August 26, 2020

Dr. Elizabeth Maull
Designated Federal Official for SACATM
Office of Liaison, Policy and Review
Division of NTP, NIEHS
P.O. Box 12233, K2–17
Research Triangle Park, NC 27709

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

Dear Dr. Maull,

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 June 25, 2020 notice "Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments" 85 FR 38149. The SACATM meeting agenda outlines five different topics for discussion, which we address individually here.

Session 1: ICCVAM –Past, Present, Future

HSUS and HSLF commend the Interagency Coordinating Committee on Validation of Alternative Methods (ICCVAM) on the important work it has been doing to develop and implement the move toward more human-relevant testing as described in the January 2018 publication, *A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States*. The work being done by ICCVAM and its member agencies has led to an increase in development, use and acceptance of new approach methodologies (NAMs) in chemical safety assessment.

We encourage the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to continue its engagement with regulators, industry, and all stakeholders on the latest information about conducting safety assessments while also minimizing the need for animal use such as those listed below:

- The July 2020 webinar, *Animal-free Antibodies Against Diseases: Rapid Response to Fight COVID-19*, co-organized with the PETA International Science Consortium and the European Union Reference Laboratory for alternatives to animal testing, which focused on the development and use of animal-free recombinant antibodies to fight the current pandemic.
- The April 2020 town hall meeting, *Development of New Approach Methodologies to Reduce Animal Use in Toxicity Testing*, held in conjunction with National Institute of Environmental Health Sciences (NIEHS) Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) program, which sought to connect NAMs developers with agency representatives to ensure that new methods are meeting current regulatory needs.
- The January 2020 ICCVAM Communities of Practice Webinar about the use of animal-free affinity reagents.

Implementation plans

HSUS and HSLF applaud the efforts of NICEATM and ICCVAM member agencies on the development of implementation plans for some acute toxicity test endpoints. When NAMs reliability and relevance have been shown, their use should be immediately incorporated into tiered testing strategies to reduce the need for additional animal testing wherever possible. When NAMs enable elimination of an animal test entirely, this information needs to be publicly communicated and its preferred use incentivized by the member agency.

For example, recent comprehensive studies have shown that non-animal approaches to evaluate skin sensitization are more reliable predictors of human outcomes than the typical animal test methods. A 2018 review of 12 different defined approaches (DA) for skin sensitization utilizing *in vitro* or *in silico* methods carried out by Cosmetics Europe and the NICEATM compared the results to both animal and human data and found that all the non-animal methods "performed as well as or better than the LLNA in predicting human skin sensitization endpoints for both hazard and potency."[1] The Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) and Office of Pollution Prevention and Toxics (OPPT) jointly released the 2018 *Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing,* which allows pesticide and industrial chemical manufacturers to choose one of two different DAs to determine skin

[1] Nicole C. Kleinstreuer, Sebastian Hoffmann, Nathalie Alépée, David Allen, Takao Ashikaga, Warren Casey, Elodie Clouet, Magalie Cluzel, Bertrand Desprez, Nichola Gellatly, Carsten Göbel, Petra S. Kern, Martina Klaric, Jochen Kühnl, Silvia Martinozzi-Teissier, Karsten Mewes, Masaaki Miyazawa, Judy Strickland, Erwin van Vliet, Qingda Zang & Dirk Petersohn (2018). Non-animal methods to predict skin sensitization (II): an assessment of defined approaches. Critical Reviews in Toxicology, 48:5, 359-374, DOI: 10.1080/10408444.2018.1429386

sensitization without using animals.[2] All ICCVAM member agencies should take similar steps to approve DAs that meet their regulatory needs and clearly state the agency's preference for their use.

Metrics work group

HSUS and HSLF were pleased to hear during the May 21, 2020 ICCVAM public forum that a white paper is being drafted[3] to address the recommendation from the 2019 Government Accountability Office Report, *Animal use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives,* "to develop metrics that the agencies could use to assess the progress they have individually or collectively made toward reducing, refining, or replacing animal use in testing."[4] These metrics will be essential for gauging agency success in NAMs uptake and identifying areas where uptake is lacking, including barriers to that uptake. We look forward to the anticipated release of the white paper by the end of the year.

Development of performance criteria

HSUS and HSLF look forward to the work of the Food and Drug Administration (FDA) Alternative Methods Working Group and hope this agency-wide group will facilitate the acceptance of new approaches that can "support decision-making in regulatory toxicology."[5] We were also encouraged to see that FDA is now working to develop performance criteria for the use of microphysiological systems (MPS) within the different centers.[6] This is an important step toward qualification and is vital to ensure that these systems are not just viewed as additional tests to be performed by industry, but as replacement for certain animal tests**.** We urge ICCVAM member agencies to also invest in chip technology employing animal cells to assess the predictive capacity of these systems for chemical safety assessment. Demonstrating the utility of chips in cross species comparison will allow vital confidence building in these new technologies and will speed the phase-out of animal use.

