PhysiciansCommittee
for Responsible Medicine
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May 10, 2019

Dr. Warren Casey, Director
National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
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Submitted via ICCVAMquestions@niehs.nih.gov

Dear Dr. Casey,

The Physicians Committee for Responsible Medicine is a nationwide nonprofit comprised of over 175,000 supporters working for efficient, effective and ethical research and testing. We appreciate the opportunity to provide written and oral comments on NICEATM and ICCVAM-related activities. We continue to be impressed by NICEATM's leadership in developing and implementing the strategic roadmap, and its ability to effectively partner with external stakeholders. Below, we offer input to help meet our shared goals of evaluating and advancing improved approaches to research and testing that focus on human biology while reducing animal testing.

FOOD AND DRUG ADMINISTRATION

We applaud FDA's efforts to advance predictive toxicology across the agency by launching its own roadmap, as we believe a regulator-driven effort is needed to more quickly integrate new methods. In its Predictive Toxicology Roadmap, the FDA affirms its support for new methodologies that reduce animal testing and encourages integration of new approaches that are more predictive of human biology. We appreciated the opportunity to provide input at the roadmap stakeholder meeting and look forward to learning which projects the agency decided to implement. As our organization has stated in previous communications with FDA, we are committed to assisting the agency in specific efforts to integrate new approaches that include: identifying regulations and policies that may act as barriers to integration of new approaches; sponsoring a workshop to discuss pathways for regulatory acceptance of new approaches and sponsoring regulator training in new approaches.

We encourage the agency to make transparent the annual report to the Chief Scientist as outlined in the roadmap, as well as any agency roadmap implementation plans. Access to this information will help us and fellow stakeholders understand how we may work most effectively to support FDA activities.

Both the ICCVAM and FDA roadmaps highlight communication as an important part of evaluating and integrating new tests, and because making change to established processes offers unique challenges, the bulk of our input revolves around the need for additional communication.

Increasingly, we hear from industry that a number of communications will help provide the level of confidence needed to submit data from human-based approaches. While industry has a responsibility to advance new methods, we are concerned that without this communication, many of the methods the roadmap seeks to advance will remain in use in-house for internal decision making in perpetuity without being integrated into regulatory submissions, while more traditional animal-based methods that the agency may no longer prefer or require will continue to be submitted.

Updating the Regulatory Framework Would Communicate FDA's Discretion to Accept NAMs

In early 2018, we provided the Regulatory Reform Task Force at the FDA with 235 regulations that mandate or prioritize animal data. To clearly communicate FDA's discretion to accept new approaches, we ask the agency to broaden these regulations to accept data from "nonclinical approaches" rather than specifically requesting data from "animals". Making these changes would neither act as a ban on animal testing nor a mandate for human-based approaches. It would however reflect the agency's discretion to accept any valid nonclinical test. It would also help build industry confidence and even help ensure the longevity of the regulations as nonclinical approaches evolve. While our regulatory review focused on the FDA, we encourage other agencies to consider this approach and "generalize" toxicology language away from specific references to *in vivo* tests, methods, or data.

Further, the pharmacology/toxicology filing checklist for new drug applications includes a check-box for whether carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, and animal ADME studies were submitted. This language implies that animal data is required, which is contrary to agency statements and works against the agency's goal of integrating new approaches that reduce or replace animal testing. We ask the agency to remove references to "animal" data in the pharmacology/toxicology filing checklist and encourage other agencies to review and neutralize commonly used checklists as well.

Establishing A Qualification Pathway for Human-Based Methods Would Communicate Acceptance of Qualified NAMs

The ICCVAM roadmap states that industry stakeholders indicate lack of clear communication on the status of regulatory acceptance is a significant reason why new approaches are not integrated into regulatory submissions. This is consistent with the above-mentioned industry feedback we have received.

Scientific evaluation of new approaches is a critical step to understanding capabilities and limitations of a method. Increasingly, the pharmaceutical industry expresses interest in using human biology-based nonclinical approaches in drug testing. This interest is often accompanied by concern about whether the agency will accept a particular approach. Contemporaneously,

many innovator companies have developed human biology-based nonclinical methods that would benefit from a clear path for evaluation that includes FDA communication regarding whether the method is accepted in regulatory submissions.

As part of ICCVAM and FDA roadmap implementation, we ask FDA to communicate preferred agency pathways for attaining regulatory acceptance of a new approach. It may be that the agency's Drug Development Tools Qualification Program (DDTQP) is a solution. Currently, the qualification program accommodates biomarkers, clinical outcome assessments, and animal models under the animal rule, and does not include a program for evaluating human-based approaches. The DDTQP is particularly appealing because once a method is qualified to be used in certain circumstances, the FDA issues Guidance stating that the specific method is qualified and accepted in regulatory submissions without the need for additional evaluation data. Expanding qualification eligibility to include human-based methods is consistent with the ICCVAM and FDA roadmaps that describes advanced in vitro and computational methods as having the potential to improve product testing.

