THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY LEGISLATIVE FUND™

September 14, 2023

Dr. Milene Brownlow
Designated Federal Official for SACATM
Office of Policy, Review, and Outreach
Division of NTP, NIEHS
530 Davis Drive, Room K2161
Durham, NC 27713

RE: Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Public Input

Dear Dr. Brownlow,

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund (HSLF), and our members and supporters, we appreciate the opportunity to provide comments in response to the August 8, 2023 notice "Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Public Input" 87 FR 48190. The SACATM meeting agenda includes a topic for discussion in which we are particularly interested.

Full Replacement of the Acute Tox Six-pack

HSUS and HSLF are pleased to see a focus on alternatives to animals for acute toxicity testing, an area that has received much attention in recent years (e.g., Hamm et al., 2017[1]; Clippinger et al., 2018[2]; Gissi, et al., 2017[3]; Kleinstreurer et al., 2018[4]; Mansouri et al., 2021[5]; Sullivan et al., 2021[6]). While some Organisation for Economic Co-operation and Development (OECD) acute toxicity test guidelines now offer animal use refinements that employ evident toxicity as the

[1] Hamm et al. 2017. Alternative approaches for identifying acute systemic toxicity: moving from research to regulatory testing. Toxicol In Vitro. 41:245–259. https://doi.org/10.1016/j.tiv.2017.01.004
[2] Clippinger et al., 2018. Pathway-based predictive approaches for non-animal assessment of acute inhalation toxicity. Toxicol In Vitro. 52:131–145. https://doi.org/10.1016/j.tiv.2018.06.009
[3] Gissi et al. 2018. Alternative acute oral toxicity assessment under REACH based on sub-acute toxicity values. ALTEX. 35(1):121–122. https://doi.org/10.14573/altex.1712011
[4] Kleinstreuer et al. 2018. Predictive models for acute oral systemic toxicity: a workshop to bridge the gap from research to regulation. Comput Toxicol. 8(11):21–24. https://doi.org/10.1016/j.comtox.2018.08.002
[5] Mansouri et al. 2021. CATMoS: collaborative acute toxicity modeling suite. Environ Health Perspect. 129(4):47013. https://doi.org/10.1289/EHP8495
[6] Sullivan et al. 2021. Mind the gaps: prioritizing activities to meet regulatory needs for acute systemic lethality. ALTEX. 38(2):327–335. https://doi.org/10.14573/altex.2012121

endpoint for systemic toxicity, many regulatory authorities still rely on lethality as the benchmark in hazard classification systems, often resulting in extreme pain and suffering of animals. The array of chemical sectors and jurisdictions that use acute toxicity data is multitudinous, the assessment and classification systems varied and not always harmonized, and the number of animals used, staggering. Acceptance by regulatory authorities of non-animal data is spotty, and when these data are accepted, it is via a number of methods including direct acceptance, waivers for the animal test, weight of evidence, or case-by-case. Strickland et al. (2023)[7] surveyed chemical regulatory authorities from multiple countries as to their requirements for acute systemic toxicity data, finding that there is a general lack of clarity in many cases regarding acceptance of data derived from non-animal acute toxicity methods, and that this ambiguity likely leads to increased animal use by chemical sponsors due to uncertainty of acceptance of alternative methods. The authors of this publication conclude that there is a need to standardize non-animal acute toxicity approaches for use throughout the world and that regulatory authorities must be clear about which of these methods are accepted and under what conditions.

The focus of the SACATM acute toxicity discussion will be on modernizing use of the acute toxicity "six-pack" in the US Environmental Protection Agency (EPA) Office of Chemical Safety and Pollution Prevention (OCSPP). While we applaud EPA's progress in developing, evaluating, and accepting new approach methods (NAMs), we are concerned at the slow pace at which this is occurring at both this and other US agencies. In an October 2015 letter to stakeholders, former EPA Office of Pesticide Programs (OPP) director, Jack Housenger, made it an immediate goal to significantly reduce the use of animals in the acute six-pack.[8] Eight years later, this goal is far from being reached. Metrics reported by OPP for the years 2018 through 2021 show a range of 12-24 waivers granted per year for the acute toxicity six-pack and 30-56 waivers granted per year specifically for the acute dermal test for the same period.[9] Use of *in vitro* eye and skin irritation and skin sensitization assays range from 12-32, 7-28, and 0-13 per year, respectively, for the same period. However, the numbers of waivers granted, and *in vitro* assays used, are relatively insignificant compared to the 250-300 six-pack submissions OPP reports receiving annually.[10] And these disappointing numbers are just for OPP. We have little information on how many or what acute toxicity animal testing reductions have been achieved for the OCSPP chemicals program under the Toxic Substances Control Act (TSCA) or by the Office of Research and Development, and thus no way to assess progress at these offices of EPA.

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[7] Strickland et al. 2023. International regulatory uses of acute systemic toxicity data and integration of new approach methods. Crit Rev Tox, Aug 2023. https://doi.org/10.1080/10408444.2023.2240852

[8] https://www.regulations.gov/document/EPA-HQ-OPP-2016-0093-0003

[9] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0

[10] OPP Progress on Acute Animal Testing Alternatives PPDC Meeting November 1, 2017 – Session 5, https://www.epa.gov/pesticide-advisory-committees-and-regulatory-partners/pesticide-program-dialogue-committee-5

It is unclear why there has been such a meager response to available acute toxicity non-animal methods by pesticide registrants. Is it a lack of understanding or awareness of these methods, uncertainty as to acceptance by the agency, or other reasons? While we believe EPA has been operating in good faith to end acute toxicity testing to the greatest extent possible, we feel that more can be done to quickly achieve Jack Housenger's goal of 2015. As outlined in the Strickland et al. (2023) publication, improved communication with chemical sponsors and clarity on the use of available alternatives and ensuring that EPA staff are trained in the interpretation of alternatives data can help accelerate adoption of these non-animal methods. Sharing experiences and results with other US and international regulatory authorities with the goal of standardizing and harmonizing approaches through OECD and International Cooperation on Alternative Test Methods (ICATM) should be actively pursued as well.

Conclusion

As we have commented in past years, HSUS and HSLF continue to encourage significant, dedicated funding for NAMs development and validation at all ICCVAM member agencies, international cooperation to ensure NAMs are accepted around the globe, and the proactive commitment with clear timelines to end reliance on animal test methods from all agencies. We welcome the opportunity to work with NICEATM or any ICCVAM agency to replace the use of animals with scientifically sound testing strategies. Thank you for the consideration of our comments.

Sincerely,

(signature redacted)

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