

FORUM

Accelerating the Development of 21st-Century Toxicology: Outcome of a Human Toxicology Project Consortium Workshop

Martin L. Stephens,^{*,1} Craig Barrow,[†] Melvin E. Andersen,[‡] Kim Boekelheide,[§] Paul L. Carmichael,[¶] Michael P. Holsapple,^{||}² and Mark Lafranconi^{|||}

^{*}*The Humane Society of the United States, Washington, District of Columbia 20037*; [†]*Craig Barrow Consulting, North Potomac, Maryland 20878*; [‡]*The Hamner Institutes for Health Sciences, Institute for Chemical Safety Sciences, Research Triangle Park, North Carolina 27709-2137*; [§]*Department of Pathology and Laboratory Medicine, Brown University, Providence, Rhode Island, 02912*; [¶]*Unilever, Safety & Environmental Assurance Centre, Sharnbrook, Bedfordshire, MK44 1LQ, U.K.*; ^{||}*ILSI Health and Environmental Sciences Institute, Washington, District of Columbia 20005*; and ^{|||}*The Procter & Gamble Company, Central Product Safety, Cincinnati, Ohio, 45252*

¹To whom correspondence should be addressed at the Center for Alternatives to Animal Testing, Johns Hopkins University, 615 N. Wolfe Street, W7032, Baltimore, MD 21205. Fax: (410) 614-2871. E-mail: mstephen@jhsph.edu.

²Present address: Senior Research Scientist, Battelle, Health and Life Sciences Global Business, Columbus, OH, 43201-2696.

Received July 1, 2011; accepted September 13, 2011

The U.S. National Research Council (NRC) report on “Toxicity Testing in the 21st century” calls for a fundamental shift in the way that chemicals are tested for human health effects and evaluated in risk assessments. The new approach would move toward *in vitro* methods, typically using human cells in a high-throughput context. The *in vitro* methods would be designed to detect significant perturbations to “toxicity pathways,” i.e., key biological pathways that, when sufficiently perturbed, lead to adverse health outcomes. To explore progress on the report’s implementation, the Human Toxicology Project Consortium hosted a workshop on 9–10 November 2010 in Washington, DC. The Consortium is a coalition of several corporations, a research institute, and a non-governmental organization dedicated to accelerating the implementation of 21st-century Toxicology as aligned with the NRC vision. The goal of the workshop was to identify practical and scientific ways to accelerate implementation of the NRC vision. The workshop format consisted of plenary presentations, breakout group discussions, and concluding commentaries. The program faculty was drawn from industry, academia, government, and public interest organizations. Most presentations summarized ongoing efforts to modernize toxicology testing and approaches, each with some overlap with the NRC vision. In light of these efforts, the workshop identified recommendations for accelerating implementation of the NRC vision, including greater strategic coordination and planning across projects (facilitated by a steering group), the development of projects that test the proof of concept for implementation of the NRC vision, and greater outreach and communication across stakeholder communities.

Key Words: toxicity testing in the 21st century; safety assessment; *in vitro* alternatives; National Research Council.

THE NATIONAL RESEARCH COUNCIL VISION: PATHWAYS TO IMPLEMENTATION

The 2007 U.S. National Research Council (NRC) report titled “Toxicity Testing in the 21st century: A Vision and a Strategy” (NRC, 2007) was the focus of a series of forum articles in *Toxicological Sciences* (Andersen and Krewski, 2009; Bus and Becker, 2009; Boekelheide and Campion, 2010; Chapin and Stedman, 2009; Cohen Hubal, 2009; Hartung, 2009; Holsapple *et al.*, 2009; MacDonald and Robertson, 2009; Meek and Doull, 2009; Walker and Bucher, 2009). The series concluded with a plea for the toxicology community to move from discussion of the NRC report to action on its implementation (Andersen and Krewski, 2010). In this spirit, the Human Toxicology Project Consortium (<http://htpconsortium.wordpress.com/about-2/>) organized a workshop focused on ways to accelerate implementation of the NRC vision for toxicity testing and risk assessment. The Consortium is a coalition of several corporations, a research institute, and a non-governmental organization, focused on making the NRC vision a reality. This paper summarizes dialog from the workshop and several key recommendations for moving forward specifically with the NRC vision.

