

May 21, 2020

Nicole Kleinstreuer

National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

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Re: ICCVAM Public Forum, May 2020

Dear Dr. Kleinstreuer and ICCVAM Committee Members:

The Physicians Committee for Responsible Medicine is an NGO supported by over 175,000 members working for effective, efficient and ethical research and testing. We appreciate the opportunity to provide input on NICEATM and ICCVAM-related activities. We continue to be impressed by NICEATM leadership as well ILS/NICEATM and agency staff that are working to advance alternative methods that replace or reduce animal testing.

## **ENVIRONMENTAL PROTECTION AGENCY**

### ***New Approach Methodologies***

We wish to recognize the EPA's leadership in adopting explicit policies notifying stakeholders of the agency's acceptance of *in vitro* and *in silico* methods and approaches. Combined with Administrator Wheeler's announcement last fall, EPA is providing momentum and scientific and policy expertise to make genuine strides towards the application of NAMs for pesticide and chemical testing. From skin sensitization to inhalation toxicity, we can point to multiple examples of EPA working with submitters to apply new approaches for hazard and risk assessment, and we encourage other agencies to consider how they might fill their own needs for product assessment in similar ways.

Regarding the List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs]) maintained by the Office to Pollution Prevention and Toxics (OPPT) under the auspices of TSCA, we appreciate that the list has already been updated once. Frequent updating of the list ensures stakeholders—including, most importantly, submitters—are aware of promising approaches and can consider using them to reduce or replace vertebrate testing. Frequent updating also ensures consistency in the acceptance of NAMs by agency staff. We are looking forward to learning more about a process to nominate NAMs for inclusion on this list. In the meantime we wish to encourage OPPT to consider adding two approaches to the list.

One is the ILS/NICEATM-developed computational approach for acute systemic toxicity, the Collaborative Acute Toxicity Modeling Suite (CATMoS). CATMoS is a free resource for screening organic chemicals for acute oral toxicity and can provide hazard classification or LD50 values. While it may not be appropriate for all OPPT-regulated chemicals, it is an approach that could be used by the agency or submitters to provide information on the acute toxicity of new and existing chemicals. We note via ChemView that Pre-Manufacture Notices sometimes contain acute toxicity data in animals, some of which could be provided instead by CATMoS.

The second approach is one utilized in a submitted PMN which considered the solubility of the material in Simulated Epithelial Lung Fluid to understand the potential for biosolubility of the material, informing on the potential for materials to accumulate in the lung and determining whether there may be a concern for lung toxicity. It is possible that this approach could be used for other materials, and adding it to the list of NAMs—along with any appropriate qualifiers—would help to highlight the possibility of other submitters using it for their assessments.

### ***Strengthening Transparency in Regulatory Science***

The EPA recently issued a supplemental notice to its proposed rule, Strengthening Transparency in Regulatory Science, proposing that the data underlying its significant regulatory actions must be publicly accessible. We are concerned that excluding data that cannot be made accessible would slow the development and implementation of alternative test methods.

The EPA's Office of Pollution Prevention and Toxics (OPPT) acknowledged this potential outcome in its Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program. OPPT stated that public access to the data used to build models that predict human outcomes may not be possible in some cases, because it uses confidential business information to update and refine its models. Under the proposed rule, OPPT could be limited to using only publicly accessible information and open source models. Requiring commercial model developers to release their intellectual property would likely restrict their ability to continue developing and supporting their models, slowing efforts to implement alternatives.

Despite hundreds of thousands of public comments calling for the withdrawal of the proposed rule, the supplemental notice expands its scope to include all data and models, not just dose-response models, and its application to influential scientific information as well as significant regulatory actions. EPA addressed public opinion by proposing to include studies with restricted data if tiered access is provided. Providing this tiered access appears to be in an exploratory phase – EPA is conducting a pilot study with a secure data enclave at the National Center for Health Statistics. EPA also proposed an alternative whereby it would consider studies with restricted data but give greater consideration to studies with unrestricted access. It is unclear what this greater consideration would entail.

We ask ICCVAM to consider how EPA’s proposed transparency policy may adversely affect its mission to ensure that new and revised test methods that reduce, refine, or replace the use of animals in testing are validated to meet the needs of federal regulatory agencies and to work with EPA to minimize its impact on the development and implementation of alternative test methods.