Communication Regarding Which Tests Are No Longer Needed Could Reduce Animal Use and Free Up Resources for Other Methods

In February of this year, the FDA sponsored a Society of Toxicology colloquium, Redesigning the Rodent Bioassay for the 21st Century. Each of the presenters, which represented multiple product sectors, concluded that the rodent bioassay provides no, or very limited, additional value in evaluating the cancer risk of test substances compared with shorter-term repeat dose studies that use fewer animals and which may be already available for many substances. One presentation included a decision tree, which begins with identifying structural alerts and testing mutagenicity *in vitro* and addresses concerns for potential non-genotoxic carcinogens by evaluating cell proliferation, endocrine activity, and immunosuppression. Exposure and thresholds of toxicological concern are taken into account as is the relevance of toxicity modes of action to humans. Another presentation included data showing that the application of such an approach for pesticides from 2011 to 2017 resulted in the acceptance of 78% of bioassay waiver requests, saving 21,840 animals and 35 million dollars.

Of particular relevance to CDER, one presentation included the results of a 2011 analysis of the PhRMA Carcinogenicity Database which showed that for cases in which histologic risk factors for neoplasia, genetic toxicity, and hormonal perturbation signals are absent, the rodent bioassay provides no added value and projected that 40% of rodent bioassays could be eliminated while maintaining patient safety and accelerating patient access to pharmaceuticals. For the approximately 50% of pharmaceuticals which do present histologic risk factors for neoplasia, transcriptomic signatures can identify common molecular initiating mechanisms and their relevance to humans can be assessed. We ask the FDA to determine if results of the bioassay are needed and to communicate that decision to stakeholders. We also suggest using the results of the colloquium to launch a larger interagency discussion with stakeholders which could identify actionable items to implement improved and integrated carcinogenesis assessments. For example, how can FDA incorporate discussions at the recent NTP Converging on Cancer workshop?

In order to get a sense of which tests are being submitted in regulatory submissions, we reviewed new drug applications (NDA) focusing on single dose toxicity, local tolerance, and sensitization. We collected information from 125 publicly accessible NDA reviews for approved applications from 2015 to 2018. Counting both dose-range finding and main studies, the results of at least 212 single dose tests were submitted, an average of 1.7 tests per application. This estimate is conservative because, in some cases, not all submitted studies were listed, while in others, *FDA reviewers noted that single dose studies were submitted but declined to review or summarize them because they were not required and presumably of little value in decision-making*. We estimate that over 4,600 animals, including dogs, mice, monkeys, rabbits, rats, and cats were killed in these tests. We ask the agency to review how often animal studies are submitted and not reviewed and take action to prevent superfluous testing. Results of these reviews would inform where communication is needed to ensure animal tests that will not be reviewed are not conducted.

In addition, the results of 95 *in vivo* local tolerance tests, including eight Draize eye tests and 31 *in vivo* sensitization tests (four of which were guinea pig maximization tests), were submitted. This is despite the availability of robust and internationally-validated *in vitro* and *in silico* methods and approaches being widely available for these endpoints. The 2018 publication *International regulatory requirements for skin sensitization testing* states that the Center for Drug Evaluation and Research "prefers that submissions include skin sensitization screening tests, which may use any scientifically valid and predictive approach including animal or non-animal assays."[1] Communication from the agency is required to help facilitate a transition away from animal tests and integrate new methods as described in the roadmap. Following the EPA's lead, we ask the FDA to issue a policy statement or Guidance on acceptance of *in vitro* methods for sensitization. After EPA issued its policy document, industry began using and submitting data from *in vitro* methods rather than *in vivo* methods.

Proposed Rules Should Not Communicate a Preference for Animal Data

In its proposed rule for sunscreen drug products for over-the-counter use, FDA specifies a default battery of *in vivo* tests which includes a mandatory dermal carcinogenicity study, as well as a likely systemic carcinogenicity study and developmental and reproductive toxicity studies. FDA described these requirements in a 2015 draft guidance for industry on which it solicited public comment. Numerous commenters objected to the testing requirements, instead recommending approaches more consistent with those presented in FDA's recent colloquium described above. For example, the Personal Care Products Council and the Consumer Healthcare Products Association noted that while ensuring that consumers have access to products containing a broad variety of sunscreen active ingredients is the goal of the Sunscreen Innovation Act, by not sufficiently considering current approaches in toxicological risk assessment, FDA's requirement for an *in vivo* test battery would likely slow the incorporation of such active ingredients already used safely in other jurisdictions. Like the presenters in FDA's recent colloquium, they recommended an approach beginning with analyses of chemical structures for structural alerts for genotoxicity, *in vitro* tests for genotoxicity, skin and eye irritation, and phototoxicity, and genomics for characterizing endocrine activity. We ask FDA ICCVAM

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

representatives to address this with the agency and work more directly with stakeholders to take their concerns into account and adopt a 21st-Century approach to evaluating these materials.