The NRC report (published in its entirety in Krewski *et al.*, 2010) calls for a fundamental shift in the way that chemicals are tested for human health effects and are evaluated in risk assessments. The proposed approach would decrease the current reliance on animal studies and move toward *in vitro* methods, typically using human cells in a high-throughput context. The *in vitro* methods would be designed to detect significant perturbations to “toxicity pathways,” i.e., key biological pathways that, when sufficiently perturbed, lead to

adverse health outcomes. The results from this *in vitro* testing would then be interpreted with the aid of new tools and approaches, including systems biology and computer-based modeling, and incorporated directly into risk assessment (Boekelheide and Andersen, 2010; Bhattacharya *et al.*, 2011).

A feature of the NRC vision that has received less attention is its shift away from the prevailing emphasis on risk assessment based on high-dose observations to a safety-based paradigm based on pathway perturbations (Andersen and Krewski, 2010). The new pathway-based approach would be used to identify the doses below which an exposure is not likely to result in harm. The research and development necessary to fully realize the NRC vision was expected to take one to two decades to develop pathway assays and the suite of tools for interpreting these results to ensure safety (NRC, 2007).

This new framework is expected to have several advantages over current practice (NRC, 2007), including a more relevant scientific foundation for human health risk assessments, lower costs and shorter duration of testing and assessment, broader coverage of chemicals, health effects, life stage targets and mixtures (given the new tools' higher throughput, lower cost, and shorter duration), and cumulative reductions in animal usage as the new models and approaches gain scientific and regulatory acceptance.

The NRC vision has led to an emphasis on "21st-century toxicology" consistent with the report's general theme of harnessing modern advances in biology and technology for use in toxicity testing. Several comprehensive initiatives are underway to modernize toxicology; many of these were featured at the workshop. Although each of these diverse efforts reflects its own priorities and mandates, they are clearly relevant to the NRC vision and are important complementary activities.

In light of the call to move from discussion of the NRC report to action on its implementation (Andersen and Krewski, 2010), the Human Toxicology Project Consortium believed the time was right for interested stakeholders to take stock of relevant current and planned initiatives and to explore potential ways to accelerate progress toward the use of dose-response information, computational toxicity pathway models, and *in vitro-in vivo* extrapolation for guiding human safety assessments from *in vitro* toxicity testing assays. Consequently, the Consortium hosted an open workshop titled "Accelerating Implementation of the NRC Vision for Toxicity Testing in the 21st Century" on 9–10 November 2010 at Gallaudet University in Washington, DC. The workshop was designed to explore ongoing and planned initiatives in North America and Europe related to the NRC vision, evaluate progress to date, and identify the highest priority needs to accelerate progress.

THE HUMAN TOXICOLOGY PROJECT CONSORTIUM

Before turning to the results of the workshop, we provide a few more details on the Human Toxicology Project

Consortium. The Consortium seeks to help catalyze the prompt, global, and coordinated implementation of a mode of action approach to the risk assessment of chemicals as proposed in the NRC vision. Specifically, the Consortium promotes (1) the establishment and implementation of an international research roadmap (including case studies of prototype pathways to establish proof of principle), (2) appropriate legislative, appropriations, and regulatory changes necessary to advance the development and implementation of the new methodology, and (3) greater appreciation of the need for a prompt and global transformation to the new paradigm among diverse stakeholders. The Consortium currently has several members and partners. (Consortium members currently include corporations [Dow, DuPont, ExxonMobil, Johnson & Johnson, L'Oréal, Procter & Gamble, and Unilever], a research institute [the Hamner Institutes for Health Sciences], and an animal protection organization [The Humane Society of the United States] and its affiliates [Humane Society Legislative Fund and Humane Society International]. The Consortium has partnered with the Johns Hopkins Center for Alternatives to Animal Testing [CAAT], the ILSI Health and Environmental Sciences Institute [HESI], and Toxicology Excellence in Risk Assessment [TERA].)

THE WORKSHOP

The workshop format consisted of plenary presentations, breakout group discussions, and concluding commentaries, with ample time for questions and answers interspersed throughout the 2-day event. The speakers and session chairs were drawn from industry, academia, government, and public interest organizations. The agenda and slides from the presentations are available online (<http://htpconsortium.wordpress.com>).