### **CONSUMER PRODUCT SAFETY COMMISSION**

The 2012 *Recommended Procedures Regarding the CPSC's Policy on Animal Testing* states it is the Commission's policy to “find alternatives to traditional animal testing that replace animals, reduce the number of animals tested, and decrease the pain and suffering in animals associated with testing household products.” For transparency, we ask the CPSC to communicate how the policy is being implemented, including through updates to the website, which currently does not endorse nonanimal tests and includes outdated content. The Agency should consider issuing updated recommendations and web text to make it clear to data submitters that alternative approaches to animal testing are an Agency priority, and that they are preferred over *in vivo* tests for the same endpoint. These recommendations can include recent alternatives approaches for skin sensitization and dermal absorption. Redundant *in vivo* regulations or guidance should be removed or their use restricted as much as possible. We also encourage the Commission to state their willingness to review nonanimal methods that have not yet been endorsed by the Commission.

In addition, we encourage the Commission to consider the revision of §1500.232 of the Federal Hazardous Substances Act Regulations. The pivotal reference link (<http://www.cpsc.gov/library/animaltesting.html>), repeated multiple times within the text, is broken. Although revised in 2018, this section should be amended to guide readers to useful and current information.

### **FOOD AND DRUG ADMINISTRATION**

#### ***Acute Toxicology***

PCRM recently examined acute toxicity studies supporting new drug applications. The results will be published in the July issue of *Regulatory Toxicology and Pharmacology* and are already available online. <https://pubmed.ncbi.nlm.nih.gov/32335206/>

We found that these studies were reported frequently: in 125 FDA reviews of NDAs approved from 2015 through 2018, we identified 228 single dose acute toxicity studies, 62 *in vivo* local tolerance studies, and 32 *in vivo* skin sensitization studies. Many different species of animals were used, including rats, mice, dogs, monkeys, rabbits, pigs, guinea pigs, minipigs, and cats. A total of 4,798 animals were reported to have been used; however, animal numbers were reported in only a fraction of these studies. Extrapolating to studies for which animal numbers were not reported nearly doubles the total (8,998).

We reviewed FDA’s guidance to industry and in some cases found opportunities for FDA to improve communication. For single dose acute toxicity, we accessed two guidance documents, one from 1996 and one from 2010, which included conflicting recommendations; in many cases, sponsors appeared to follow the older guidance, which

recommends that stand-alone acute toxicity studies be conducted generally, in at least two mammalian species using two routes of exposure. The 2010 guidance states that when acute toxicity information is available from any study, stand-alone single dose studies are not recommended. When studies are conducted, it recommends they be limited to one test species and to the route intended for human administration. We found that the intended route was the only route used in just over half (57.8%) of reviews that reported these studies, while studies conducted by more than one route were reported in more than one quarter (29.7%). In addition, studies conducted in more than one species were reported in more than three quarters (76.6%). We ask the agency to revise its 1996 single dose acute toxicity guidance to be consistent with the more recent 2010 guidance or retire the 1996 guidance.

For local tolerance, FDA recommends using the route intended for human administration as part of general toxicity studies; stand-alone studies are generally not recommended, but industry has not followed the recommendations. Of reviews in which local tolerance studies were reported, the intended route was the only route used in less than one quarter (23.6%). FDA recommends evaluating skin sensitization only when a drug is intended for topical administration; however, only two of the 24 reviews in which the results of skin sensitization studies were reported are for drugs intended for topical administration. Although we understand guidance is only a recommendation and industry has autonomy, in order to reduce animal use, we ask the agency to develop plans to more effectively communicate to sponsors that the evaluation of local tolerance and skin sensitization by routes not intended for human administration is not recommended.

We were encouraged to find that for evaluating eye irritation, the Bovine Corneal Opacity and Permeability (BCOP) test was used more than twice as frequently as the rabbit test, and almost as many skin irritation tests used reconstructed human epidermis as used rabbits. A 2015 guidance applying to reformulations of topical drugs recommends eye irritation be evaluated using *in vitro* and *ex vivo* methods; in order to continue increasing use of alternative eye irritation studies, we ask the agency to extend this recommendation to other classes of drugs.

