



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCE
NATIONAL TOXICOLOGY PROGRAM**

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Introduction

In 2007, the National Academy of Sciences National Research Council issued a report (Toxicity Testing in the 21st Century: A Vision and a Strategy (TT21C)) that recommended that the Environmental Protection Agency (EPA) fundamentally change the way chemicals are tested for their effects on human biology. Instead of a reactive, end-pointed based approach, the NAS/NRC endorsed a proactive approach that would place greater reliance on in-vitro testing using human cell lines, and much more emphasis on understanding the pathways that lead to disease. The report concluded that this proactive approach will better equip researchers to evaluate the effects of chemicals on biological processes in a manner that is more predictive of human disease and toxicology.

The TT21C report's vision and strategy are significant because they are a departure from the reliance on animal based studies that can lack human relevance and often take far too long to execute. As the TT21C report notes, in-vitro models have the potential to provide the most human-relevant platforms to look at how chemicals affect individuals and populations. This is valuable data in assessing both the dangers of chemicals and compounds as well as the potential benefits of other substances on the treatment of disease. In addition to its application to regulatory toxicology, it is consistent with, and has the potential to advance, the Precision Medicine Initiative of the National Institutes of Health (NIH), which seeks to provide top quality individualized care and the NIH Cancer Moonshot Initiative, which seeks to accelerate cancer research and therapies. In short, it is clear that fostering and implementing the vision of TT21C is important not only for toxicity testing, but for improving approaches to prevent and treat disease.

In his “spotlight” comments published on-line at alttox.org, Dr. Warren Casey states that since the publication of the TT21C report, “significant advances in technology development and biomedical research have resulted in many transformative scientific breakthroughs ... However, these advances have yet to be met with a concomitant increase in our ability to more accurately predict adverse human health effects” In other words, there has been “limited translational impact” of these advances. An important goal of today's meeting is to seek ways to accelerate translational progress, and in implementing the vision and strategy of the TT21C report (See <http://alttox.org/implementing-the-vision-for-toxicity-testing-in-the-21st-century-an-opportunity-for-action/>)

The webpage announcing this meeting contains a background document (http://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/vision20160927_508.pdf) that poses 4 broad questions for discussion. They are:

1. Is there a place in our current paradigms to begin to apply a fundamental non-animal strategy that allows prospective validation without compromising near term human safety?
2. What obstacles currently prevent the collection and use of human toxicological data and what are some potential solutions to facilitate the use of human data in the future?
3. What strategies and mechanisms could be employed to increase communication and coordination of activities amongst and between the federal government and key stakeholders?
4. What are the most important “non-scientific” issues and how should they be prioritized?

The brief comments that follow are primarily directed to question 4. However, they are relevant as well to questions 1, 2 and 3.

Law and Policy Aspects of Implementing the TT21C report

By way of background, my group at the Johns Hopkins Bloomberg School of Public Health has been actively studying, and seeking to advance, the TT21C report recommendations and the application of in vitro methodologies since shortly after the report was released in 2007. As set out in greater detail in Appendix 1, we have authored or co-authored 6 journal and/or law review articles; organized and/or participated in 6 Congressional briefings on Capitol Hill in Washington, DC; and sponsored or co-sponsored a series of 5 international symposia on the potential impact and implementation of the TT21C report. Based on our work, and the work of other scholars and medical and public health practitioners, we have explained below what we believe are among the most important “non-scientific” (policy and legal) action steps that can be taken to further translational progress and assist in implementing the vision and strategy of the TT21C report .

1. *Actively participate in the development of EPA’s efforts to reduce the use of vertebrate animal tests, and the implementation plan for alternatives, under the new TSCA.*

The Toxic Substances Control Act (TSCA) was recently reauthorized (see <https://www.congress.gov/bill/114th-congress/house-bill/2576/text>.) This new TSCA contains a provision on reduction of testing on vertebrates. It states that EPA “shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures.” (See PL 114–182, 130 Stat. 452 – 3 (22 June 2016)). To advance alternatives to animal testing, the new TSCA also requires that within two years EPA draft and adopt a strategic plan to promote the development and implementation of alternatives, and strategies that reduce, refine and replace vertebrate animal testing. (See PL 114–182, 130 Stat. 453 (22 June 2016)). These provisions in the new

TSCA offer opportunities to advance the use of alternative methods and chart the course of their future use. It is imperative that the NIEHS be actively involved in this effort.

