

Moving toward a new framework for chemical risk assessment

By Kristen Ryan

Russell Thomas, Ph.D., (<http://www.thehammer.org/scientists/entry/russell-s-thomas>) proposed a practical, data-driven framework that can provide a near-term solution for making economical, efficient, and health-protective decisions on chemicals during a presentation March 15 at NIEHS.

Thomas, who is director of the Institute for Chemical Safety Sciences at The Hamner Institutes for Health Sciences, summarized the movement towards modernized toxicity testing for chemical risk assessment over the past decade, and the difficulties of transitioning the vision proposed in 2007 by the National Research Council (NRC) report on "[Toxicity Testing in the 21st Century: A Vision and a Strategy](http://www.nap.edu/catalog.php?record_id=11970)" (http://www.nap.edu/catalog.php?record_id=11970) into reality.

Hosted by NIEHS Program Administrator David Balshaw, Ph.D., the presentation set the stage for what Thomas described as an initial application of 21st century technology to toxicology and risk assessment. "It's not the ideal solution," he conceded. "In an ideal world, we will be able to take pathway-based approaches to predict toxicity [using *in vitro* assays only], but let's be realistic, that's a couple of decades away. This represents a near term strategy for how to use these approaches, while we begin to figure out how to effectively make those predictions."

Putting new technologies to the test

During his eight years with Hamner, Thomas' research interests have ranged from cancer biology to applied studies in toxicology and chemical risk assessment, with a special emphasis on the development and application of genomic technologies and bioinformatic tools. In his lecture, Thomas focused on evaluating the utility of both high-throughput *in vitro* assays and *in vivo* transcriptomic studies in the three main areas of chemical risk assessment — hazard identification, dose response assessment, and exposure assessment. The studies led him to these conclusions:

- Hazard identification — *In vivo* hazard cannot be accurately predicted with the current high-throughput *in vitro* screening data. However, the data can still be used to both separate chemicals based on their relative selectivity in interacting with biological targets, such as nuclear receptors, kinases, and G-protein-coupled receptors, as well as identify the concentration at which these interactions occur.
- Dose response assessment — For those chemicals that interact selectively with specific biological targets, dose response assessment can be performed in a mode-of-action context. For those chemicals that interact non-selectively, dose response assessment can be performed using either high-throughput *in vitro* assays or short-term *in vivo* transcriptomic studies, to identify the dose that causes significant biological perturbation.
- Exposure assessment — Understanding exposure provides an important context to the dose-response behavior and can be applied to both *in vitro* high-throughput screening data and *in vivo* transcriptomic data.

Thomas concluded his lecture with a tiered approach (see [graphic](#)) for utilizing the available data to make decisions in the near future, by relating the level of chemical exposure and the dose of the toxic effect. The tiered approach focuses on the prioritization of chemicals for standard toxicity testing, saving time and money.

Audience response to a new framework for toxicity testing and risk assessment

Among the audience were NTP toxicologists Scott Auerbach, Ph.D., and Chad Blystone, Ph.D. Auerbach responded to Thomas' presentation by saying, "I think the approach that Dr. Thomas is proposing is a practical and efficient solution to challenges we face in relation to untested chemical space."

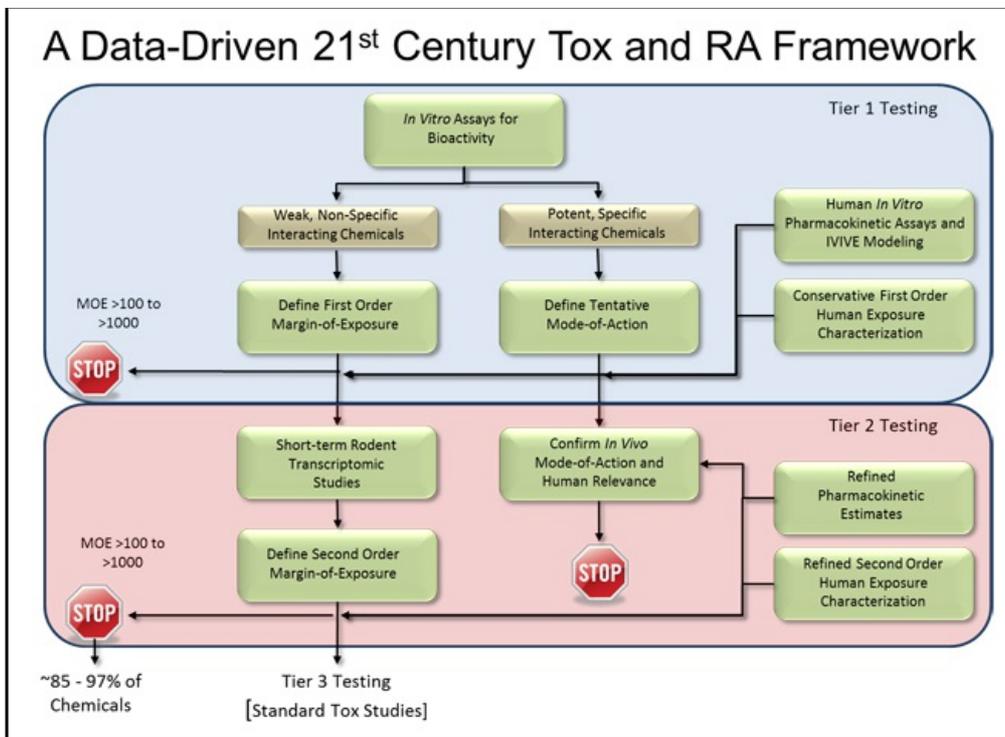
"While the approach does not necessarily identify specific hazards, it does tackle the issue of safety," Auerbach continued. "However, it should be noted that if we are to effectively employ Dr. Thomas's approach, it will be necessary to generate significantly more exposure data."

Blystone concurred by noting, "Dr. Thomas gave a judicious assessment of where high-throughput assays are and are not useful, and provided an interesting path forward to address the issue of lack of toxicity data for many chemicals that the public is potentially exposed to."

(Kristen Ryan, Ph.D., is an Intramural Research Training Award Fellow in the NTP Toxicology Branch.)



Thomas' presentation drew a capacity audience that included many NTP scientists, along with others from throughout the institute, interested in data-driven research and toxicology. (Photo courtesy of Steve McCaw)



Thomas estimates that high-throughput screening, combined with short-term rodent transcriptomic studies, may rule out the need for expensive, long-term rodent studies for 85 to 97 percent of inadequately characterized chemicals. (Photo courtesy of Rusty Thomas)

Landmark report advances predictive toxicology

“Toxicity Testing in the 21 Century: A Vision and a Strategy” addressed the growing backlog of chemicals on the market that have not received adequate toxicology testing. The number of these chemicals is estimated to exceed 80,000.

The report proposed development of an *in vitro* high-throughput screening program for identifying chemicals of concern through perturbation of biological or toxicity pathways. The report also helped to support creation of the Tox21 consortium, involving NTP, the NIH Chemical Genomics Center, U.S. Environmental Protection Agency, and U.S. Food and Drug Administration, the consortium’s newest member.

In 2012, the consortium began testing **10,000 compounds** (http://www.epa.gov/ncct/dsstox/sdf_tox21s.html) for potential toxicity. The compounds cover a wide variety of classifications, and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs. Consortium members are acquiring new databases and sharing their existing resources in an ongoing effort to marshal as much information as possible about chemicals and mixtures now in use.

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