For evaluating skin sensitization, no non-animal methods were reported, despite the increasing acceptance of such methods in other sectors and the length of time for which NAMs have been available. There is opportunity to change this by revising FDA's draft guidance for Nonclinical Safety Evaluation of Immunotoxic Potential before it is finalized. We ask FDA to strengthen language to advance alternatives in this guidance by stating that evaluating skin sensitizing potential is recommended only for topically applied drugs, removing references to the guinea pig tests, and giving preference to *in vitro* and computational methods.

Finally, reporting of animal numbers and species is important in order to measure progress toward reduction. We ask the FDA to standardize its reporting of animal use, ideally extending that reporting beyond approved NDAs to include all new drug applications.

### ***Pyrogen Testing***

Through its Appropriations funding bill, Congress has tasked the agency with establishing processes for evaluating nonanimal pyrogen tests and to report back on steps taken to increase their use and effectiveness. The human-based Monocyte Activation Test can replace the Rabbit Pyrogen Test in most cases. We ask the agency to task reviewers and agency staff with recommending its use.

### ***Advancing Alternatives Workgroup***

Earlier this month, we learned that FDA has established a workgroup dedicated to advancing alternative methods. We were pleased to see group activities listed on the website and request continued transparency around workgroup projects. We encourage ICCVAM representatives to determine how ICCVAM activities may align with workgroup activities.

### ***Regulatory Framework and Guidance***

In the recent publication, *An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs)*, FDA describes current regulations as flexible to accept animal or *in vitro* data. While this is true of many regulations, there are also many regulations that require animal **and** *in vitro* data, all of which neglect to include *in silico*. We have heard from industry that these regulations lead to animal testing even where a company may want to use a nonclinical approach that does not use animals. We ask the FDA to change references from “in vivo,” “animal” and “in vitro” to “nonclinical,” which encompasses *in vivo*, *in vitro* and *in silico* methods.

Multiple FDA guidance documents recommend specific animal tests; some guidance also intend to allow for the use of alternatives by noting that alternative approaches may be used where appropriate. Listing an animal test by name as accepted then lumping all nonanimal tests into a category that *may* be accepted in some instances favors the enumerated animal test. While including general language is appreciated as a sign that agency thinking regarding alternatives is evolving, additional guidance is needed around how a sponsor can show a method is appropriate. We ask the agency to gather internal and external experts to establish what standard must be met in order for a method to be considered appropriate for use.

### ***Pathway for Acceptance***

Scientifically evaluating NAMs is crucial to understanding the NAMs’ strengths and limitations. Currently, NAMs can be introduced to the agency by drug sponsors on a case-by-case basis within a drug package. Test developers and other outsiders also need an avenue for working with the agency to review a tool outside of a drug package. Establishing a new program for *in vitro* and computational methods under the FDA’s Drug Development Tools Qualification Program appears to be a strong option. We ask the FDA to decide whether the DDTQP or another enumerated avenue is best, then work to establish the pathway.

## **NATIONAL INSTITUTES OF HEALTH**

### ***Adoption of Nonanimal Derived Antibodies***

The European Commission's Joint Research Centre has just released its recommendations on non-animal-derived antibodies in accordance with the EU Directive 2010/63/EU on the protection of animals used for scientific purposes. The commission calls for an immediate end to the use of nearly all animal-derived antibodies for research, regulatory, diagnostic, and therapeutic applications.

The report states, "In order to support higher scientific quality, meet ethical standards and ensure the limitations of animal-derived antibodies are overcome, it is recommended that the use of non-animal-derived antibodies is endorsed by government authorities, funding agencies and publishers."

Our organization and several others have been taking various actions to promote non-animal antibodies for several years. However, given the high number of animal-derived antibodies in use across the country government agency policies are needed to facilitate this change. We would like to encourage ICCVAM member agencies to review the EU report and consider relevant follow up actions.

Furthermore, we ask the NIH to require funded researchers to switch to nonanimal-derived antibodies and provide the support they need to do that. Funding should also be provided to antibody producers to support the production and promotion of nonanimal antibodies.

## **CONCLUSION**

In conclusion, the Physicians Committee recognizes much work is underway to replace and reduce animal testing. We applaud the EPA's leadership in replacing animal experiments and ask ICCVAM representatives to request their respective agencies set similar goals to prioritize replacement work. We look forward to continued collaboration over the next year to carryout our specific requests described above.

Sincerely,



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