THE HUMANE SOCIETY
OF THE UNITED STATES



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On behalf of The Humane Society of the United States (HSUS), the nation's largest animal protection organization representing millions of supporters, we thank the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for the opportunity to provide suggestions on ICCVAM mission and activities.

In recent decades, there have been great advances in our understanding of biology and great strides in engineering and computer science. This has allowed the development of new approaches to evaluated safety in-vitro and in-silico, as well as supported the development of more strategic and focused testing strategies. A major focus of The HSUS is to modernize toxicity assessment by supporting the use of these new technologies and approaches and encourage regulatory agencies around the globe to incorporate these approaches.

We would like to address two main points of interest for our organization in our comments, including the reporting on species not covered by the Animal Welfare Act and suggestions of activities to reduce, refine and eventually replace animal use (the 3Rs).

## Reporting Species Not Covered Under the Animal Welfare Act

It is estimated that out of the 115 million or more animals currently used each year in experiments around the world, 10 to 15% are used for toxicology testing to evaluate the safety or effectiveness of chemicals, pharmaceutical drugs, cosmetics, pesticides, food additives and other regulated products. The majority of the animals used for toxicity testing are rats and mice, which are not covered under the Animal Welfare Act (AWA). Therefore, institutions conducting such testing don't need to report their use of rats and mice to the U.S. Department of Agriculture (USDA). While the United States severely

lags behind on the issue of under reporting, the United Kingdom requires reporting of all animal use and issues an annual report analyzing the various uses of different species, trends over time, and for the first time in 2014, the severity of the procedures.
In the 2014 annual report[1], the United Kingdom reported that 508,000 procedures were conducted for regulatory purposes, divided as such:

- 60% for toxicity and other safety testing including pharmacology (acute and sub-acute toxicity testing methods accounted for 144,000 procedures, ecotoxicity accounted for 13,000 procedures);
- 29% (146,000 procedures) for routine production (e.g., vaccines and diagnostic reagents); and
- 10% (50,000 procedures) for the quality control of marketed medicines.

This type of reporting should be required, as this information is essential for ICCVAM in order to prioritize activities as well as measure ICCVAM's impact on the 3Rs.

In 2015, The HSUS submitted comments to the USDA under the Petition to Amend the Reporting Requirements for Research Facilities under the AWA Regulations (Docket No.APHIS-2015-0033).[2] We asked the agency to require research facilities to document the type of research in which animals are used, as well as the level of pain and distress experienced by those animals. In regards to the USDA's mission, we believe that this type of information is needed in order for the USDA to promptly act on animal welfare issues.

Additionally, research institutions with a Public Health Service Animal Welfare Assurance must keep record of their animal use, therefore requiring mandatory reporting of their animal use would not add additional burden on investigators. A reporting requirement would also help prioritize the development of methods that do not require the use of animals, reduce the number of animals and reduce the pain and distress in such animals, as required under the National Institutes of Health (NIH) revitalization Act of 1993.[3]

Therefore, we urge ICCVAM to work with the NIH, the U.S. Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA) and other agencies as well as the industry, in order to issue an annual report on the use of animals and pain and distress.

## ICCVAM Activities to Reduce, Refine and Eventually Replace Animal Use

As mentioned above, the total number of animals use and the level of unrelieved pain and distress are not known in the United States. By compiling all USDA annual reports in 2013, we estimated that over 80,000 regulated animals have experienced unrelieved pain and distress in research. This number doesn't include rats and mice which are not covered by the AWA, which according to the 2014 report from the United Kingdom; represent 72% of all animal used.
We want to stress the importance of developing non-animal alternatives in the three following area due to the high number of animals use, the duration of the treatment and the high level of pain and distress experienced by the animals.

[1] http://www.understandinganimalresearch.org.uk/files/3314/4552/1574/2014_Home_office_animals_stats.pdf
[2] https://www.regulations.gov/#!documentDetail;D=APHIS-2015-0033-1663
[3] https://grants.nih.gov/grants/olaw/pl103-43.pdf

## 1. Vaccines

Currently, a high number of vaccines exist, which still require batch testing. With the increasing needs for the development of new vaccines to target existing and emerging viruses, for example Ebola and Zika, we urge ICCVAM to put a stronger emphasize on the validation of non-animal methods for vaccine potency and safety testing. Additionally, attention to vaccines should be one of ICCVAM's priorities, as testing requires the use of a large number of animals in some of the most painful experiments.