Society of Toxicology (SOT)-FDA Colloquium Offers Valuable Cross-Cutting Discussions

The partnership between SOT and FDA's Center for Food Safety and Applied Nutrition (CFSAN) has delivered high-quality, cutting-edge, future-oriented toxicological science to inform US FDA employees and the general public. It also provides an excellent forum to spotlight how nonanimal methodologies and the 3Rs can be applied to food and ingredient safety, which is sometimes an overlooked chemical sector. We encourage FDA to continue this partnership and to proactively apply the approaches explored during the workshops to reduce and replace animal testing conducted under its purview.

Botanical Safety Consortium Transparency, Redbook Revisions Needed

PCRM is interested to note the formation of the Botanical Safety Consortium and the reform of the Dietary Supplement Health and Education Act (DSHEA). We request the FDA be transparent as to how interested stakeholders can participate and provide input concerning the activities of the Botanical Safety Consortium.

And, similar to DSHEA, the Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook) should be updated to reflect FDA's interest in receiving data from emerging technologies and to put a more flexible regulatory framework into place with clear guidance for industry and other stakeholders. A revised Redbook would balance adequate evaluation of product safety and minimization of animal tests.

ENVIRONMENTAL PROTECTION AGENCY

The EPA's Office of Pollution Prevention and Toxics (OPPT) has met the many aggressive deadlines set forth in the amended TSCA including the issuance of a strategic plan to promote the development and implementation of alternative test methods and a list of alternative test methods and strategies that it will accept. While in its early implementation of the amended TSCA OPPT requested a dramatically greater number of animal tests for new chemicals under review, it listened to stakeholders' concerns and has since modified language in its regulatory documents to reflect a preference for tiered testing and the use of non-vertebrate testing strategies first. These developments represent significant progress; however OPPT still has not completely updated its significant new use rules (SNURs) to reflect these changes. For example, a recent group of SNURs reproduced consent order requirements for *in vivo* skin sensitization studies even though EPA has stated that such studies will generally no longer be requested under TSCA. While we are excited to see some *in vitro* approaches being submitted and/or recommended, unexplained inconsistencies risk confusion and *in vivo* testing where none is required—a situation which must be avoided.

For pesticides, the agency can be commended for the way in which it is involving stakeholders in assessing new approaches for pesticide testing. We appreciate in particular the approach taken to communicate a case study for inhalation testing using in vitro testing and computational

modeling. This active discussion between industry, the agency, and the scientific community is essential for the iterative application process we already see taking place as regulatory toxicology transitions towards more 21st-Century tools for chemical assessment.

Specifically with regard to the chlorothalonil case study, we look forward to hearing more from the agency as to how it expects the *in vitro* and modeling approach can be applied to other pesticides and chemicals and encourage additional communication on this topic. The *in vitro* airway and alveolar models are extremely promising tools and we have just begun to scratch the surface of potential applications for the assessment of products under OPP's and OPPT's regulatory purview.

And finally, we are excited by the progress the agency is making for other acute endpoints and encourage continued progress in testing *in vitro* approaches for skin and eye irritation for pesticide formulations so these methods can be used in place of *in vivo* tests as soon as possible.

NATIONAL INSTITUTES OF HEALTH

The ICCVAM roadmap describes the need to encourage adoption of new approaches by incentivizing the use of new approaches and identifying measures of success. To assist with implementing these objectives and to better establish how new approaches are currently used, it would be helpful for the NIH to improve transparency regarding the kind of extramural research the agency funds. Comprehensive unbiased information about the amount of funding allocated toward human-based approaches and the number of studies using such approaches—compared to studies using non-human animals—is not easily accessible in the current system. We recommend that the NIH modify its reporting system to include classifications for "human-based" and "animal-based" studies, organized by Institute or Center. The information gathered could be added to or modeled after existing databases, such as the NIH RePORTER.

This modified tracking system would help ICCVAM measure progress toward roadmap implementation of new approaches and the translational effectiveness of specific methods. This information could then be used to guide funding priorities, justify to Congress the need for increased funding of more human-based approaches, and encourage transparency in communication among stakeholders.