2. *Actively participate in the NIH Precision Medicine Initiative and the Cancer Moonshot.*

The Precision Medicine Initiative (see <https://www.nih.gov/precision-medicine-initiative-cohort-program>) seeks to bring personalized medical care to individuals. According to the NIH, “[p]recision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. While some advances in precision medicine have been made, the practice is not currently in use for most diseases.” The Cancer Moonshot, which seeks to accelerate cancer research, detection and therapy, recently released its blue ribbon panel report. (See <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel>). Among other things, the report notes that we need to do a better job of understanding why certain people respond to therapies, while others do not, as well as studying new immunotherapies and developing enabling cancer technologies.

Alternatives, especially alternatives that utilize biomimetic methods such as organs-on-a-chip, hold great promise for understanding individual organ, cellular and molecular differences. Accelerating the application of these technologies will get us closer to achieving the ambitious goals of the Precision Medicine Initiative and Cancer Moonshot. NIEHS has important roles to play in each of these programs. The closer to human biology that our predictive technologies for therapy, drug development, and disease detection can get, the more likely we are to have success in reducing the burden of disease and its costs.

3. *Adopt a “replacement-first” approach in research and testing.*

The “3Rs” (replacement, reduction and refinement) are the principles that underlie the internationally accepted philosophy and practice of humane science in toxicity testing, biomedical research and laboratory work involving animals. The 3Rs were first systematized in The Principles of Humane Experimental Technique, a 1959 study commissioned by the Universities Federation for Animal Welfare in the United Kingdom. The 3Rs are codified in law and practice in the United States. (See, for example, Guide for the Care and Use of Laboratory Animals, found at <https://www.nap.edu/catalog/12910/guide-for-the-care-and-use-of-laboratory-animals-eighth>). The TT21C vision advocates an evolution in toxicity testing that, if fully implemented, would substitute virtually all animal use with non-animal tests. In this regard, it is consistent with, and an advocate for, replacement. Accordingly, the NIEHS should adopt an approach that places the replacement R above refinement and reduction. This policy should be made clear in NIEHS extra- and intramural funding requirements, contracts and research initiatives.

4. *Build a bridge from “old” to “new” data*

A very important thing to remember, and a critical challenge, is how we can integrate the old or legacy information with the new data that we will be creating. How can we effectively utilize the data we now have, much of which is animal-based data, and how can we effectively combine

it with the data from alternatives? We need to create a path for evolution as we transition away from old methods. Fortunately, we have several techniques at our disposal. One of the most promising ones involves computational methods – an example is computational toxicology. Using computer-generated models, it is possible to begin to predict outcomes. We can use computational techniques to put new and old data on the same playing field. This is a tool for the future that will also be very useful in risk assessment. NIEHS has an important role to play as we transition from legacy data and methods to approaches based on human biology. We cannot and should not abandon old information; instead to the extent possible we must seek to harmonize it with new and evolving technologies.

Conclusion

Law and policy have an important role to play in assuring the translational success of new methodologies and championing the new scientific techniques that do not use vertebrate animals.. While we cannot now replace all animal-based methodologies with in vitro ones, we should recognize that creating incentives and opportunities using law and policy have the potential to advance these important techniques. More and more alternatives are becoming available, and more and more are being used every day. Even if we cannot move away entirely from animals in research, we should do everything we can to advance alternatives for the benefit of scientific research, medical progress and public health protection.

It is important to acknowledge that animal models and biomedical research based on animals have provided useful insights that have been effective in developing public health and medical solutions. It is clear that science and medicine are not at a point where animal research can be entirely abandoned. By the same token, non-animal based alternatives provide great promise for many new endeavors of disease research and can build quickly on what we already understand about causes of disease. Further, alternatives can provide valuable data on individuals' responses to treatments that exist today and therapies that will be developed in the future.