Current Efforts

Most of the plenary presentations focused on ongoing efforts. They illustrated the diversity of projects currently underway to advance 21st-century toxicology in the United States and the European Union (EU) through not only research but also conceptual development, coordination, advocacy, and regulatory implementation initiatives (Table 1). These projects include efforts by various sectors, including government (e.g., Tox21 in the United States and AXLR8 in the EU), industry (e.g., Unilever and Procter & Gamble), academia (e.g., the Trans-Atlantic Think Tank on Toxicology), and multi-stakeholder consortia (e.g., HESI's Risk21 Project).

These projects seek to expand the frontiers of 21st-century toxicology by harnessing advances in modern science and technology. The efforts are diverse, each with its own goals and aims (Table 1), as well as project management and funding. Consequently, they overlap to varying degrees with the NRC vision itself. However, it was apparent that no one project fully captures all the elements of the NRC vision and it is arguable as

TABLE 1

Workshop Presentations on Current Efforts Related to the Implementation of the NRC Vision for Toxicity Testing in the 21st Century

Workshop presenter	Project	Lead organization(s)	Description	Notes regarding the NRC vision
Research and development efforts				
Raymond Tice	Tox21	U.S. NIH Chemical Genomics Center, Environmental Protection Agency, National Institute of Environmental Health Sciences, Food and Drug Administration	Developing ultra high-throughput testing systems and bioinformatic tools to assess the biological activity of chemicals on cells in order to predict <i>in vivo</i> toxicities	Currently focusing on rapid screening for hazard identification
Robert Kavlock	ToxCast	U.S. Environmental Protection Agency	Developing high-throughput testing systems to predict potential toxicity and to cost effectively prioritize the thousands of chemicals that need toxicity testing	Currently focusing on rapid screening for prioritization of animal testing
Maurice Whelan	<i>In Vitro</i> Assay Technologies for the Development of Alternative Methods	Institute for Health and Consumer Protection, Joint Research Center, European Commission	Developing high-throughput and high-content assays to move from empirical to predictive toxicology	Scaling up <i>in vitro</i> assays for high-throughput systems to meet a variety of challenges
Cameron MacKay	Skin Sensitization Programme	Unilever	Developing nonanimal methods and a systems biology approach to assure consumer safety with respect to skin sensitization	Focusing on risk assessment
Mel Andersen	Pilot Projects	The Hamner Institutes for Health Sciences in partnership with the Human Toxicology Project Consortium	Developing the tools and approaches to explore individual "toxicity pathways" as case studies	Pursuing the NRC vision by proof of concept with data-rich chemicals targeting well-characterized pathways
George Daston	Systems Approach	Procter & Gamble	Developing a systems approach to predictive toxicology through the application of cheminformatics, dynamic modeling, and toxicogenomics	Employing sophisticated tools and approaches without explicit mapping to the NRC vision
Conceptual development efforts				
Thomas Hartung	t ⁴	Center for Alternatives to Animal Testing (United States and EU) and Utrecht University	Spearheading conceptual developments to help promote the transition to 21st-century toxicology	Pioneering "evidence-based toxicology" as a means of quality assurance of new methods
Tim Pastoor	Risk21	ILSI Health and Environmental Sciences Institute	A multi-sector collaboration developing conceptual frameworks for applying the new tools to quantitative risk assessment	Basing its efforts on a variety of frameworks, including the NRC vision
Advocacy efforts				
Martin Stephens	Human Toxicology Project	Human Toxicology Project Consortium	Advocating for an accelerated implementation of the NRC vision	Advocating for a "Human Toxicology Project" on a par with the Human Genome Project
Coordination efforts				
Horst Spielmann	AXLR8	European Commission	Providing tools and opportunities for increased networking, information exchange, problem solving, strategic planning, and collaboration among a variety of scientific disciplines and stakeholder groups	Accelerating the transition toward "21st century" approaches in toxicology and risk assessment

TABLE 1—Continued

Workshop presenter	Project	Lead organization(s)	Description	Notes regarding the NRC vision
Regulatory implementation efforts				
Jack Fowle	Incorporating 21st-century toxicology	U.S. Environmental Protection Agency	Incorporating “21st-century” toxicology into its regulatory practices in the short-, medium-, and long-term, as developments permit.	Putting the NRC vision into regulatory practice as research and development efforts bear fruit (the agency had funded the NRC’s work on the vision report)

to whether they do so collectively. Many of these projects currently do not feature the NRC vision’s proposed interpretative tools for dose-response and *in vitro-in vivo* extrapolations for risk assessment and the elucidation of regions of exposures that are predicted to be without adverse effects.

