

A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century

In 2007 the National Research Council (NRC) published the seminal report, *Toxicity Testing in the 21st Century: A Vision and a Strategy*, which envisioned using information derived from human-based assays and models to provide a more efficient, predictive, and less costly system for assessing the effects of xenobiotics on human health. Over the ensuing decade, significant investments in technology development and biomedical research have resulted in many transformative scientific breakthroughs necessary for implementing the NRC vision. However, these advances have yet to be met with a concomitant increase in our ability to more accurately predict the adverse human health effects caused by ubiquitous exposure to xenobiotic chemicals, whether alone or in mixtures. This limited translational impact is attributable, at least in part, to rapid scientific advancements outpacing the change in institutional standards required for their effective utilization. Specifically, legacy test methods and classification systems developed using animal models cannot always evaluate the nuances of human pathophysiology and genetic variability important for modern risk assessment. Ironically, however, the institutionalized use of animal-based methods may limit more human-predictive approaches from being developed and adopted by both government and industry stakeholders. Left unaddressed, this growing disparity between information gained from human-relevant approaches and reliance on animal data for safety and risk evaluations could impede our ability to capitalize on the remarkable knowledge and tools arising from projects such as ToxCast, Tox21, Human Tissue Chips, and the Precision Medicine Initiative.

Although the United States leads the world in biomedical research and technology development, we lag significantly behind almost all other “advanced economies” in developing a strategy and roadmap for implementing the use of 21st century science for assessing the impact of xenobiotics on human health and the environment. For example, the EU is now two years into its ambitious program, *Horizon 2020: Roadmap to Next Generation Safety Testing*¹, and *A non-animal technologies roadmap for the UK: Advancing predictive biology*² was published in 2015. These and other efforts recognize the important benefits to public health that can be achieved using more human-predictive/non-animal approaches. In addition, many of our international trading partners (e.g., EU, India, Brazil, South Korea, Canada, Australia, Russia) have already moved towards banning the sale or import of cosmetic products or ingredients which have been tested on animals, and a bill with the same intent has recently been introduced in the U.S.³ Without validated non-animal alternatives in place, these testing bans could stifle innovation and also put the public, especially sensitive populations, at risk for exposure to insufficiently characterized chemicals.

In order to realize the full potential for improving and protecting human health offered by advances in science and technology, the U.S. must develop a strategy for the safe, effective, and timely implementation of human-based predictive approaches for toxicity testing. The recently enacted Frank R. Lautenberg Chemical

Safety for the 21st Century Act, which calls for increased use of information from alternative test methods and strategies, and the Precision Medicine Initiative, a bold new research effort to revolutionize how we improve health and treat disease, both speak to the urgent need to develop a strategy for evaluating the impact of xenobiotics on human and environmental health. A pending report from the National Academy of Sciences (NAS) on Incorporating 21st Century Science into Risk-Based Evaluations will certainly help inform future efforts. However, developing a holistic approach for establishing confidence in these new approaches may require significant changes in policy, practice, and regulation; a challenge so complex and broad in scope that it cannot adequately be addressed by any single agency or existing government entity. Engagement of the Office of Science and Technology Policy (OSTP) may be needed to charge a high level workgroup with drafting a roadmap for implementing the NRC vision for Toxicity Testing in the 21st Century. In support of this effort, the National Academy of Sciences (NAS) could convene a series of workshops or panels that identify and address the enablers of, and impediments to, progress. Outcomes from these activities could then be used to help inform the group ultimately charged by OSTP to identify the best path forward in developing a U.S. strategy for the safe, effective, and timely implementation of toxicity testing for the 21st century.

SACATM Discussion

SACATM is asked to comment on the need for a U.S. Strategy and Roadmap for implementing 21st century toxicity testing approaches, and to provide advice on the specific topics identified below as important for this effort.

1. The historical use of animal models by regulated industries, coupled with the institutionalized use of animal-based data as the “gold standard” against which all new methods must be compared, could impede the validation and adoption of human-based methods and approaches that may be cheaper, faster, and more physiologically relevant. There exists an urgent need to identify and understand informative animal models, while also developing a scientific framework for validating more human-relevant (non-animal) methods.

Traditional approaches to validation often rely on comparing data obtained from a new method/strategy with results from an existing animal-based test. This becomes problematic for toxicity tests that have species-specific biases and also precludes any new test from performing “better” than the animal test, as any discordance will be assessed in favor of the existing method. In the absence of sufficient human data, how can new methods be validated as having equivalent (or better) performance than the animal-based test without a direct comparison to data from the animal test intended for replacement?

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. The utilization of human data will be an essential component of future validation efforts needed to establish confidence in new approaches for screening, prioritization and testing. Therefore, mechanisms for the ethical collection and sharing of data derived from human subjects exposed to xenobiotics need to be addressed.

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. Increased strategic coordination amongst and between Federal agencies and stakeholders (including international partners) would improve scientific and fiscal efficiency, providing greater return on investments while expediting the development and utilization of new technologies.

What strategies and mechanisms could be employed to increase communication and coordination of activities amongst and between the federal government and key stakeholders?

4. While advancements in science and technology are essential to the development of 21st century approaches, there a number of “non-scientific” considerations (e.g., political, institutional, international, social, ethical, trade, policy, education, training, and legal challenges) that could impede the adoption and implementation of such approaches. These issues must be delineated and addressed as part of a comprehensive implementation plan.

What are the most important “non-scientific” issues and how should they be prioritized?

References

1. Horizon 2020

<https://ec.europa.eu/programmes/horizon2020/>

2. UK Roadmap

http://nc3rs.org.uk/sites/default/files/documents/NonAnimalTechC0082_RYE_4_nrfinal2.pdf

3. HR2858: The Humane Cosmetics Act

<https://www.congress.gov/bill/114th-congress/house-bill/2858>