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Truth in the Serum? Estimating PFAS Relative Potency for Human Risk Assessment

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The adverse human health effects of exposure to per- and polyfluoroalkyl substances (PFAS) have been documented since the 1980s.[1] Two common long-chain subtypes, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS),[2] are gradually being phased out globally because of their persistence in the human body and the environment. They are being replaced by short-chain alternatives that in most cases show reduced bioaccumulation. However, a chemical's potency derives from both its toxicity and how it accumulates within an organism; these characteristics differ among PFAS. The authors of a recent study in *Environmental Health Perspectives*[3] used published rat liver toxicity data for nine different PFAS to calculate the internal relative potency factor (RPF) for each.

"Most toxicity studies report only external doses administered to animals," says first author Wieneke Bil, a regulatory toxicologist at the Dutch National Institute for Public Health and the Environment. "Converting these external doses to modeled blood concentrations allowed us to estimate blood-specific RPFs that we can apply to human biomonitoring studies."

The authors chose relative liver weight increase in male rats as the end point because it had the most published dose–response curves for subchronic exposures to the chemicals of interest. PFOA, which also has been heavily studied, was chosen as the reference chemical.

The researchers found that six of the nine PFAS—including three supposedly safer replacement chemicals—had greater relative potency than PFOA when serum levels (internal doses) were compared. Only two of the PFAS had a lower calculated potency than PFOA. Moreover, the study showed that previously developed[4] potency rankings of the PFAS based on external doses differed greatly from the new rankings based on internal doses. For example, GenX was a less potent liver toxicant than PFOA based on administered doses but was more potent than PFOA when considering blood serum levels.

Biomonitoring in recent decades suggests that, on average, people's exposures to older "legacy" PFAS are declining, likely due to limits set on uses and emissions of these chemicals.[14] However, the health effects of the chemicals that replaced them are not yet clear. Image: ©.shock/adobe.stock.com.

These findings are consistent with earlier work on mice[5,6] and zebrafish.[7] The new study builds on that work by examining a more complex PFAS mixture and by using a toxicokinetic model to derive RPFs. The results highlight the importance of toxicokinetic differences between PFAS when conducting risk assessments.

The RPF method assumes that chemicals do not interact biologically with one another and contribute to a common effect—in this case, the relative liver weight increase in male rats. This assumption results in dose–response curves on a logarithmic scale[8,9] that are parallel for each chemical examined.

To illustrate the method's application to human data, the researchers first assumed that relative potency rankings are similar in rats and humans. Then they used measurements of six PFAS in 1,929 U.S. National Health and Nutrition Examination Survey participants to calculate a single PFOA-equivalent dose for each individual. Researchers can then estimate how exposure to a mixture of these six PFAS is related to an outcome of interest.

Species differences in PFAS half-lives and bioaccumulation are poorly understood but may be due to different PFAS transporter proteins in the kidney or liver[10,11] and hormonally mediated processes.[12] To calculate PFOA-equivalent doses for non-liver outcomes, such as immune suppression end points,[13] researchers can apply similar methodology to different animal or *in vitro* experimental data. The main limitation of the method, Bil says, is its need for extensive existing data on the chemicals of interest.

Nevertheless, the new method is a significant advance in PFAS toxicology according to Carolina Vogs, a staff scientist at the Swedish University of Agricultural Sciences in Uppsala, Sweden, who was not involved in the project. "The study confirms that external and internal RPFs may generate very different toxicity rankings," says Vogs. "Identifying three short-chain substitutes as more potent than PFOA when accounting for differences in internal uptake, distribution, and excretion processes is both important and disconcerting."

Jamie DeWitt, a professor of pharmacology and toxicology at East Carolina University, who also was not involved in the project, says the new findings are compelling and generate many follow-up questions. "A key takeaway for me is that we really need to understand how PFAS are acting at the site of toxicity to better predict their effects," she says. For example, studying how GenX interacts with liver cells and receptors may clarify whether its higher internal potency results from faster cell entry or slower excretion from the body because transport to the kidneys is less efficient.

Carla Ng, an assistant professor of environmental engineering at the University of Pittsburgh, who also was not involved in the study, points to another research need: understanding the potential competition within a mixture of similar chemicals for protein-binding sites. Such competition could lead the mixture's behavior to deviate from simple additivity.

At the same time, Ng appreciates the ability of the method to simplify risk communication by comparing a single number across studies, and she echoes Vogs' concern about the implications of the potency findings. "Describing the short-chain substitutes as less toxic because they are more quickly excreted is incorrect," she says. "By decoupling the concepts of bioaccumulation and toxicity, this study clearly shows that the opposite may be true and that we have not landed in a safer space yet."

