November 20, 2019

Environmental Working Group Comments to the National Toxicology Program Subject: Peer Review of the Draft NTP Technical Reports on the Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid

Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, Minn., San Francisco and Sacramento, Calif., is submitting comments to the National Toxicology Program on the draft technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid, or PFOA.

EWG has researched PFOA toxicity, use and human exposure since the early 2000s and appreciates the opportunity to comment on the report. PFOA shows carcinogenicity in animal studies as well as in highly exposed human populations. Notably, the NTP research took place during the same period as the C8 Science Panel studies and adds to those results, which found probable links between PFOA exposure in people and testicular and kidney cancer.[1,2] From the public health perspective, EWG is very concerned about the cancer risks of PFOA in light of the increased susceptibility of children to carcinogens generally[3] and widespread human exposure to PFOA, which starts in utero and continues through life.[4,5]

EWG presents comments regarding three main conclusions of the report.

1. EWG agrees that there is clear evidence of carcinogenic activity of PFOA in male rats.
2. EWG recommends reevaluating the finding that there is some evidence of carcinogenic activity of PFOA in female rats.
3. Overall results indicate that gestational, lactational and postweaning exposure to PFOA increases the incidence of tumors in both male and female rats.

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[1] Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ Health Perspect. 2013 Mar;121(3):318-23.

[2] Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect. 2013 Nov-Dec;121(11-12):1313-8

[3] California Office of Environmental Health Hazard Assessment, In Utero and Early Life Susceptibility to Carcinogens. The Derivation of Age-at-Exposure Sensitivity Measures. 2009. Available at oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

[4] Ye X, Kato K, Wong LY, Jia T, Kalathil A, Latremouille J, Calafat AM. Per and polyfluoroalkyl substances in sera from children 3 to 11 years of age participating in the National Health and Nutrition Examination Survey 2013-2014. Int J Hyg Environ Health. 2018 Jan;221 (1):9-16.

[5] Starling AP, Adgate JL, Hamman RF, Kechris K, Calafat AM, Dabelea D. Prenatal exposure to per- and polyfluoroalkyl substances and infant growth and adiposity: the Healthy Start Study. Environ Int. 2019 Oct;131:104983.

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1. EWG agrees that there is clear evidence of carcinogenic activity of PFOA in male rats.

For male rats, there were statistically significant increases in hepatocellular adenocarcinomas and pancreatic acinar cell adenomas in the perinatal – defined as gestational and lactational – and postweaning exposure groups, as well as the postweaning-only exposure group. Both tumor sites showed evidence of a dose response and a statistically significant increase in pancreatic tumors was observed at all doses tested. Together these data point to clear evidence of carcinogenic activity of PFOA in male rats. Notably, in the NTP study, a "No Effect" level was not identified for PFOA exposure in male rats, since elevated incidence was observed at all doses tested.

2. EWG recommends reevaluating the finding that there is some evidence of carcinogenic activity of PFOA in female rats.

The NTP report identified "increased incidences of pancreatic acinar cell adenoma or adenocarcinoma (combined) neoplasms" and noted that the "higher incidence of hepatocellular carcinomas and adenocarcinomas of the uterus may have been related to exposure." These results were the basis for the NTP's conclusion that there was some evidence of carcinogenic activity of PFOA in female rats.

To summarize the data for the female rats, there was a statistically significant increase in uterine neoplasms in the highest postweaning exposure group, a nonsignificant increase at the middle postweaning exposure group, and evidence of dose response (trend test p=0.028). A similar increase in uterine neoplasms was observed in the perinatal exposure group, but this finding was not statistically significant. Similarly, a statistically significant increase in pancreatic neoplasms at the highest postweaning exposure group was observed, with a nonsignificant increase observed in the perinatal exposure group.

EWG recommends that the NTP reevaluate its conclusions of "some" versus "clear" evidence of carcinogenic activity for the female rats study in light of the treatment-related increase in pancreatic and uterine tumors, as well as the well-documented fact that female rats metabolize PFOA more quickly than male rats, requiring a higher external dose to reach comparable internal exposure doses.[6] Although in the NTP study, the female rats did receive higher external PFOA doses to account for differences in metabolism, the internal exposure dose in the highest exposure group of female rats was lower than the lowest exposed group of male rats, 72.25 ug/L compared to 81.4 ug/L. In addition, female rats were exposed to only two doses of PFOA above the

[6] Dzierlenga A, Robinson V, Waidyanatha S, DeVito M, Eifrid M, Gibbs S, Granville C, Blystone C. Toxicokinetics of perfluorohexanoic acid (PFHxA), perfluorooctanoic acid (PFOA), and perfluorodecanoic acid (PFDA) in male and female Hsd:Sprague Dawley SD rats following intravenous or gavage administration. Xenobiotica. 2019 Nov 7:1-11.

control, whereas male rats were exposed to three doses, which limited researchers' ability to identify a dose response in female rats. Therefore, it is reasonable to suggest that at a higher exposure dose in females, more comparable to the internal doses received by male rats, a higher tumor incidence would be observed.