Similarly, much of the current activity in 21st-century toxicology is at least temporarily anchored in the prevailing conceptual framework centered on high-dose animal studies and hazard identification, e.g., using high-throughput *in vitro* testing as a means of more rapidly prioritizing chemicals for follow-up testing in animals. In contrast, the NRC proposal would replace this framework with a new platform of safety-based risk assessments centered on pathway testing in human cells.

At the workshop, a framework was offered to categorize efforts to promote 21st-century toxicology with respect to how they advance the NRC vision. One of the three overlapping categories in this framework is “laissez-faire,” in which efforts in academic research labs and elsewhere make incremental contributions and the field develops organically over time. Another is “indirect,” in which the new tools and approaches are applied initially as enhancements within the prevailing hazard identification framework centered on animal studies, and perhaps at later stages, would evolve toward the NRC safety assessment framework centered on pathway studies. The third approach is “direct,” in which the new tools and approaches are applied directly in an attempt to develop proof of concept examples to show the NRC vision in action.

Ongoing efforts to advance 21st-century toxicology follow primarily the laissez-faire and indirect approaches. These orientations are hardly surprising given the formidable scientific, technical, and regulatory challenges in charting a direct path to the NRC framework. At the workshop itself, most of the plenary presentations described projects in the indirect camp (Table 1).

From the perspective of those seeking a prompt, global implementation of the NRC vision for 21st century toxicology, including the Human Toxicology Project Consortium, the direct approach remains most appealing. However, enthusiasm for rapid action toward the NRC goal is tempered by the fact that current initiatives represent a diverse landscape with many stakeholders. Coalescing these disparate camps around a more common vision for rapid action presents both challenges and opportunities.

Recommendations

Strategic planning, coordination, and a steering group. As was evident from the presentations on the first day of the workshop, many projects are currently expanding the frontiers of 21st-century toxicology. They overlap to varying degrees with the NRC vision. One way to achieve better collective focus and progress on the goals noted in the NRC report would be to enhance any existing coordination and planning among those projects that overlap most heavily with the NRC proposal. To help provide the necessary leadership for this, the workshop participants recommended that a “steering group” be established. This group could comprise the leadership of the relevant projects along with representatives from interested stakeholder communities, including risk assessors.

Some level of strategic planning and coordination is already evident in several projects presented or discussed at the workshop. For example, Tox21 (<http://htpconsortium.files.wordpress.com/2010/11/tice.pdf>) is a collaboration across four federal entities in the United States, and Risk21 (<http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3492>) is a multi-stakeholder collaboration. Nonetheless, these are examples of planning and coordination within a given project. Planning and coordination across projects is less common. AXLR8 (<http://axlr8.eu/>) is a coordination project addressing relevant EU-funded efforts, and its scientific panel includes scientists based outside the EU. The Molecular Screening Project, which was mentioned at the workshop, promotes collaboration across relevant projects of member states of the Organization for Economic Cooperation and Development (http://www.oecd.org/document/29/0,3746,en_2649_34373_34704669_1_1_1_1,00.html).

Nonetheless, there was a strong sense at the workshop that greater cooperation across relevant projects was the key to speeding up the NRC vision. Where appropriate, such cooperation should span research sectors (government, academia, and industry) and international borders. It could entail collaboration on the generation of new data using pathway testing and targeted testing, as well as on the interpretation of what the data mean in a human health context. Both the testing assays and data interpretation tools will require new methodological approaches.

Data sharing surfaced as another way to facilitate coordination and collaboration. Data repositories should be developed for others to mine and interpret, as well as to factor into their

research plans. The Environmental Protection Agency's (EPA's) ToxRefDB (Toxicity Reference Database) contains study design and effect information on thousands of *in vivo* studies of hundreds of chemicals (<http://www.epa.gov/ncct/toxrefdb/>). Obtaining data from the pharmaceutical industry—with its direct focus on human biology—may also accelerate implementation of 21st century chemical risk assessment.

