



May 15, 2024

**Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
National Toxicology Program Interagency Center for the Evaluation of Alternative
Toxicological Methods**

Re: 2024 ICCVAM Public Forum

Dear ICCVAM Committee Members,

I am a member of the Johns Hopkins University Toxicology Policy Research team, an interdisciplinary group of scientists and lawyers at the Johns Hopkins Bloomberg School of Public Health. We advocate for the use of the best science in decision-making, which is increasingly focused on developing and utilizing New Approach Methodologies (NAMs). I am writing regarding ICCVAM's current policies on assessing per- and poly-fluoroalkyl substances (PFAS). The views expressed here are my own, and do not necessarily reflect the official policy or position of the Johns Hopkins University or the Johns Hopkins Bloomberg School of Public Health. We are pleased that a workgroup has been established to address the public health challenges posed by PFAS and commend ICCVAM for its ongoing efforts to promote the validation of alternative methods for toxicological testing. Prioritizing the development and acceptance of alternative methods for PFAS assessment is increasingly necessary.

As member agencies know, exposure to PFAS is a significant concern because of their potential deleterious impacts on the environment and public health and their widespread presence and persistence. The multitude of possible adverse effects resulting from PFAS exposure are continually being discovered, making it imperative for regulatory agencies to adopt robust and reliable testing methods to assess the toxicity of PFAS. We are grateful for the efforts of the ICCVAM PFAS Working Group in recognizing the need to confront PFAS. Nevertheless, progress in addressing PFAS-related issues is too slow.

In 2019, the EPA and the NTP selected 75 PFAS chemicals for testing, with another 75 being selected. Unfortunately, these 150 compounds represent only a fraction of the entire chemical class. While this initiative marks a step forward in toxicity testing, ***we must broaden our scope to encompass the entire spectrum of PFAS compounds.*** While the federal approach seems to handle PFAS issues on a case-by-case basis, many states and international partners are taking a more holistic approach, addressing the chemical class collectively. Given the pervasive nature and lasting impact of PFAS compounds, swift action is necessary to understand their full effects and devise successful mitigation strategies. ICCVAM agencies must recognize the need to

address PFAS holistically, considering the breadth of compounds within this class and their cumulative impact on public health and the environment.

The emergence of issues with short-chain PFAS compounds after research primarily targeted long-chain variants highlights the necessity for a holistic approach.¹ Previously, the scientific community predominantly focused on the risks associated with long-chain PFAS compounds, overlooking the potential dangers of their short-chain counterparts. Recent research has debunked this assumption, demonstrating that short-chain PFAS compounds may pose a more extensive public health risk than initially thought.² This oversight underscores the importance of a comprehensive assessment of the entire PFAS class. Consequently, expediting the implementation of rapid toxicity testing capable of assessing the whole PFAS chemical class in a timely manner is vital. Investing in developing and validating high-throughput, cost-effective technologies to address the PFAS issue will bolster current assessment methodologies and serve as a preventative measure against future chemical-related crises.

I urge ICCVAM to increase its efforts in enhancing collaboration and streamlining regulatory processes while ensuring confidence and transparency to better address the PFAS class in a timely manner. I suggest the following comments for consideration as ICCVAM advances its PFAS strategy:

Enhance Collaboration

1. **Standardize the PFAS Definition:** While ICCVAM has recognized the need for a clear and standardized definition of PFAS, it seems misguided for the EPA to refuse to align with the definition currently adopted by OECD and recognized by several U.S. states.³ As the U.S. is a member of the OECD, encouraging the EPA and other federal agencies to adopt the OECD definition can promote consistency and streamline the assessment process for PFAS globally. This can also reduce the resource burden as it facilitates enhanced international collaboration.
2. **Promote Data Sharing and Stakeholder Involvement:**
 - a. **Provide guidance and resources for data owners to share datasets in compliance with confidentiality regulations:** Data sharing and accessibility play a crucial role in addressing the multifaceted challenge of PFAS, which spans regulatory jurisdictions. Facilitating data sharing among researchers, regulatory agencies, and other stakeholders fosters collaboration and enhances the reproducibility and refinement of assessment methods. By pooling resources and expertise from diverse sources, we can collectively better understand PFAS and its impact on human health and the environment.
 - b. **Develop standardized data formats and standards to facilitate international interoperability:** Collaborating with our international partners to establish standardized definitions, data standards, and promote data transparency and accessibility is essential for tackling PFAS comprehensively. PFAS

¹ Pollack, J. (2023). *PFAS Deskbook*. West Academic.

² Li, F., Duan, J., Tian, S., Ji, H., Zhu, Y., Wei, Z., & Zhao, D. (2020). Short-chain per- and polyfluoroalkyl substances in aquatic systems: Occurrence, impacts and treatment. *Chemical Engineering Journal*, 380, 122506. <https://doi.org/10.1016/j.cej.2019.122506>

³ Safer States, *PFAS Definition Factsheet.*, https://www.saferstates.org/wp-content/uploads/PFAS-Definition-Factsheet_2.7.2024.pdf (2024)

contamination knows no borders, and its mitigation requires a concerted global effort. Establishing common frameworks and platforms for data sharing ensures that insights and findings are disseminated efficiently across the international community, enabling quicker responses to emerging challenges and facilitating the development of harmonized regulatory approaches. Promoting these robust data-sharing mechanisms encourages scientific progress and lays the foundation for a more efficient and coordinated response to the complex and widespread issue of PFAS contamination.

