW, Suite 400 • Washington, DC 20016 • Tel: 202-686-2210 • Fax: 202-686-2216 • pcrm@pcrm.org

February 14, 2020

Dr. Mary Wolfe, Designated Federal Official for the BSC
Office of Liaison, Policy and Review
Division of NTP, NIEHS
P.O. Box 12233, K2-03
Research Triangle Park, NC 27709

Dear Dr. Wolfe:

The Physicians Committee for Responsible Medicine (PCRM) thanks the National Toxicology Program (NTP) for the opportunity to comment on its *NTP Studies of Per- and Poly-fluoroalkyl Substances* [PFAS]*: Understanding Human Translation*. PCRM is a nationwide nonprofit organization comprised of over 175,000 supporters advocating for efficient, effective and ethical medical practice, nutrition, and research.

While NTP's extensive PFAS research program appropriately includes studies evaluating immunotoxicity and neurotoxicity *in vitro*, it is otherwise based primarily on animal toxicity studies. These studies have so far consumed 5,930 rats, not counting the immunotoxicity *in vivo* and mitochondrial toxicity studies, for which the number of animals used was not reported.

In the meeting materials provided, Dr. Chad Blystone notes the challenge in providing context for understanding the potential human health impacts evaluated in NTP's studies of PFAS, considering that 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 fact, in its 2006 SIDS Initial Assessment Report, OECD concludes that the data clearly demonstrate that PFOA induces liver toxicity and adenomas via a PPARα agonist mode of action in rats, noting that PFOA activates the PPARα and that the requisite dose-response and temporal associations of the key events for this mode of action have been characterized.[1] For example, it has been well documented that PFOA is a potent peroxisome proliferator, inducing peroxisome proliferation in the liver of rats and mice,[2,3,4] and a clear relationship exists between peroxisome

[1] https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=FF9EAC38-0716-432E-B30A-C190FDEDDAF7
[2] Ikeda T, Aiba K, Fukuda K, and Tanaka M (1985). The induction of peroxisome proliferation in rat liver by perfluorinated fatty acids, metabolically inert derivatives of fatty acids. J. Biochem. 98:475-482.
[3] Pastoor TP, Lee KP, Perri MA, and Gillies PJ (1987). Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. Exp. Mol. Pathol. 47:98-109.
[4] Sohlenius AK, Andersson K, DePierre JW (1992). The effects of perfluoro-octanoic acid on hepatic peroxisome proliferation and related parameters show no sex-related differences in mice. Biochem. J. 285:779-783.

proliferation, hepatocellular hypertrophy, and increases in liver weight at doses close to and below doses that result in liver adenomas following chronic exposures.[5,6]

Further, in a recent review article, Corton et al. (2018) conclude that the PPARα‐dependent rodent liver tumor response is not relevant to humans, noting that PPARα activators are unlikely to induce liver tumors in humans due to biological differences in the response of key events downstream of PPARα activation.[7] In particular, minimal or no effects are observed on cell growth pathways and hepatocellular proliferation in human primary hepatocytes, and an absence of alteration in growth pathways, hepatocyte proliferation, and tumors are observed in the livers of species that are more appropriate human surrogates than mice and rats.

Thus, prior to beginning its own carcinogenicity studies in rats, NTP was aware that at least some of its findings would likely be irrelevant to humans. Nevertheless, NTP went on to test its hypothesis that including exposure during gestation and lactation with postweaning exposure would change the PFOA carcinogenic response, producing either more neoplasms or different neoplasm types compared to postweaning exposure alone. While these studies would require an exceptionally large number of animals, 5,232, in its technical report, NTP says little regarding study design other than it was based on NTP assessments, from the 1990s, of early developmental exposures influencing carcinogenic activity. In addition, there is no discussion of whether reducing the number of animals required was even considered. In particular, while for the 150 ppm and 300 ppm dose groups in the first study, NTP began with 36 time-mated females, it used 103 females for the 0 ppm dose group in this study and 147 females for both dose groups in the second study. Using 36 females for all dose groups would have reduced the number of animals required by more than 3,000. At a minimum, NTP should have considered whether such an approach was appropriate, applying experience gained in the nearly 30 years since conducting the assessments on which these studies' design was based. If NTP nevertheless determined that several times the minimum number of animals was required for some dose groups, it should have presented its reasoning in order to potentially avoid missing opportunities to reduce animal use in similar, future studies.

From these studies, NTP concluded that the additional effect of combined perinatal and postweaning exposure was limited to a higher incidence of hepatocellular carcinomas in male rats compared to postweaning exposure alone, specifically, four incidences versus none. This finding is of questionable significance in rats and likely to be completely irrelevant to humans for the reasons noted above. While hypotheses are not always confirmed by the experiments in which they are tested, it is reasonable to ask in this case whether the mere possibility of more meaningful results justified the use of so many animals. The challenge in providing context for understanding the potential human health impacts evaluated in NTP's studies is compounded

---

[5] Palazzolo MJ (1993). Thirteen-week dietary toxicity study with T-5180, ammonium perfluorooc-tanoate (CAS No. 3825-26-1) in male rats. Final Report. Laboratory Project Identification HWI 6329-100. Hazleton Wisconsin, Inc. U.S. Environmental Protection Agency Administrative Record 226-0449.

[6] Liu RCM, Hurtt ME, Cook JC, and Biegel LB (1996). Effect of the peroxisome proliferator, ammo-nium perfluorooctanate (C8), on hepatic aromatase activity in adult male Crl:CD BR (CD) rats. Fund Appl Toxicol 30: 220-228.

[7] Corton JC, Peters JM, Klaunig JE (2018). The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Arch Toxicol. 92:83-119.

when that context is weak, when the cost of those studies is especially high, and when the studies' design is not adequately justified.

Thank you for your attention to these comments. I can be reached at [redacted] or at [redacted].

Sincerely,

Joseph Manuppello
Senior Research Analyst
[redacted]