This coordination and planning could focus systematically on each of the NRC vision components—*in silico* approaches for chemical characterization, toxicity pathway testing, targeted testing, and dose-response and extrapolation modeling—and link these together. The planning should ensure some level of balance among the vision components being implemented. In the United States, for example, a doubling in funding of the Tox21 initiative as currently designed would reportedly saturate the ability of the project to deal with the increased volume of data. Thus, there must be a clear recognition that increased capacity to generate data must be accompanied by an increased capacity to process and utilize the information for chemicals management. Ultimately, the goal of strategic planning and coordination across projects is to accelerate application of the new technology in a regulatory context.

Support for pilot projects on the NRC vision as a way forward. Among its goals, the Human Toxicology Project Consortium seeks funding for several “direct approach” projects to evaluate the steps required to use toxicity pathway assay results for human health risk assessment. These projects are intended to jumpstart implementation of the NRC vision. An example of such projects is now underway at The Hamner Institutes for Health Sciences (<http://www.the-hamner.org/tt2>). This research (Andersen, 2011), pursued with endorsement from the Consortium, directly probes the NRC vision through case studies with data-rich prototype compounds that are known to target specific toxicity pathways. This program was presented in a plenary session and discussed in a breakout session. The first studies on these prototype pathways are underway with support from Dow, ExxonMobil, Unilever, and the American Chemistry Council. The project involves the design and validation of human cell or tissue assays to examine adverse effects as envisioned by the NRC. These techniques are intended to identify and evaluate key toxicity pathway perturbations (Boekelheide and Andersen, 2010; NRC, 2007) and to create the knowledge base required to apply *in vitro* pathway assay test results, bioinformatic analysis of pathway function, and *in vitro-in vivo* extrapolation tools to human health risk assessment. Success with these prototypes could refine aspects of the NRC vision and pave the way for more rapid widespread application of tools with more diverse pathways.

Workshop participants were in general agreement that a pilot project approach to implementing the NRC vision could augment other existing approaches and should be pursued as one of the options to move the NRC vision forward. There was

a strong feeling that any “direct” project, including that proposed by the Hamner Institutes, should also seek advice from regulators up front, have clear human relevance, and focus on relevant exposures in a risk assessment context.

Some participants, however, cautioned against putting too many eggs in a single basket, believing strongly that approaches that move progressively to a systems toxicology focus or that more directly investigate mechanisms of toxic end points (Daston and Naciff, 2010; Rusyn and Daston, 2010) will likely also be essential in the long-term realization of the NRC vision. The discussions about direct versus indirect and laissez-faire approaches highlighted the different motivating factors between these various options. The evolutionary path via indirect and laissez-faire approaches was attractive to some participants because the present knowledge base for systems toxicology does not yet appear to provide unequivocal guidance about the optimum approaches. In addition, there was concern that moving too quickly with a single direct option could impede acceptance of new technologies if the direct approach failed to fulfill expectations. On the other hand, the direct approach could implement current knowledge with prototypes and evaluate strengths and weaknesses of current systems toxicology tools for more immediate implementation. There is clearly a healthy tension between incremental advancement of a variety of tools with natural selection of preferred methods (a hallmark of the laissez-faire approach) versus a direct approach that tries to focus on a preferred path forward (e.g., proof of concept of an explicit interpretation of the NRC vision) and make necessary course corrections as work progresses.

Notwithstanding expressions of support for pilot projects and other direct approaches as a means of accelerating the vision, many participants underscored the need for a mix of approaches, given the inevitable uncertainties over the best path forward. Implementation is likely to be slower with this mix rather than with a direct approach, but a unified direct approach would entail the challenge of developing more of a consensus about the best path forward. Moreover, many participants felt that the indirect approach to implementation was a practical necessity for regulators, for both confidence building and bridging between the current and new approaches for toxicity testing and risk assessment.

Communication. Reinventing toxicity testing and risk assessment requires a high level of communication among those carrying out the work, but perhaps as importantly, considerable outreach and discussion with interested stakeholders, including relevant congressional decision makers and advocates for public health, environment protection, and animal protection. This outreach should happen early in the process by seeking input and “buy-in.” Stakeholders should not be presented with finished products and only then asked for their support.