In sum, EWG finds that the results for the female rats may meet the criteria for "clear evidence of carcinogenic activity." EWG urges the NTP to clarify this aspect of the results in the final report.

3. Overall results indicate that gestational, lactational, and postweaning exposures to PFOA increase the incidence of tumors in both male and female rats.

Although the NTP study design was adequate to achieve its goal of comparing perinatal and postweaning exposure, this study design does not fully address early life susceptibility to PFOA exposure. The study design compares both perinatal and postweaning exposure to postweaning exposure alone. However, to fully address early life susceptibility and sensitivity to carcinogen exposure, gestational and lactational exposure should be compared not to postweaning exposure only, which includes the vulnerable period of sexual maturation, but also to adult exposure only. In fact, in the design of previous NTP studies, three exposure groups were used, including adult-only exposure beginning after eight weeks of age, not the postweaning three weeks of age used in this study.[7,8,9]

In the absence of an adult-only exposure group in the present study, NTP should perform a qualitative comparison to historic adult exposures that may lend insight into early life sensitivity to PFOA exposure. In a 2001 PFOA carcinogenicity study (two-year bioassay), dosing began at post-natal day 49, after sexual maturation, and induced liver, pancreatic and Leydig cell tumors in male rats at a dose of 300 ppm.[10] In the current study, a dose of 300 ppm was not tolerated by male rats, potentially indicating increased sensitivity to PFOA toxicity when dosing began in young animals. In addition, increased liver and pancreatic tumor incidence was observed in the current study at lower doses than the 2001 study, further suggesting increased sensitivity to PFOA carcinogenicity when exposure occurs during critical windows of development.

Finally, data from the NTP report did identify an increase in male hepatocellular carcinomas for the highest exposure in the perinatal exposure group (300/80) that was not

[7] Chhabra RS, Eustis S, Haseman JK, Kurtz PJ, Carlton BD. Comparative carcinogenicity of ethylene thiourea with or without perinatal exposure in rats and mice. Fundam Appl Toxicol. 1992; 18(3):405-417.
[8] Chhabra RS, Bucher JR, Haseman JK, Elwell MR, Kurtz PJ, Carlton BD. Comparative carcinogenicity of 5,5-diphenylhydantoin with or without perinatal exposure in rats and mice. Fundam Appl Toxicol. 1993; 21(2):174-186.
[9] Chhabra RS, Bucher JR, Haseman JK, Elwell MR, Kurtz PJ, Carlton BD. Comparative carcinogenicity of polybrominated biphenyls with or without perinatal exposure in rats and mice. Fundam Appl Toxicol. 1993; 21(4):451-460.
[10] Biegel LB, Hurtt ME, Frame SR, O'Connor JC, Cook JC. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. Toxicol Sci. 2001; 60(1):44-55.

present in the postweaning-exposed group only (0/80). Although this increase was not statistically significant in pairwise comparisons, the trend analysis for the perinatal exposure group was statistically significant (p=0.049). Furthermore, for other carcinogens, hepatocellular carcinomas have been identified as a tumor site susceptible to increases from perinatal carcinogen exposures, compared to adult exposures[8]. Similarly, the NTP study showed an increase in acinar cell adenoma and adenocarcinoma in the 300/1000 ppm group of female rats (trend test p=0.018), which was not present in the postweaning-only group. In EWG's assessment, these data point to the possibility that early life exposure may increase the carcinogenic potential of PFOA.

In concluding these comments, EWG applauds the NTP for undertaking such an experiment, one that is critical to the future protection of public health from exposure to PFOA and other PFAS. The scientific understanding of PFOA toxicity has evolved significantly since NTP initiated this study more than a decade ago. Public health and policymaking would benefit significantly from this assessment, once completed and NTP should work expeditiously to finalize the report.

Thank you for the opportunity to comment.

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Submitted on behalf of the Environmental Working Group