In May of last year, NICETAM requested data and information on non-animal approaches for developmental toxicity. The results were projected to 1) assess the state of the science for these approaches and technologies and 2) determine technical needs for approaches to assess developmental toxicants. We see that the call-in, as with the 2016 call-in, generated a number of responses.

Reproductive and developmental toxicity are complex and yet essential endpoints in which multiple regulatory agencies require information; currently that information is mostly gathered with methodologies that use large numbers of animals with uncertain human relevance.

To promote the development and evaluation of more efficient methods with respect to predictivity and resources, we encourage NICETAM, in cooperation with other ICCVAM member agencies, to routinely update the Non-animal Methods and Strategies for Developmental Toxicity webpage with information or a brief summary on how the information is being used or is expected to be used to inform the future direction of developmental test method evaluation for regulatory acceptance, including links to relevant activities.

MULTI-AGENCY COMMENTS

Acute Oral Systemic Toxicity

Recently, NICEATM led an international effort[2] to develop predictive models for acute oral systemic toxicity, culminating in the CaTMOS consensus model, now available via US EPA's Chemicals Dashboard[3]. This model provides acute oral predictions and classifications for chemicals and other products. We encourage each ICCVAM member agency, and especially EPA, CPSC, and DOT, to release guidance or other communication for their respective regulated industry stakeholders encouraging the use of this model and detailing how it may be used to fulfill product assessment and classification requirements without *in vivo* lethality testing.

Skin sensitization

This past April the Working Group of National Coordinators of the Test Guidelines programme (WNT), an Organisation for Economic Co-operation and Development (OECD) subcommittee, held their annual meeting in which OECD member countries (Netherlands and Denmark) proposed the removal of the Buehler test from OECD Test guideline (TG) 406: Skin Sensitization, because other, more advanced *in vivo* and *in vitro* approaches are now available which are more sensitive and offer replacements, or at the very least, refinements, to the use of animals.

The proposal aimed not only to update TG 406 with the removal of the Buehler, but also to assess regulatory requirements for the Guinea pig maximization test (GPMT) for potentially later revision or deletion of the TG. This is consistent with OECD procedures to revise or delete tests when they have been superseded by more modern tests and is essential to maintain international regard for the relevance of the OECD Test Guidelines Programme.

Unfortunately, US agencies argued against deleting the test, providing specious reasoning that deletion of the test would somehow trigger re-testing of older chemistries for regulatory needs. OECD guidance explicitly recommends against this kind of duplicative testing.

We challenge ICCVAM agencies to reconsider the deletion of the Buehler and assessment of the continued need for the GPMT in TG 406. We recommend that agencies continue to assess *in vivo* test requirements and preferences with a critical eye to make room for implementation of *in*

[2] Kleinstreuer et al., 2018. Predictive models for acute oral systemic toxicity: A workshop to bridge the gap from research to regulation. *Computational Toxicology* 8:21-24,
[3] https://comptox.epa.gov/dashboard

vitro, *in chemico*, and *in silico* approaches that are already in use or under advanced development to predict skin sensitization.

We would like to highlight the progress EPA has made in this regard by assessing new approaches for skin sensitization and proactively communicating the agency's acceptance of them to the regulated community. As a result of this, companies are actively using the new approaches where possible.

Education and outreach

We are happy to see multiple post-doctoral opportunities and job openings at the EPA and other agencies which seek specific expertise such as computational toxicology and in vitro models for organ toxicity. We would like to highlight the need to vigorously train the next generation of scientists in 21st Century approaches; current instructional opportunities in toxicology programs across the country are not reflective of workforce needs. We encourage ICCVAM member agencies, perhaps NIEHS/NTP in particular, to partner with other entities and Universities to improve curricula and course offerings in *in vitro*, *in silico*, and regulatory toxicology.

PCRM has been involved in organizing and facilitating educational outreach, especially in-career training, for several years. In 2018 we launched a training program entitled New Approach Methodology Use for Regulatory Application (NURA). Though NURA we offer education on advancing science, in addition to how to apply in vitro and computational tools for regulatory submissions. We aspire to continue to offer need-based training on relevant topics to targeted audiences and offer our assistance to ICCVAM member agencies to develop and organize future trainings or workshops of interest.

In conclusion, the Physicians Committee continues to be impressed by NICEATM's leadership in modernizing safety assessment and appreciate ICCVAM member agency efforts to evaluate and integrate human-based approaches. Following the FDA's lead, we encourage other ICCVAM member agencies to consider the development of agency roadmaps to guide activities in coordination with the ICCVAM-wide roadmap. We look forward to continued collaboration over the next year to advance our shared goals.

Sincerely,

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