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References

1. Ubel FA, Sorenson SD, Roach DE. 1980. Health status of plant workers exposed to fluorochemicals—a preliminary report. Am Ind Hyg Assoc J 41(8):584–589, PMID: 7405826, https://doi.org/10.1080/15298668091425310.
2. Tarapore P, Ouyang B. 2021. Perfluoroalkyl chemicals and male reproductive health: do PFOA and PFOS increase risk for male infertility? Int J Environ Res Public Health 18(7):3794, PMID: 33916482, https://doi.org/10.3390/ijerph18073794.
3. Bil W, Zeilmaker MJ, Bokkers BGH. 2022. Internal relative potency factors for the risk assessment of mixtures of per- and polyfluoroalkyl substances (PFAS) in human biomonitoring. Environ Health Perspect 130(7):77005, PMID: 35881550, https://doi.org/10.1289/EHP10009.
4. Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E, Bokkers B. 2021. Risk assessment of per- and polyfluoroalkyl substance mixtures: a relative potency factor approach. Environ Toxicol Chem 40(3):859–870, PMID: 32729940, https://doi.org/10.1002/etc.4835.
5. Cope HA, Blake BE, Love C, McCord J, Elmore SA, Harvey JB, et al. 2021. Latent, sex-specific metabolic health effects in CD-1 mouse offspring exposed to PFOA or HFPO-DA (GenX) during gestation. Emerg Contam 7:219–235, PMID: 35097227, https://doi.org/10.1016/j.emcon.2021.10.004.
6. Bevin BE, Cope HA, Hall SM, Keys RD, Mahler BW, McCord J, et al. 2020. Evaluation of maternal, embryo, and placental effects in CD-1 mice following gestational exposure to perfluorooctanoic acid (PFOA) or hexafluoropropylene oxide dimer acid (HFPO-DA or GenX). Environ Health Perspect 128(2):27006, PMID: 32074459, https://doi.org/10.1289/EHP6233.
7. Vogs C, Johanson G, Näslund M, Wulff S, Sjödin M, Hellstrandh M, et al. 2019. Toxicokinetics of perfluorinated alkyl acids influences their toxic potency in the zebrafish embryo (*Danio rerio*). Environ Sci Technol 53(7):3898–3907, PMID: 30844262, https://doi.org/10.1021/acs.est.8b07188.
8. Bosgra S, van der Voet H, Boon PE, Slob W. 2009. An integrated probabilistic framework for cumulative risk assessment of common mechanism chemicals in food: an example with organophosphorus pesticides. Regul Toxicol Pharmacol 54(2):124–133, PMID: 19303907, https://doi.org/10.1016/j.yrtph.2009.03.004.
9. Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E, Bokkers B. 2022. Response to letter to the editor on Bil et al. 2021 "Risk assessment of per- and polyfluoroalkyl substance mixtures: a relative potency factor approach." Environ Toxicol Chem 41(1):13–18, PMID: 34967046, https://doi.org/10.1002/etc.5236.
10. Fragki S, Dirven H, Fletcher T, Grasl-Kraupp B, Bjerve Gützkow K, Hoogenboom R, et al. 2021. Systemic PFOS and PFOA exposure and disturbed lipid homeostasis in humans: what do we know and what not? Crit Rev Toxicol 51(2):141–164, PMID: 33853480, https://doi.org/10.1080/10408444.2021.1888073.
11. Cheng W, Doering JA, LaLone C, Ng C. 2021. Integrative computational approaches to inform relative bioaccumulation potential of per- and polyfluoroalkyl substances across species. Toxicol Sci 180(2):212–223, PMID: 33483745, https://doi.org/10.1093/toxsci/kfab004.
12. Weaver YM, Ehresman DJ, Butenhoff JL, Hagenbuch B. 2010. Roles of rat renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. Toxicol Sci 113(2):305–314, PMID: 19915082, https://doi.org/10.1093/toxsci/kfp275.
13. EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Schrenk D, Bignami M, Bodin L, Chipman JK, Del Mazo J, et al. 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J 18(9):e06223, PMID: 32994824, https://doi.org/10.2903/j.efsa.2020.6223.
14. Agency for Toxic Substances and Disease Registry. 2022. PFAS in the US population. [Website.] Page last reviewed 6 July 2022. https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html [accessed 9 September 2022].