For these purposes, a communication strategy was also recommended. The communication that has taken place to date

has been largely within the scientific community, researcher to researcher. Wider outreach has not been a priority. The U.S. EPA's Pesticide Program Dialogue Committee (<http://www.epa.gov/pesticides/ppdc/>) was mentioned as an existing structure that may be instructive in this regard. A communication strategy could be developed by interested stakeholders perhaps in consultation with the steering group (should one be formed). The strategy should convince interested parties, including the public at large, that the new approach reduces uncertainties in the risk assessment process, compared with the current approach.

DISCUSSION

The NRC vision was designed to modernize current toxicity testing. Animal-based methods are low throughput and do not sufficiently reflect advances in modern biology or human responses to chemical exposure (NRC, 2006). The resulting vision has received broad support. Collins *et al.* (2008) elaborated on it in a high-profile perspective in *Science*, in which they proposed “a shift from primarily *in vivo* animal studies to *in vitro* assays, *in vivo* assays with lower organisms, and computational modeling for toxicity assessments.”

The workshop generated a number of recommendations for accelerating implementation of the NRC vision. These centered on the expected value of (1) coordination and planning across relevant projects, facilitated by a steering group, (2) more direct approaches to implementation the NRC vision to supplement current research efforts, and (3) greater communication across stakeholder communities regarding the NRC vision and its promise.

Coordination and Planning

The 2-day workshop was not the forum to elaborate the details of the proposed steering group, such as its size, composition, and governance, nor debate whether steering group was the most appropriate name for the group. Indeed, in subsequent discussions, concerns have been raised that the label steering group might imply that the *ad hoc* body would have executive authority to dictate the future course of events. The Human Toxicology Project Consortium organizers of the November workshop have provisionally settled on “Implementation Group” as a more apt name that is more reflective of the fact that the group would not be empowered to mandate how individual projects should be run. (For the purpose of this summary, however, we retain the steering group label.) Any recommendations developed by the group would be just that—recommendations. Nonetheless, a properly constituted motivated group could have a catalyzing influence on the course and pace of developments.

The NRC report discussed the possibility of a stand-alone institute being established to implement its proposed vision.

The institute would be roughly on the scale of the U.S. National Toxicology Program. Such a dedicated implementation mechanism would foster—virtually by definition—a high degree of coordination and strategic planning. However, no such institute has been created for this purpose, nor does one seem likely in the near future. Nonetheless, a steering group, if implemented, could markedly increase the level of collaboration across projects and thereby accelerate progress.

One speaker (Andrew Rowan, Humane Society International) proposed a “big biology” project along the lines of the Human Genome Project to accelerate implementation of the NRC vision. This effort was termed the “Human Toxicology Project” (see <http://htpconsortium.files.wordpress.com/2010/11/rowan.pdf>). The workshop also included a presentation by Christopher Austin (National Institutes of Health) on lessons learned from the Human Genome Project that would need to be carefully considered if a large scale project were to be considered as an implementation strategy (see <http://htpconsortium.files.wordpress.com/2010/11/austin.pdf>). These key lessons (Collins *et al.*, 2003) were: build the best teams, ensure the process is science-driven, meet managerial challenges, seek international participation, establish explicit milestones and quality assessments, strive for technological advancement that can accelerate the project, release data rapidly to demonstrate the project's value to the community, and address social consequences as part of the project.

Many of these lessons speak to the crosscutting issues of coordination and planning. The Human Toxicology Project Consortium believes that a Human Genome Project-type effort, even if fairly decentralized, should be marshaled to realize the NRC vision. The themes and recommendations that emerged from this workshop can help guide such an effort.

A central challenge for a steering group should be to hasten the application of the new tools and approaches beyond screening and priority-setting, to hazard identification and dose-response analysis—two key components of risk assessment. Similarly, the steering group should also expedite the use of the new methods to diverse risk contexts (NRC, 2007), not all of which demand assays that are high-throughput. Collaboration between the ultimate users of the technology (risk assessors) and the developers will help clarify regulatory expectations and facilitate timely application of the new techniques (Dellarco *et al.*, 2010), allowing decision makers to use the next generation of tools and approaches to make more informed and efficient responses to diverse public health concerns faced by regulators, industry, and the public (NRC, 2007).