Specific agency commitments

In his September 20, 2019 memorandum, EPA Administrator Andrew Wheeler put forth a public commitment by the agency to "reduce its requests for, and [its] funding of, mammal studies by

---

[2] US EPA Office of Chemical Safety and Pollution Prevention. (2018, April 4). Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing. Retrieved from: https://www.epa.gov/newsreleases/epa-releases-draft-policy-reduce-animal-testing-skin-sensitization

[3] Casey, Warren. (2020, May 21). ICCVAM Workgroup Update. ICCVAM Public forum. https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2020/ppt/03-iccvam-casey-508.pdf

[4] GAO. (2019, September). Animal use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives. https://www.gao.gov/assets/710/701635.pdf

[5] FDA. (2020, April 20). Advancing Alternative Methods at FDA. https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

[6] https://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2019/september/presentations/3-3-fitzpatrick-508.pdf

30 percent by 2025 and eliminate all mammal study requests and funding by 2035."[7] Other agencies should develop and publicly release similar forward-thinking plans to reduce animal use and reliance and provide the incentive needed to ensure NAMs are incorporated into regulatory decision-making.

NAMs funding

There continues to be a need for a significant investment of both time and money in the development and regulatory acceptance of NAMs. HSUS and HSLF encourage all ICCVAM member agencies to devote funding to NAMs development, evaluation, and acceptance as these offer the promise of providing more human-relevant data, often at a lower cost than traditional animal methods. For example, the National Center for Advancing Translational Science (NCATS) issued a notice allowing awardees to apply for competitive revisions to their research grants in order to maximize tissue chips for COVID-19 modeling, advancement of diagnostic tools, and rapid development and assessment of new therapeutics.[3] The need to rapidly develop and test new therapeutics has never been more clear than in the current pandemic, and utilization of NAMs will be critical for this and any future health emergencies. As stated in previous comments, we continue to urge modification of National Institutes of Health (NIH) grant review criteria to identify and specifically fund NAMs development. ICCVAM agencies should explore all opportunities for prioritizing funding of non-animal approaches.

Session 2a: Fostering International Partnerships

In order to see a true reduction on animal use by regulated industries, global acceptance and harmonization of testing methods and requirements will ultimately be needed. HSUS and HSLF strongly encourage ICCVAM and its federal member agencies to increase involvement with the International Cooperation on Alternative Test Methods (ICATM), the Organisation for Economic Cooperation and Development (OECD) working and expert groups, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in order to accelerate international acceptance of NAMs. NAMs implementation would benefit from the committed participation of all ICCVAM member agencies in these international efforts.

[7] Wheeler, Andrew. (2019, September 10). Directive to Prioritize Efforts to Reduce Animal Testing [Memorandum]. Washington, DC: Environmental Protection Agency. Retrieved from: https://www.epa.gov/sites/production/files/2019-09/documents/image2019-09-09-231249.pdf

Session 2b: Moving Away from Animal-based Antibodies

HSUS and HSLF strongly support efforts to move away from animal-based antibodies in favor of recombinant antibodies (rAbs). There are several scientific limitations to the continued use of animal antibodies including concerns about quality, lack of versatility, and speed of development.[8] The EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) mandated that the Scientific Advisory Committee (ESAC) review the available animal-free technologies to replace animal antibodies. The resulting Joint Research Centre (JRC) Science for Policy report, *EURL ECVAM Recommendation on Non-Animal-Derived Antibodies*, recommended that "animals should no longer be used for the development and production of antibodies for research, regulatory, diagnostic, and therapeutic applications."[9] We support the continued work of NICEATM and ICCVAM member agencies to evaluate rAbs and urge the agencies to make similar recommendations against the continued use of animal antibodies.

Session 3: Curating and Characterizing Data for Alternative Methods Use

HSUS and HSLF were pleased to see that the issue of animal test variability will be discussed during the SACATM meeting. The inherent problems with variability and uncertainty in animal data needs to be clearly recognized when evaluating NAMs against this standard. We encourage NICEATM to continue the important work of critically comparing the results obtained from animal data with those from non-animal testing strategies such as the studies done on skin sensitization[10] and acute oral toxicity.[11] This work will be vital for building additional confidence and this type of comparative analysis should be a key component incorporated into the evaluation of NAMs. However, the potential fallacy of relying on animal data as "the gold standard" must be considered when performing these types of analyses.

