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To the members of the Scientific Advisory Committee on Alternative Toxicological Methods:

We appreciate the opportunity to submit these comments for consideration by the Scientific Advisory Committee on Alternative Toxicological Methods. The following comments include some general comments directed at all agencies and some comments specific to certain agencies or agency departments.

Overall, we are quite encouraged with the way NICEATM has begun implementing its strategic plan, and how ICCVAM member agencies have followed its example to create plans of their own. We have found in our discussions with regulated industry that confusion or uncertainty discourages risk-taking and maintains the status quo. In other words, companies may be leery of submitting new or alternative approaches without some certainty that they will be accepted and found useful.

Therefore we encourage SACATM to advise federal agencies to be abundantly clear about the alternative methods and approaches that may be or are accepted for regulatory purposes. The policy documents and lists of potential New Approach Methodologies (NAMs) published by the Environmental Protection Agency (EPA) are one great example. In previous comments to SACATM and ICCVAM, we have suggested strategies to aid in this process, which we will briefly overview in this written comment:

- Increase transparency of each agency policy on alternative methods through frequent updates in agency guidance and website resources
- Remove redundant or inadequate animal tests and outdated guidelines
- Disclose specific regulatory needs and use of data to substantiate safety assessment decisions

We also encourage ICCVAM member agencies to consider following the EPA's lead and set tangible, specific goals for reducing animal use or increasing use of new approaches by respective regulated industries. Specific goals galvanize activity and support, ensure steady funding and resources, and demonstrate a prioritized commitment to achieving success.

Increase transparency

Some agency test guidelines, guidance, or other printed or online guidance is outdated. The need to maintain modern resources inclusive of practical reduction and replacement methodologies is essential to increase regulatory implementation of alternative toxicology methods. We appreciate EPA's practice of publishing draft and final policies, which help share the agency's thinking with stakeholders and encourage engagement and use of alternative approaches. However, while OPP and OPPT web resources on alternative approaches are available, they are not immediate accessible unless someone is already aware of them and where to find them. We encourage all agencies to view your web pages from

the perspective of a prospective submitter and think about how to make those resources easy to find—for example, by adding links to pages that list "Testing Requirements".

Similarly, we encourage agencies to produce webpages like the 2012 Consumer Product Safety Commission's (CPSC) webpage[1] regarding their policy on animal testing and recommended procedures. However, we also recommend CPSC update this page regularly.

Recently, the FDA produced a Predictive Toxicology Roadmap highlighting promising new technologies such as (MPS) physiological systems, computational tools, and in vitro assays. To complement the roadmap, we challenge the FDA and other US federal agencies to commit to cataloging or prioritizing alternative approaches within context-of-use for respective agency needs. We also challenge the FDA to update the Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook, last revised in 2007) to reflect emerging technologies and remove redundant or inadequate animal tests.

Remove redundant or inadequate animal tests

The research and regulatory community have made substantial progress in moving towards nonanimal methods for skin sensitization assessments. Efforts to map international regulatory requirements (Daniel et al., 2018)[2] and various nonanimal methods to predict skin sensitization (Hoffmann et al., 2018)[3] have been documented. Despite these advancements, there are still a number of animals used for this endpoint and only limited federal documentation (e.g., EPA's 2018 Interim Science Policy) specifying what approaches will be accepted as replacements. We are aware that EPA has been receiving dossiers with in vitro skin sensitization methods, exemplifying the promise of clear communication. We encourage other agencies to do the same. Finally, relevant to this endpoint, is that there are still guidelines in place for guinea pig assays for skin sensitization. Given how much progress has been made, we encourage agencies to remove these guidelines to ensure they are not conducted.