Based on our research and practice activities, we believe that the four action steps set out in this comment have the potential to greatly accelerate the translational impacts of in vitro technologies as applied to toxicology, medicine and public health. We look forward to working with NIEHS and NTP on these initiatives.

I would like to thank the National Toxicology Program and NIEHS for holding this meeting and keeping these issues at the forefront of the public discussion.

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The views expressed do not necessarily reflect the official policy or position of Johns Hopkins University or Johns Hopkins Bloomberg School of Public Health.

Appendix 1

A. ARTICLES:

1. PA Locke and DB Myers. Implementing the National Academy's Vision and Strategy for Toxicity Testing: Opportunities and Challenges Under the U.S. Toxic Substances Control Act. *Journal of Toxicology and Environmental Health, Part B*. 13:376–384. 2010
2. PA Locke & DB Myers. A Replacement-first Approach to Toxicity Testing is Necessary to Successfully Reauthorize TSCA. *ALTEX* 28: 266-72. April 2011
3. DB Myers and PA Locke. Modernizing U.S. Chemicals Laws: How the Application of Twenty-First Century Toxicology Can Help Drive Legal Reform. *NYU Environmental Law Journal*. 20:35-98. 2012
4. R. Borotkanics, M. Trush, PA Locke. Analysis of ToxCast Data—In Vitro and Physiochemical Properties—In the Accurate Classification of Chemicals That Induce Hepatocarcinogenesis In Vivo. *Applied In-Vitro Toxicology*, 1(4):262 – 275. 2015 (available at <http://online.liebertpub.com/doi/pdfplus/10.1089/aivt.2014.0006>)
5. R. Borotkanics and PA Locke. EPA's Methodology to Inform TSCA Pre-Manufacturing Notification decision-making: A critical analysis based on chemicals regulated by consent order. *International Journal of Risk Assessment and Management*. Available on-line at <http://www.inderscience.com/info/ingeneral/forthcoming.php?jcode=ijram>
6. PA Locke, M Westphal, J Tischler, et al. Implementing toxicity testing in the 21st century: challenges and opportunities. *International Journal of Risk Assessment and Management*. Available on-line at <http://www.inderscience.com/info/ingeneral/forthcoming.php?jcode=ijram>

B. CONGRESSIONAL BRIEFINGS

April 17 th , 2012	EU and US Animal Welfare Law in Research and Safety Assessment: Similarities, Differences and Harmonization
June 2 nd , 2014 Sept 12 th 2014	Advances and Challenges in Replacing Animal Use in Cosmetic Testing Water-Based Hazards: Risk Mitigation*
April 6 th , 2015	21 st Century Understanding of Chemicals*
July 9 th , 2015	The Humane Cosmetics Act: Ending Animal Testing for Cosmetics
Sept 13 th , 2016	Alternatives to Animal Testing: Emerging Uses and Policy Implications*

*Briefing sponsored by American Chemical Society

C. SYMPOSIA

June 29 th & 30 th , 2009	The International Implications of the U.S. National Council's
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Ottawa, Ontario, Canada	Report on Toxicity Testing in the 21 st Century: Challenges and Opportunities in Implementation
Sept 12 th , 2009 Portland, OR, USA	The Science, Ethics, and Law of Animal Testing in the 21st Century: Are We on the Verge of a Paradigm Shift?
Nov. 5 th , 2009 Chicago, IL, USA	Implementation of the US National Research Council report on Toxicity Testing in the 21st Century: Can We Make the Business Case for Alternatives?
June 21 st , 2010 Baltimore, MD, USA	The Future of Chemical Toxicity Testing in the United States: Creating a Roadmap to Implement the National Research Council's Vision and Strategy
June 22 nd , 2010 Washington, DC, USA	Implementing the U.S. NAS Toxicity Testing Report: An EU Perspective on the Way Forward