We also ask NICEATM and ICCVAM agencies to regularly conduct retrospective analyses of data obtained for regulatory purposes to investigate whether the data were actually used in conducting hazard and risk assessments. In those instances where specific types of animal data were never or rarely used by the agency in regulatory decision-making, agencies should be encouraged to remove the requirement or publicize acceptance of waivers as EPA has done with the release in February 2020 of its *Final Guidance for Waiving Sub-Acute Avian Dietary*

[8] Dübel, Stefan. (2020, July 23). Animal Free Generation of Antibodies. Retrieved from: https://www.piscltd.org.uk/wp-content/uploads/2020/07/STEFAN-DUEBEL_webinar-slides.pdf

[9] Joint Research Centre. (2020). EURL ECVAM Recommendation on Non-Animal-Derived Antibodies. Luxembourg: Publications Office of the European Union. Retrieved from: https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/eurl-ecvam-recommendation-non-animal-derived-antibodies

[10] Kleinstreuer, Nicole et.al (2018): Non-animal methods to predict skin sensitization (II): an assessment of defined approaches, Critical Reviews in Toxicology, DOI: 10.1080/10408444.2018.1429386

[11] Kleinstreuer, Nicole et.al (2018): Predictive models for acute oral systemic toxicity: A workshop to bridge the gap from research to regulation, Computational Toxicology, DOI: 10.1016/j.comtox.2018.08.002

Tests for Pesticide Registration and Supporting Retrospective Analysis.[12] Critical review of if and when animal data were of value will enable regulators to make decisions based on weight of evidence without compromising human or environmental safety.

Session 4: Computational Resources

HSUS and HSLF strongly support the use of available computational tools and encourage NICEATM and ICCVAM agencies to continue to develop and improve upon them in collaboration with all stakeholders. In an effort to address acute oral toxicity, NICEATM made curated sets of rat oral acute toxicity data available to modelers allowing them to develop and evaluate predictive models, which culminated in the now publicly available Collaborative Acute Toxicity Modeling Suite (CATMoS).[13] This thoughtful process facilitated an exchange of knowledge and information needs among agencies, industry, academia, and other stakeholders. The current collaboration between EPA, HSUS and NICEATM to evaluate CATMoS as a replacement for the rat LD_{50} test in ecological risk assessment may serve as a model for other agencies if they conduct their own evaluations of CATMoS prior to accepting the model's acute toxicity predictions for new chemicals. In any case, demonstrating that new computational tools can reliably answer questions in a regulatory context will be essential for their uptake and acceptance by ICCVAM agencies.

HSUS and HSLF also encourage an increased focus on exposure when developing NAMs for risk assessment. High-throughput exposure prediction models that can rapidly and accurately estimate exposure potential for thousands of chemicals is an important part of prioritizing chemical safety evaluations since even the most toxic chemicals do not present a public health concern without exposure. Exposure considerations contribute to a reduction of animal use as only those chemicals with increased probability of toxicity and exposure may require further testing. The Environmental Protection Agency's ExpoCast can evaluate exposure to chemicals that are released into the environment as well as those used in consumer products[14] and was used by EPA in the Endocrine Disruptor Screening Program along with hazard information to prioritize for further assessment only those chemicals that displayed sufficient levels of hazard and exposure for concern.[15] All agencies should be incorporating exposure considerations into their product safety evaluations to develop real-world risk assessments. However, an ongoing

[12] Environmental Protection Agency (2020, February). Final Guidance for Waiving Sub-Acute Avian Dietary Tests for Pesticide Registration and Supporting Retrospective Analysis. Retrieved from: https://www.epa.gov/sites/production/files/2020-02/documents/final-waiver-guidance-avian-sub-acute-dietary.pdf

[13] National Toxicology Program. (2019). Predictive Models for Acute Oral Systemic Toxicity. Retrieved from: https://ntp.niehs.nih.gov/pubhealth/evalatm/test-method-evaluations/acute-systemic-tox/models/index.html

[14] Environmental Protection Agency. (n.d.). Rapid Chemical Exposure and Dose Research. Retrieved from: https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

[15] Friedman et al. 2016. A predictive data-driven framework for endocrine prioritization: a triazole fungicide case study. Crit Rev Tox 46(9): 785-833. https://doi.org/10.1080/10408444.2016.1193722

concern about the ability to reduce animal use through incorporation of exposure data is the continued focus on chemical hazard without regard for exposure that is the regulatory approach in other countries, notably the European Union. ICCVAM agencies should work within the international regulatory associations to encourage global alignment of exposure-based risk assessments.

Conclusion

We welcome the opportunity to work with NICEATM or any ICCVAM agency to help achieve the common goal of replacing animals with scientifically sound and human relevant test methods and strategies. Thank you for the consideration of our comments.

Sincerely,

Vicki Katrinak
Manager, Research and Testing
Animal Research Issues
Humane Society of the United States

Gillian Lyons
Senior Regulatory Specialist
Humane Society Legislative Fund