Disclose specific regulatory needs and uses of data

PCRM is active in the training of NAMs for regulatory needs (New Approach Methodology Use for Regulatory Application (NURA)[4]. Often at NURA we hear circular discussions between industry and regulators: each expects the other to go first. Industry waits for requirements to change and regulatory agencies wait for industry to submit new approaches. While of course there are examples where federal agencies and companies have taken the initiative to forge a path of communication for regulatory acceptance of NAMs; however, to increase implementation and use of these approaches it is imperative

[1] Recommended Procedures Regarding the CPSC's Policy on Animal Testing, published November 26, 2012 https://www.cpsc.gov/Business--Manufacturing/Testing-Certification/Recommended-Procedures-Regarding-the-CPSCs-Policy-on-Animal-Testing/

[2] Daniel et al., 2018. International regulatory requirements for skin sensitization testing. *Reg Tox Pharm* 95:52-65.

[3] Hoffmann et al., 2018. Non-animal methods to predict skin sensitization (I): the Cosmetics Europe database. *Crit Rev Toxicol.* 48(5):344-358.

[4] www.pcrm.org/NURA

for agencies to disclose how information is used and what information is needed to make a regulatory decision for each endpoint of interest. This will not only spur innovation of NAMs but lead to better communication between regulators and industry scientists. Furthermore, we encourage this public disclosure of regulatory needs and use of data to open more opportunities for targeted training that will increase confidence, quality, and reproducibility of NAMs. This is in line with the aims of the NICEATM roadmap and some agency efforts and so we offer these comments as support and encouragement for continued collaboration and for other agencies to start to take more initiative in this regard.

EPA/INDUSTRIAL CHEMICALS

Recently, EPA stated that it had modified language in TSCA Section 5(e) Consent Orders to contain a statement of need that explains the basis for any decision that requires the use of vertebrate animals. In addition, EPA would modify language in its Significant New Use Rules (SNURs) to more generally describe the information it believes would help characterize potential human health and environmental effects of chemical substances, rather than list specific recommended tests.

While we are unaware of any new statements of need in Consent Orders, this is likely due to far fewer consent orders for new chemicals being issued currently compared with the early months of TSCA implementation in 2016 and 2017. This change is the result of another policy shift under which EPA regulates reasonably foreseeable, but not currently known or intended, chemical exposures mainly through SNURs. In its most recent SNURs, EPA has indeed described potentially useful information rather than list specific tests, even for substances that are subject to Consent Orders in which specific tests *are* recommended. In addition, for SNURs with time or production volume limits, or if a Significant New Use Notice (SNUN) submitter is required to conduct testing, EPA has stated that it will include consideration of TSCA section 4(h)(3), which requires any person developing information on a voluntary basis to first attempt to develop the information by means of an alternative test method or strategy.

In its prioritization of existing chemical substances for risk evaluation, EPA appropriately looked to its *TSCA Work Plan for Chemical Assessments: 2014 Update* for high priority candidates and to its *Safer Chemicals Ingredients List* and *Chemical Assessment Management Program*, as well as the OECD's *Screening Information Data Sets*, for low priority candidates. EPA's approach supports completion of the risk evaluation process within the time periods allowed by TSCA without requiring the development of new information before initiating prioritization.

We welcome these policies which demonstrate EPA's continuing commitment to reduce the use of vertebrate animals in chemical testing. As a next step, the resources currently available through EPA's website could be expanded to guide submitters of Pre-Manufacture Notices and SNUNs from the "potentially useful information" identified in Consent Orders and SNURs to appropriate alternative methods and strategies that reduce animal use. EPA lists the launch of a TSCA NAM website among its near-term activities for implementing its *Strategic Plan to Promote the Development and Implementation of Alternative Test Methods within the TSCA Program*. Currently, the website includes the strategic plan and the statutorily mandated *List of Alternative Test Methods and Strategies* as pdf files. An update of this list, expected summer 2019, has not yet posted. The list consists mainly of 30 OECD test guidelines, including the endpoints assessed in each. We recommend expanding the functionality of this website to link the most frequently requested information to specific NAMs along with information on applicability domains and examples illustrating the use of such methods in regulatory applications.