Such cross-sector collaboration is already a feature of the HESI Risk21 project (<http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3492>), in which the elements of the NRC vision for toxicity testing in the 21st century have been integrated into the project objective to create a systematic approach for incorporating novel approaches and technologies, as available and when appropriate, to aid in advancing human health assessments.

Funding Issues

Although no specific recommendations emerged from the workshop on ways to increase funding for research and development in support of the NRC vision, financial issues were discussed in a general way. The resources needed to facilitate the transformation proposed in the NRC report are substantial—estimated to be on the order of 1 billion to 2 billion dollars over 10–20 years (Andersen and Krewski, 2009; NRC, 2007). However, an estimated \$200 million per year is already spent across various sectors on developing new methods for toxicity testing (Rowan, personal communication). Some of this research has been inspired by the NRC report, but much of it has the aim of replacing existing animal-based methods on a test-for-test basis (e.g., National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, 2006) or otherwise modernizing hazard identification (e.g., Food and Drug Administration, 2004). Properly targeted and coordinated, this existing funding could go a very long way toward implementing the NRC vision.

Concluding Remarks

Implementation of the NRC vision should be seen as an iterative progressive transformation, not an all-or-nothing switch that will take place 20 years from now. In this context, stakeholders should be attuned to opportunities to ensure incorporation of emerging 21st-century toxicology tools and approaches into regulatory decisions that are on the horizon. For example, efforts are underway to revise the Toxic Substances Control Act (TSCA) in the United States and biocides regulation in the EU. The introduction of the tools and data derived from the new approaches could be accelerated by supportive language placed in revisions to these existing statutes. A recent paper (Locke and Myers, 2010) discussed the challenges and opportunities of implementing the NRC vision and strategy for toxicity testing that will arise under the key provisions of TSCA, concluding that TSCA, as currently written, creates a sufficient legal foundation for the NRC vision.

In summary, the Human Toxicology Project Consortium workshop illustrated the diversity of projects underway that are advancing pathway-based approaches to toxicity testing, which underpin the NRC vision for toxicity testing in the 21st century. Workshop participants made several recommendations for accelerating the implementation of this vision, including enhancing collaboration across relevant projects via a steering group, complementing existing efforts with more direct approaches to implementing the NRC vision, and crafting a communications strategy that reaches out to diverse stakeholders on the nature and benefits of implementing the new paradigm. Policy-oriented stakeholders should be attentive to opportunities to incorporate NRC vision-friendly provisions into new or amended public policies.

These recommendations fall primarily in the realm of science policy and not “hard science.” Nonetheless, they bear

quite heavily on the question of how soon the new science of toxicology will be brought online. For this reason, we offer them to the broad toxicology community as possibilities for action.

FUNDING

Alternatives Research and Development Foundation; DuPont; ExxonMobil; L’Oréal; Procter & Gamble; Unilever.

ACKNOWLEDGMENTS

The organizers of the workshop would like to thank the Society of Toxicology for its endorsement of the event, Dawn McPherson for managing the myriad practical details associated with hosting the workshop, Michelle Embry and Eric Moore of HESI for general advice and support with the workshop website; Neil Mason and Geoffrey Bock of the Hamner Institutes for Health Sciences for production of workshop materials; and Jennifer Ball, Carol England, Leah Gomez, and Loree Talley for assisting at the workshop. Special thanks to the workshop sponsors: the Alternatives Research and Development Foundation, DuPont, ExxonMobil, L’Oréal, Procter & Gamble, and Unilever.

A report based on a Human Toxicology Project Consortium workshop on “Accelerating Implementation of the NRC Vision for Toxicity Testing in the 21st century.”

