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Overgeneralization by Anderson et al. and Luz et al. regarding safety of fluorotelomer-based chemistry

To the Co-Editors-in-Chief Drs. Aylward and van den Berg

We read with great interest the recent articles by Luz et al. and Anderson et al. published in Volume 103 issue of Regulatory Toxicology and Pharmacology. The two-part publications reported on perfluorohexanoic acid (PFHxA) toxicity, exposure and biomonitoring data available for the chemical. The analysis included the estimation of a toxicity reference dose and drinking water and residential groundwater screening levels. Significant conclusions included 1) PFHxA "is less hazardous to human health than PFOA"; 2) PFHxA is not expected to bioaccumulate due to its "rapid and nearly complete elimination" from the body; and 3) "PFHxA levels currently present in the environment are well below levels that may present a concern for human health."

Even though the authors narrowly focused on a single chemical, they extended their conclusion to the entire fluorotelomer-based chemical process when they say that 1) "**PFHxA and related fluorotelomer precursors** currently appear to present negligible human health risk to the general population and are not likely to drive or substantially contribute to risk at sites contaminated with PFAS mixtures", and 2) "**PFHxA may also represent a suitable marker for the safety of fluorotelomer replacement chemistry** used today." [Emphasis added] These broad statements, however were not fully explained and deserve a closer look based on previously published data from scientists at the U.S. Food and Drug Administration (FDA) (Kabadi et al., 2018).

Evidence from Kabadi et al. appears to contradict Luz et al. (2019) and Anderson et al. (2019) wide-ranging conclusions about the safety of the entire C6 class of per-and poly-fluorinated alkyl substances (PFAS). The FDA scientists performed a thorough evaluation of publicly available animal and human exposure data on 6:2 FTOH, a type of fluorotelomer alcohol commonly used as a raw material to make grease- and water-proof paper and cardboard for food contact applications (Rice, 2015).

The FDA scientists identified three metabolites, namely the PFHxA mentioned above, 5:3 fluorotelomer carboxylic acid (5:3 A) and perfluoroheptanoic acid (PFHpA) that could be used as markers of 6:2 FTOH exposure. For each metabolite, they also provided internal exposure estimates. As a result of their analysis, Kabadi and colleagues identified 5:3 A as an important biomarker for the potential biopersistence of 6:2 FTOH because 1) 5:3 A had the highest internal exposure and the slowest elimination by the body; and 2) 5:3 A's elimination was reduced when exposure to 6:2 FTOH increased.

Following the reasoning presented by Luz and Anderson, any short-chain PFAS used in fluorotelomer-based products would be assumed to be as safe as PFHxA, including 6:2 FTOH. The authors, however, did not attempt to discuss the discordance between their conclusion and FDA's scientists' finding that 6:2 FTOH metabolite 5:3 A is an important biomarker for the potential biopersistence of 6:2 fluorotelomer alcohol.

The discrepancy between Luz et al. and Anderson et al. and FDA's scientists' analysis clearly demonstrate that we are far from understanding the pharmacokinetics and risks posed by short-chain PFAS to human and environmental health. This is partly due to inadequate safety study designs lacking a pharmacokinetics component, biopersistence assessment and developmental exposures. It also demonstrates that even though there are structural similarities between short chain PFAS, wide-range assumptions about similar risks are unwarranted.

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