In a joint workshop on Alternative Methods for Vaccine Potency and Safety Testing[4] organized in 2010 by ICCVAM and NICEATM, many recommendations for veterinary and human vaccines were brought forward. The HSUS encourages a follow up workshop in order to assess the level of implementation of those recommendations, as well as identify new priorities. We urge ICCVAM and NICEATM to collaborate with agencies and organizations around the globe, such as the USDA, the FDA, the European Medicines Agency, the Veterinary International Conference of Harmonization, and the World Health Organization, as well as the industry, in order to identify the most urgent needs in developing, validating and implementing non-animal methods as well as facilitating global harmonization.

We also ask that ICCVAM follow up with agencies to ascertain that the recommendations and validated alternatives are being communicated to the industry and implemented for regulatory purposes. The HSUS has found that often times, a disconnect may exist between what is recommended or communicated by agencies and what is implemented by industry. For instance, following a series of workshop[5] on Pertussis, it was determined that the use of CHO cells assay could replace the murine Histamine Sensitization Test (HIST) for acellular pertussis vaccines, however we are not aware of any official guidance or communication to the industry from the FDA.

## 2. Carcinogenicity

As described in the Organisation for Economic Co-operation and Development (OECD) TG 451[6], a carcinogenicity study requires a large number of animals and the pain experienced can be severe and for long period of time. The guidance requires a minimum of 50 animals/group, at least three dose levels, and animals are being treated for 24 months. While two endpoints, carcinogenicity and chronic toxicity, can be combined to reduce animal use, as described in OECD TG 453[7], there is still an urgent need to develop, validate and implement non-animal methods from carcinogenicity studies.

Due to the complexity of the carcinogenicity process, which involves many organs, it has been challenging to develop non-animal methods that would give access to the full process. However, recent efforts at the OECD on developing an Integrated Approach to Testing and Assessment (IATA) of non-genotoxic carcinogens could help regulators. In a recent paper, Jacobs *et al.*,[8] describe a multi-steps approach on how an IATA could be developed and what elements would be required to make this approach successful. We strongly encourage ICCVAM to follow closely the OECD's efforts to develop alternative methods for a complex process, as it will lead to a substantial reduction of animals used.

[4] https://ntp.niehs.nih.gov/pubhealth/evalatm/3rs-meetings/past-meetings/vaccine-wksp-2010/index.html
[5] http://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2014/september/presentations/13murine_508.pdf
[6] http://www.keepeek.com/Digital-Asset-Management/oecd/environment/test-no-451-carcinogenicity-studies_9789264071186-en#page7
[7] http://www.oecd-ilibrary.org/docserver/download/9745301e.pdf?expires=1463430686&id=id&accname=guest&checksum=ED6EE488D9995B0698C82B9CBA269D53
[8] http://www.ncbi.nlm.nih.gov/pubmed/27120445

### 3. Reproductive and Developmental Toxicity

It's estimated that in order to comply with REACH in the European Union, 54% of the testing done will be to assess reproductive and developmental toxicity, which cost between $500,000 and $750,000 and uses about 3200 animals in order to conduct the two-generation test[9][10].

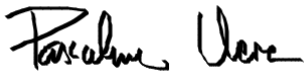
The evaluation of reproductive and developmental toxicity *in silico* and *in vitro* is very difficult due to in part to the numerous organs and endpoints at play in the developmental process and to the availability of adequate data.

For example, as highlighted by Hewitt and al., there is a great need to generate additional data that would make the current in- silico models more predictive. Indeed, using weight-of-evidence (WOE) combining various *in silico* methods (including CEASAR (Q)SAR, Derek) to predict the toxicity of 57 compounds, they show that while successfully predicting 89% of the chemicals, the WOE was not over-performing each individual methods used[11].

As there is a great need to gain a greater understanding of the pathways involved in the process, but also develop non-animal methods for reproductive and developmental toxicity, we strongly encourage ICCVAM to remain inform and participate as needed in various undergoing efforts such as the development of new Adverse Outcome Pathways[12], computer models, or organoid models.

We thank ICCVAM for the opportunity to comment.

Sincerely,



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[9] Scialli AR. The challenge of reproductive and developmental toxicology under REACH. Regul Toxicol Pharmacol 2008;51:244–50.
[10] Höfer T, Gerner I, Gundert-Remy U, Liebsch M, Schulte A, Spielmann H, et al. Animal testing and alternative approaches for the human health risk assessment under the proposed new European chemicals regulation. Arch Toxicol 2004;78:549–64.

[11] Hewitts M, Ellison CM, Enoch SJ, Madden JC, Cronin MTD. Integrating (Q)SAR models, expert systems and read-across approaches for the prediction of the developmental toxicity. Reproductive Toxicology 2010, 147-160.
[12] Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, and Knoblich JA. Cerebral organoids model human brain development and microcephaly. Nature, 2013; 501:7467.