3. **Establish Agency Commitment:** ICCVAM's role as a coordinating body is instrumental in driving change and encouraging agencies to commit to utilizing NAMs for PFAS assessment. While ICCVAM cannot mandate federal agencies to adopt specific practices, its recommendations, collaborative efforts, and influence within the scientific and regulatory community can significantly shape the policies and practices of federal agencies involved. To encourage action ICCVAM should develop interagency agreements or directives for agencies to commit to prioritizing NAMs for PFAS assessment. These should include clear timelines and benchmarks for validation studies to ensure efficient action.
4. **Continue to Engage Stakeholders:**
 - a. **Develop tailored training programs and workshops that address different stakeholders' specific needs and challenges:** Engaging stakeholders in decision-making can build trust and address concerns to accelerate the adoption of NAMs for PFAS assessment.
 - b. **Provide continued guidance and educational opportunities to build expertise, hear concerns, and promote the adoption of NAMs into PFAS assessment across sectors:** Fostering dialogue and collaboration with industry stakeholders and advocacy groups is necessary to consider all perspectives when advancing assessment strategies.

Streamline Regulatory Processes

1. **Increase NAMs Funding:** ICCVAM member agencies should allocate additional resources to developing NAMs to incentivize research in this field. The proposed FY25 funding allocation for the Complement-ARIE program is \$35 million – a small fraction of the NIH's proposed budget of \$50.1 billion. While this program will undoubtedly contribute to advancements in alternative testing methods, its limited scale constrains the pace and breadth of research and development efforts.⁴ Expanding the program would provide researchers with the financial support needed to explore innovative solutions and enable the scaling up of promising technologies for widespread adoption.
2. **Establish Reasonable Timelines and Aspirational Goals:** ICCVAM should establish clear and transparent guidelines for setting realistic goals for NAMs. These guidelines should consider the complexity of the biological systems being studied, the available resources, and the intended regulatory applications. Encourage agencies to reduce reliance on toxicology testing by 50% in 5 years and end animal toxicology testing within ten years. The EPA previously announced aspirational goals to substantially reduce mammalian toxicology testing by 2035 but has unfortunately backed away from this goal. Insights from a workshop involving over a hundred scientists and policy experts stressed

⁴ Krebs, C. (2024, February 13). *The time is now: Celebrating momentum toward human-centered research at the NIH*. [www.pcrm.org](https://www.pcrm.org/news/good-science-digest/time-now-celebrating-momentum-toward-human-centered-research-nih). <https://www.pcrm.org/news/good-science-digest/time-now-celebrating-momentum-toward-human-centered-research-nih>

the importance of timely implementation of advanced technology for risk reduction despite ongoing validation processes.⁵ One pivotal lesson from the workshop was the profound impact of delayed actions in response to early warnings of PFOA. While striving for perfection in PFAS assessment methods is noble, it is also impossible. It is crucial to recognize that no scientific method is flawless, and the stringency of metrics used to evaluate and validate NAMs should strike a balance between ensuring accuracy and feasibility.

3. **Build Scientific Confidence:** To garner scientific confidence, ICCVAM must also emphasize that NAMs are not intended to replicate traditional animal tests but to produce scientifically reliable results that inform risk assessment and regulatory decision-making. This distinction is critical for managing expectations and garnering support for adopting NAMs as valuable tools in toxicological testing. Many animal tests were not stringently examined but grandfathered into regulatory agencies, and emerging NAMs were not designed to replicate them precisely. By aligning goal setting with practical considerations, ICCVAM can ensure that NAMs are developed and validated within feasible timeframes and resource constraints. Regulatory agencies must factor in the context of use and combinatorial approaches to ensure the validation process occurs within a reasonable timeframe.
4. **Encourage Accountability and Transparency:** Establish ongoing evaluation and refinement practices of NAMs based on emerging scientific evidence so assessment methods remain relevant in addressing the complexities of PFAS.
 - a. **Regular reviews and updates of assessment criteria should be conducted and made publicly available to refine NAMs over time:** This iterative process allows for incorporating new scientific knowledge, technological advancements, and stakeholder feedback into developing and validating NAMs, enhancing their accuracy and relevance.
 - b. **Produce comprehensive reports containing data on the methodologies being used in PFAS assessment and make publicly available:** Utilize these reports to monitor the implementation of NAMs in federal programs and evaluate their effectiveness.

By adopting a proactive and collaborative approach, ICCVAM can contribute to developing more efficient, ethical, and scientifically sound approaches to chemical safety testing, ultimately enhancing public health and environmental protection.

Thank you for your attention to this serious matter. I look forward to continued progress in alternative toxicological methods for PFAS and other emerging health threats.

Sincerely,

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⁵ Chartres, N., Sass, J. B., Gee, D., Bălan, S. A., Birnbaum, L., Coglianò, V. J., Cooper, C., Fedinick, K. P., Harrison, R. M., Kolossa-Gehring, M., Mandrioli, D., Mitchell, M. A., Norris, S. L., Portier, C. J., Straif, K., & Vermeire, T. (2022). Conducting evaluations of evidence that are transparent, timely and can lead to health-protective actions. *Environmental Health*, 21. <https://doi.org/10.1186/s12940-022-00926-z>