EXPRESS STATEMENT*

Scientific, Regulatory, and Public Perspectives on the Use of Alternative Toxicological Test Methods to Inform Decision Making

By SOT Members John R. Fowle, III, PhD, DABT, and J. Craig Rowlands, PhD, DABT

Approved in September 2016 by the SOT Council

Introduction

The public expects that food, drugs, and consumer products are safe and effective and that the production of commercial chemicals improves quality of life without harm to the environment or public health.

Since the mid-20th century, animal testing has served as the basis for evaluating safe use of chemicals, consistent with the intent of a wide range of legislation and associated regulations. The relevance, reliability, and complexity of tests using laboratory animals have evolved throughout the past 70 years. Extensive experience has demonstrated that information derived from such studies have informed human and environmental risk assessments and product safety determinations, yet there is also evidence that these methods can be improved upon using technological advances that have occurred over the past few decades.

There is increasing societal, economic, and scientific concern about the use of animals in toxicity testing, and the Society of Toxicology (SOT) supports the minimizing and replacement of the use of animals, as summarized in the Society's "Guiding Principles in the Use of Animals in Toxicology" Issue Statement. In addition, conventional animal testing lacks the efficiency, rapidity, and cost-effectiveness — as well as the flexibility and, in some situations, the predictability — to more thoroughly assess the backlog of existing chemicals in commerce and the increasing numbers of new chemicals under development. Yet, at the same time, there is an increasing demand for more testing and more data to support safety evaluations and decisions. To address these challenges, toxicology is undergoing a transformation by utilizing the tremendous advances that have been made in the understanding of genetics, molecular biology, biological pathways, disease processes,

exposure science, and dosimetry to modernize toxicity testing and better inform safety determinations.

Proposed Changes: Toxicity Testing in the 21st Century

The challenges in developing and applying alternative toxicological test methods were articulated in two National Research Council (NRC) reports. The 2007 report *Toxicity Testing in the 21st Century* described a vision and a strategy to harness advances in high-speed computing and biology to develop predictive, alternative approaches to toxicity evaluation for human health. A subsequent 2012 NRC report, *Exposure Science in the 21st Century: A Vision and a Strategy*, described the needs and approaches to forecast exposures with improved accuracy and efficiency. These reports have engendered government, commercial, academic, and not-for-profit organizations to actively engage in efforts to realize these NRC visions for 21st century risk assessment, and the NRC is working on a new report to advance these visions that will be entitled "Incorporating 21st Century Science into Risk-Based Evaluations."

For 21st century risk assessment approaches to be widely used to inform regulatory decisions, stakeholders must gain confidence that alternative toxicological test methods provide information as good as or better than the data provided by traditional animal toxicity tests to reliably inform safety decisions. In addition, the acceptability of these alternatives must be established in the political and legal processes. Thus, the role of toxicology and toxicity testing in regulatory decision-making continues to change and an understanding of the opportunities, as well as challenges, that accompany the consideration of alternative test methods in a legislative framework is critical for forward progress in public health and environmental protection.

Issues for Legislation and Regulation

Regulatory frameworks will not be able to always reflect the pace at which primary research in toxicology, toxicity testing, and exposure science advance. One of the hurdles for incorporating new approaches, technologies, and tools in toxicology into the regulatory framework is establishing confidence that these methods have achieved the degree of scientific rigor needed to support public health and environmental protection decisions.

A "consensus" must be reached that the proposed replacements to the conventional approaches provide data which society-at-large and stakeholders accept as suitably

predictive (or protective) of the relevant ecological or human health outcomes and can be relied upon to enable confident determination of margins of safety when integrated with knowledge of exposure. In order to successfully reach consensus, deliberation involving not only the scientific and regulatory communities, but also the general public, which in recent years has become more interested, educated, and vocal on the subject, will be needed. This requires effective and increased risk communication by SOT members and other scientists to inform the regulatory communities and general public about the science.

While progress has been made in conceptually formulating integrated, tiered testing regimens and developing proof-of-concept applications, moving from concept to application is now needed. For instance, programs like the US Environmental Protection Agency (US EPA) Endocrine Disruptor Screening Program are using non-animal testing to identify chemicals that may be of concern to inform more detailed testing and, eventually, regulatory decisions. In Europe, the Cosmetics Directive requires submission of non-animal alternative data to inform decisions.

It will be important to build upon the lessons learned as experience is gained to advance toxicology, toxicity testing, and exposure science in a manner that demonstrates their advantages to protect public and environmental health. Along these lines, the US EPA recently announced the acceptability of non-animal data for some endpoints assessed in the approval and use of pesticide products along with an ambitious plan to expand the use of alternatives and reduce animal testing.

At the same time, it is necessary to allow for regulatory science to evolve so that the new scientific advances are not prematurely forced into legislative and regulatory framework, as the consequences of this can be significant and enduring. (More information on SOT's views on this subject: "Role of Government in Science Regulation" Issue Statement.)

Conclusion

New and improved toxicity evaluation tools, technologies and integrated frameworks will continue to be developed, and it will be important to continually engage stakeholders in deliberation about how best to use these advanced approaches to inform decisions about the risk potential of chemicals and about the extent to which they are suitable to replace whole animal testing. The process will likely proceed through a series of successive approximations, or stages of use, since the utility, accuracy, and predictability of toxicity

from these new advanced approaches will improve over time, as innovative technologies are brought on line and confidence increases through experience gained from fit for purpose applications.

References

Society of Toxicology (SOT). "Guiding Principles in the Use of Animals in Toxicology": http://www.toxicology.org/pubs/statements/Guiding_Principles.pdf

US National Academy of Sciences. "Toxicity Testing in the 21st Century: A Vision and Strategy, Report in Brief": http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/Toxicity_Testing_final.pdf

US National Academy of Sciences. "Exposure Science in the 21st Century: A Vision and a Strategy (2012), Summary Chapter". http://www.nap.edu/read/13507/chapter/3

US National Academy of Sciences. "Incorporating 21st Century Science into Risk-Based Evaluations" (In Preparation, 2016): http://www8.nationalacademies.org/cp/meetingview.aspx?MeetingID=8664&MeetingNo=7

US EPA Endocrine Disruptor Screening Program: https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-overview

European Commission Cosmetics Directive: http://ec.europa.eu/growth/sectors/cosmetics/animal-testing/index_en.htm

Letter to Stakeholders on EPA Office of Pesticide Programs's Goal to Reduce Animal Testing from Jack E. Housenger, Director Office of Pesticide Programs: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0093-0003

Society of Toxicology (SOT). "Role of Government in Science Regulation": http://www.toxicology.org/pubs/statements/SOT_Position_Statement.pdf

Additional Sources of Information

International Cooperation on Alternative Test Methods (ICATM): https://ihcp.jrc.ec.europa.eu/glossary/icatm-international-cooperation-on-alternative-test-methods

SEURAT-1: http://www.seurat-1.eu/

US EPA National Center for Computational Toxicology: https://www.epa.gov/aboutepa/about-national-center-computational-toxicology-ncct

US Food and Drug Administration (US FDA) National Toxicology Program on Tox 21: http://ntp.niehs.nih.gov/results/tox21/index.html

US National Institutes of Health National Center for Advancing Translational Sciences Tox21 Program: http://www.ncats.nih.gov/tox21