We would also recommend that OPPT take stock of the skin sensitization information it is receiving, and cases where an animal test is still being conducted by submitters or being requested by EPA. Are there specific classes or types of chemicals for which the currently accepted Defined Approaches are not appropriate, for technical or practical reasons? This information will be necessary for test method developers and other stakeholders looking to fill in the gaps and achieve complete replacement.

Finally, while EPA encourages consultation on the use of alternative test methods and strategies to determine how best to meet both information needs and the objective of TSCA's animal protection provisions, we urge EPA to me more proactive in its outreach to members of the regulated community by partnering with NGOs to expand its offerings of workshops and training sessions on the use of NAMs.

EPA/PESTICIDES

EPA's recent successes in implementing new approaches for pesticides are welcomed, and EPA, NICEATM, and industry partners are to be commended for continued progress. We are looking forward to an update on some ongoing initiatives in the Office of Pesticide Programs. These include progress in waiving the dermal LD50 for active ingredients, replacement of the dermal absorption test, and implementation of NAMs for portal of entry effects in the respiratory system.

We are also looking forward to a report—similar to what EPA has given in years past—of metrics around waiving of animal tests and acceptance of alternative approaches. This information is crucial to help plan outreach, training, and engagement activities with the regulated community and is much appreciated.

FDA/SUNSCREENS

FDA is currently finalizing a proposed rule on sunscreen active ingredients. For twelve ingredients, FDA found the available information to be insufficient to support a GRASE determination. To address these information needs, FDA would require a dermal carcinogenicity study in mice or rats and developmental toxicity studies in rats and rabbits. At least 30,000 animals would be used in these studies. In most cases, FDA would also require a systemic carcinogenicity study and additional developmental and reproductive toxicity (DART) studies, potentially doubling this number. In its proposed rule, FDA omits discussion of any efforts to reduce this very large number of animals.

FDA first requested comment on this testing battery for a 2015 draft guidance to industry. Despite numerous comments from industry representatives and public health advocates questioning the need for these studies and proposing alternatives based on new toxicological methods, FDA states only that its recommendations generally remained unchanged in the final version.

Furthermore, FDA describes in detail only the data gaps it identified for two of these twelve ingredients. However, all are registered or pre-registered under the EU's REACH regulation, and most have full dossiers including relevant toxicological information. In addition, eight of these ingredients have been evaluated by the National Toxicology Program (NTP). NTP's toxicological characterization of one ingredient, oxybenzone, includes a completed one-generation reproductive toxicity study as well as ongoing DART studies and carcinogenicity studies in rats and mice for which a report is currently being drafted.

We ask SACATM to encourage FDA's ICCVAM representatives to work with CDER's Office of Drug Evaluation to address the shortcomings of this proposed rule. Specifically, FDA should review all available information for each ingredient and reevaluate the data gaps it has identified. In addition, FDA should review the comments submitted on its 2015 guidance in the context of the proposed rule and respond to them in the final version.

FDA/PHARMACEUTICALS

We are pleased to learn about the newly established In Vitro Systems Working Group, which will start by increasing the agency's involvement in MPS. We note the agency has already been quite active in this space and commend FDA for its activities -from collaborating with DARPA and NIH, to participating in targeted workshops, to bringing the technology in house. We agree with the agency that establishing performance standards for MPS is needed and are delighted the agency is taking this on.

In addition to MPS evaluation, we ask for consideration of how companies with non-MPS in vitro systems should approach evaluation and regulatory acceptance of their tools outside of submissions. The planned seminar series will certainly provide a welcome avenue for interaction with the agency. Could the seminar be paired with a more formal option such as a pathway for evaluation similar to/under the Drug Development Tools Qualification Program?

Thank you to SACATM, NICEATM and staff at ICCVAM member agencies for the progress and hard work on these issues. Our organization is eager to collaborate over the next year to carry out the many suggestions included in this comment.

Sincerely,

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