A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP12062.

Comment on "Internal Relative Potency Factors for the Risk Assessment of Mixtures of Per- and Polyfluoroalkyl Substances (PFAS) in Human Biomonitoring"

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https://doi.org/10.1289/EHP12062

Refers to https://doi.org/10.1289/EHP10009

We welcome the recent paper by Bil et al. on differential biologic activity of per- and polyfluoroalkyl substances (PFAS).[1] That paper, along with others that show disparate binding of specific PFAS to albumin protein (such as Alesio et al.[2]), offers improved methodologic approaches to exposure science and epidemiologic research. Using biology-driven properties of dilution and relative toxicity, risk models can appropriately correct or adjust for exposure biomarker concentrations.

PFAS toxic equivalents, similar to toxic equivalent factors (TEFs) for the dioxin family,[3] can be validated, as can dilution normalization (such as creatinine for urine and lipids for serum biomarkers). Unlike TEFs used for the dioxins, however, a single TEF approach may be inappropriate for PFAS, chemicals that can interact with several receptors.[4] PFAS are an enormous, complex family of chemicals with a wide range of binding and response factors (the range was four orders of magnitude among 23 PFAS reported in two recent articles[1,5]) The development and incorporation of a PFAS TEF approach has the potential to improve the increasingly popular use of mixtures analysis in epidemiologic investigations where individual PFAS chemical exchangeability is often an underlying assumption.

Matrix dilution of PFAS (by, e.g., albumin, fatty acid binding proteins, organic anion transporters) can be affected by factors such as reproductive age and temperature that alter distribution, accumulation, and elimination of PFAS in biological systems.[6] Thus, a broad generalization about PFAS toxicology and biomarker representation of external exposure may lead to exposure misclassification. If so, measured concentrations will reflect neither actual nor average exposure.

These key points are underappreciated by the environmental health research community and indicate the need for analyte-specific understanding of individual components of mixtures such as PFAS. The explosion of epidemiologic studies investigating PFAS exposure and human health outcomes—as reflected by a PubMed literature search we conducted, illustrated in Figure 1—and the vastness of exposures require our attention. We are reminded that many years ago McLachlan recommended using receptor-based functional equivalents for endocrine-disrupting chemicals in toxicology.[7] The idea has been developed further by Reif et al.[8] and others, but it has yet to be incorporated into epidemiology. The work of Bil et al.[1] brings us closer. Application of biomarker relative toxicity and availability has become a critical need if we are to understand the countless exposures that we can now measure. Otherwise, broad generalization will lessen the utility and value of PFAS measurements in human biomonitoring.

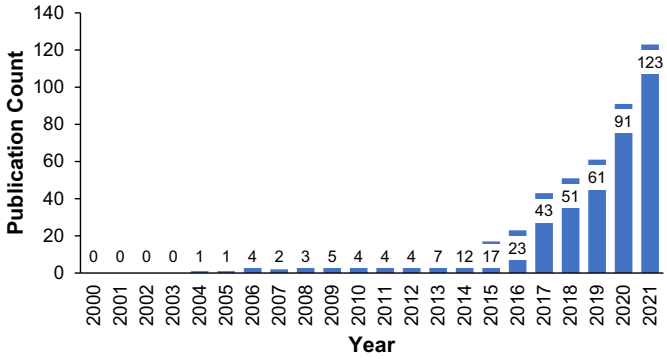

Figure 1. Number of publications indexed in PubMed over the period 2000–2021 and extracted using the Boolean operation "PFAS" AND "Epidemiology." Note: Only one publication from 1997 was indexed prior to the year 2000.

Editor's Note: In accordance with journal policy, Bil et al. were asked whether they wanted to respond to this letter. They chose not to do so.

Acknowledgments

This work was supported by the National Institutes of Health/National Institute of Environmental Health Sciences under award nos. P30 ES023515 to Robert O. Wright (Mount Sinai Transdisciplinary Center on Early Environmental Exposures), U2CES026561 to Robert O. Wright (Mount Sinai HHEAR/CHEAR Network Laboratory Hub), and to Susan L. Teitelbaum U2CES026555 (HHEAR/CHEAR Data Center).

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The authors declare they have no conflicts of interest.

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