REFERENCES

- Andersen, M. E. (2011). Toxicity testing and safety assessment in the 21st century: Creating a research program to accelerate change. *AltTox.org*. Available at: <http://alttox.org/trc/overarching-challenges/way-forward/andersen2>. Accessed October 5, 2011.
- Andersen, M. E., and Krewski, D. (2009). Toxicity testing in the 21st century: Bringing the vision to life. *Toxicol. Sci.* **107**, 324–330.
- Andersen, M. E., and Krewski, D. (2010). The vision of toxicity testing in the 21st century: Moving from discussion to action. *Toxicol. Sci.* **117**, 17–24.
- Bhattacharya, S., Zhang, Q., Carmichael, P. L., Boekelheide, K., and Andersen, M. E. (2011). Toxicity testing in the 21st century: Defining new risk assessment approaches based on perturbation of intracellular toxicity pathways. *PLoS ONE* **6**, e20887. doi:10.1371/journal.pone.0020887.
- Boekelheide, K., and Andersen, M. E. (2010). A mechanistic re-definition of adverse effects—A key step in the toxicity testing paradigm shift. *ALTEX* **27**, 243–252.
- Boekelheide, K., and Campion, S. N. (2010). Toxicity testing in the 21st century: Using the new toxicity testing paradigm to create a taxonomy of adverse effects. *Toxicol. Sci.* **114**, 20–24.
- Bus, J. S., and Becker, R. A. (2009). Toxicity testing in the 21st century: A view from the chemical industry. *Toxicol. Sci.* **112**, 297–302.
- Chapin, R. E., and Stedman, D. B. (2009). Endless possibilities: Stem cells and the vision for toxicology testing in the 21st century. *Toxicol. Sci.* **112**, 17–22.
- Cohen Hubal, E. A. (2009). Biologically relevant exposure science for 21st century toxicity testing. *Toxicol. Sci.* **111**, 226–232.

- Collins, F. S., Morgan, M., and Patrinos, A. (2003). The human genome project: Lessons from large scale biology. *Science* **300**, 286–290.
- Collins, F. S., Gray, G. M., and Bucher, J. R. (2008). Toxicology. Transforming environmental health protection. *Science* **319**, 906–907.
- Daston, G. P., and Naciff, J. M. (2010). Predicting developmental toxicity through toxicogenomics. *Birth Defects Res. C Embryo Today* **90**, 110–117.
- Dellarco, V., Henry, T., Sayre, P., Seed, J., and Bradbury, S. (2010). Meeting the common needs of a more effective and efficient testing assessment paradigm for chemical risk management. *J. Toxicol. Environ. Health B Crit. Rev.* **13**, 347–360.
- Food and Drug Administration. (2004). *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*. U.S. Department of Health and Human Services, Washington, DC.
- Hartung, T. (2009). A toxicology for the 21st century: Mapping the road ahead. *Toxicol. Sci.* **109**, 18–23.
- Holsapple, M. P., Afshari, C. A., and Lehman-McKeeman, L. D. (2009). The “vision” for toxicity testing in the 21st century: Promises and conundrums. *Toxicol. Sci.* **107**, 307–308.
- Krewski, D., Acosta, D., Andersen, M., Anderson, H., Bailar, J. C., Boekelheide, K., Brent, R., Charnley, G., Cheung, V. G., Green, S., et al. (2010). Toxicity testing in the 21st century: A vision and a strategy. *J. Toxicol. Environ. Health B Crit. Rev.* **13**, 51–138.
- Locke, P. A., and Myers, D. B., Jr. (2010). Implementing the National Academy’s vision and strategy for toxicity testing: Opportunities and challenges under the U.S. Toxic Substances Control Act. *J. Toxicol. Environ. Health B Crit. Rev.*, **13**, 376–384.
- MacDonald, J. S., and Robertson, R. T. (2009). Toxicity testing in the 21st century: A view from the pharmaceutical industry. *Toxicol. Sci.* **110**, 40–46.
- Meek, B., and Doull, J. (2009). Pragmatic challenges for the vision of toxicity testing in the 21st century in a regulatory context: Another Ames test ... or a new edition of “the Red Book”? *Toxicol. Sci.* **108**, 19–21.
- National Research Council (NRC) (2006). *Toxicity Testing for Assessment of Environmental Agents*. National Academies Press, Washington, DC.
- National Research Council (NRC) (2007). *Toxicity Testing in the 21st Century: A Vision and a Strategy*. National Academies Press, Washington, DC.
- National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). (2006). *Current Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants: Bovine Corneal Opacity and Permeability Test Method Background Review Document*. National Institute of Environmental Health Sciences, Research Triangle Park, NC.
- Rusyn, I., and Daston, G. P. (2010). Computational toxicology: Realizing the promise of the toxicity testing in the 21st century. *Environ. Health Perspect.* **118**, 1047–1050.
- Walker, N. J., and Bucher, J. R. (2009). A 21st century paradigm for evaluating the health hazards of nanoscale materials? *Toxicol. Sci.* **110**, 251–254.