PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
5100 Wisconsin Ave. NW, Suite 400 • Washington, DC 20016 • Tel: 202-686-2210 • Fax: 202-686-2216 • pcrm@pcrm.org

September 17, 2021

Mary S. Wolfe, M.S., Ph.D.
Acting Deputy Director for Policy and Communication
Division of NTP
Director, Office of Policy, Review, and Outreach
530 Davis Dr.
Durham, NC 27713

RE: Scientific Advisory Committee on Alternative Toxicological Methods; Request for Input

Dear SACATM members:

The Physicians Committee for Responsible Medicine (PCRM) appreciates the opportunity to comment on SACATM activities. PCRM is a nationwide nonprofit organization comprised of over 175,000 supporters advocating for efficient, effective, and ethical medical practice, nutrition, and research. This written comment will focus on the section of the agenda titled *Evolving Approaches to Validation*.

In their meeting materials, Drs. Browne and Casey cite the experience gained in the use of NAMs in a regulatory context through OECD's IATA Case Studies Programme, which has led to the development of standards to assure scientific validity and quality that permit the acceptance of data derived from New Approach Methodologies (NAMs). OECD's *Guideline No. 497: Defined Approaches on Skin Sensitisation* is an outcome of this experience that illustrates the value of human-based approaches to qualify NAMs. With its 2018 interim science policy on the use of alternative approaches to evaluate skin sensitization, EPA hastened the development of this international guideline, and we urge EPA and ICCVAM member agencies to continue their leadership role through the issuance of similar policy documents. Such published policies describing the conduct of a NAM along with its applicability domain and the regulatory context in which data derived from it will be considered facilitate the NAM's uptake by the regulated community, supplementing the rule-making process.

One NAM that is ripe for such policy development was recently accepted by EPA's Office of Pesticide Programs' for evaluating the risk of exposure to contact irritants in lieu of a 90-day inhalation toxicity study for the pesticide chlorothalonil. The approach uses a point of departure derived from human airway cells in conjunction with aerosol deposition results from a computational fluid dynamics model of the human upper respiratory tract to calculate human-equivalent concentrations, thereby avoiding any uncertainty due to species extrapolation. Another is the GHS additivity formula which integrates evidence from acute systemic toxicity testing of agrochemical formulations to propose an exposure- and data-based waiving strategy to determine classification and adequate PPE. A final example is using only *in vitro* data to calculate an

estimated human dermal absorption factor, instead of the "triple pack" approach which includes *in vivo* rat data, for evaluating the potential dermal toxicity of pesticides.

In its report, *Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing*, the Metrics Workgroup (MW) describes its charge to be developing metrics that the ICCVAM member agencies could use to assess the progress they have made toward reducing, refining, or replacing animal use in toxicity testing. In its 2019 report on animal use in research, the Government Accountability Office (GAO) also recommends that these metrics be incorporated into ICCVAM's biennial progress reports so that ICCVAM and its member agencies can better monitor progress across the range of the committee's efforts and report their progress to the public.

Disappointingly, the MW reports no progress whatsoever toward achieving these goals. Instead, the MW's only recommendation is that each agency develop its own metrics that are relevant and practical to its unique situation. In support, the MW simply restates "challenges" to measuring the results of ICCVAM and its member agencies' efforts that were already cited in the GAO report. These include differences in the regulatory contexts in which agencies use data generated through animal research and the limited ability to quantify animals used for toxicity testing. However, the exclusion from US Department of Agriculture annual reports of species commonly used in research, along with the reasons for which those animals who are included are used, only emphasizes the need for agencies to collect and report more complete information on animal use.

The MW's reasoning is described in just two paragraphs on quantitative and qualitative metrics. The purpose of the paragraph on quantitative metrics appears to be to excuse agencies' refusal to count animals used, the most intuitive metric for measuring progress toward reducing that use. Without support, the MW asserts that raw numbers may not provide a complete picture of the extent to which an alternative is being implemented. On the contrary, in our analysis of animal use to support approved new drug applications, counting the animals used has revealed missed opportunities to reduce animal use. These include the great number of mice used to evaluate toxicokinetics which could be reduced or eliminated by the application of microsampling techniques, the acceptance of New Approach Methodologies that are not yet recommended in guidance, and the availability of multiple guidance documents containing conflicting recommendations.

Instead of developing metrics that monitor progress across ICCVAM's efforts that can be reported to the public, the MW has baselessly shifted responsibility to ICCVAM's member agencies, abandoning the committee's primary charge to increase the efficiency and effectiveness of U.S. federal agency efforts to replace, reduce, and refine the use of animals for toxicity testing. The least we can do for the animals that are used in research and testing is to count them, while working towards reduction.

Thank you to SACATM, NICEATM, and ICCVAM member agencies for progress made over the past year. Our organization is eager to continue our existing collaborations, and to build more. I can be reached at JManuppello@PCRM.org.

Sincerely,

Joseph Manuppello
Senior Research Analyst
Phone: 202.717.8677
Email: JManuppello@pcrm.org