ECHA-EPA Workshop: Accelerating the Pace for (Chemical) Risk Assessment (APCRA)

Presenter: Dr. John Bucher, NIEHS/DNTP

A group of representatives from major chemical regulatory agencies from around the world has been working over the past several years to understand how the findings from alternative toxicological methods might be appropriately brought into the risk assessment arena. The group has met face-to-face on several occasions, most recently October 10-11 in Helsinki, at the European Chemicals Agency (ECHA). This followed an initial meeting held in Washington in September of 2106, hosted by the US EPA. Following the meeting, Dr. Robert Kavlock published a short article in BNA outlining the goals of the group, and the "case study" approach that was to be used in moving the group towards a consensus opinion of the value of different data streams for different regulatory purposes. This report is appended.

NTP has been represented at both meetings and Dr. Bucher will discuss the way in which some current NTP efforts contribute to these case studies, and provide a description of a series of short exposure *in vivo* hepatic transcriptomic assessments applying Bench Mark Dose analyses to generate "genomic-based screening level BMDs." Thoughts on how these initial studies might be expanded to provide more complete information and more confidence in translating genomic findings in the context of the more comfortable apical endpoint assessments will be discussed.

Appendix 1

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Practitioner Insights: Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious

Chemicals

The recently amended toxics law requires the EPA to take significant strides towards using non-animal safety tests for chemicals. EPA's Dr. Robert Kavlock explores this challenge and reports on a recent international workshop the agency convened that lays the groundwork for tests that can reduce reliance on animals, costs and in many cases provide better information.

Dr. Robert Kavlock

Disease prevention is the goal of chemical risk assessments, and done efficiently and properly they minimize the societal cost of environmentally-induced diseases. Indeed, risk assessments are essential for the protection of human health and the environment from the exposures to hazardous chemicals in the industrial world. For the past several decades, toxicology has followed a well-trod path of studying the effects of individual chemicals using high dose exposures in laboratory animals, and employing various adjustment factors to predict safe levels of human exposure for use in risk assessments.

Robert Kavlock is the Deputy Assistant Administrator for Science in the EPA's Office of Research Development in Washington. ORD is the scientific research arm of the EPA, whose leading-edge research helps provide the underpinning of science and technology for the agency.

The views expressed in this commentary are those of the author and do not necessarily represent the views and/or policies of the Environmental Protection Agency or Bloomberg BNA, which welcomes other points of view.

This strategy appears to have prevented overt impacts of chemicals on humans that had been seen, for example, in the pre-testing era for birth defects from thalidomide, neurologic disorders from kepone, and cancers from vinyl chloride, but because of the expense and time required to evaluate a chemical, most chemicals receive little or no testing. This lack of information contributes to a poor understanding of disease causation and hence hinders prevention.

It is estimated that intrinsic factors (e.g., those that result in mutations due to random errors in DNA replication) account for only 10 to 30% of many common cancers and other causes are largely unknown. Similarly, the causes of 70% of birth defects are unknown. For some human diseases, such as cardiovascular and

 ISSN 1060-2976

metabolic disorders, we also lack readily available animal models. Furthermore, the increasing frequency of adverse outcomes, and indeed even their types, noted in epidemiological studies indicates a discordance between what have been predicted levels of safe exposure and reinforces concerns about the adequacy of contemporary risk assessment practices.

Anticipating the need for new approaches to evaluate the safety of chemicals, the Environmental Protection Agency produced a Framework for a Computational Toxicology Research Program in 2003. The strategic objectives of this framework called for (1) improving the linkages in the source to outcome paradigm, (2) developing approaches for prioritizing chemicals for subsequent testing, and (3) producing better methods and predictive models for quantitative risk assessment. The envisioned research program was to be a technology-based, hypothesis-driven effort to increase the soundness of risk assessments within the agency. It was designed to increase the capacity to prioritize, screen and evaluate chemicals, with success measured by the ability to understand the effects of chemicals on molecular and biochemical pathways of concern.

With the creation of the EPA's National Center for Computational Toxicology (NCCT) in 2005, the expertise and resources to implement the framework became a reality. Further support of the direction was provided by the National Academies of Science (NAS) in 2007 with the issuance of its report Toxicity Testing in the 21st Century: A Vision and a Strategy that called for transformation of toxicity testing using modern molecular techniques to elucidate so-called toxicity pathways, ultimately without the use of traditional animal testing approaches. According to the NAS report, success would require significant funding over a 10 to 20 year period given the challenges in creating the transformation.

Here we are, 13 years since the release of the EPA's computational toxicology framework, 11 years since formation of the national center, and almost 10 years since the NAS vision report with a cumulative investment by the U.S. government in excess of $100 million. So where do we stand in terms of progress? The NCCT and other collaborators in the EPA have gone on to create the infrastructure to support the effort as evidenced by databases such as ToxRef, DSSTox, ACToR, CPCAT, ExpoCast and portfolio of CompTox dashboards and has tested more than 2,000 chemicals in hundreds of high-throughput screening assays. In conjunction with the Tox21 partners in the U.S. government (EPA, National Institute of Environmental Health Sciences, Environment Health and Safety, National Center for Advancing Translational Sciences and the Food and Drug Administration) more than 8,000 chemicals have been examined in dozens of additional biological assay. These large databases are being used to construct robust quantitative structure-activity models, one display of the possibilities for applications of these new approaches.

The EPA and its Tox21 partners have demonstrated that robust and high-quality data on thousands of chemicals can be generated. New technologies also are being incorporated into the EPA's research program to broaden the range of chemistry and biology, including metabolic capacity and genomic technologies, covered in these testing systems, thus making them even more informative on biological effects. But where do we stand in terms of acceptance of these new approach methodologies, or NAMs, by regulatory agencies? Has this effort to cover the data landscape had any impact on the practice of risk evaluation?

The answer is mixed, as there are examples of use, but they remain relatively few and far between. In two instances, the Deepwater Horizon incident and the Elk River spill, NAMs were used with good success in emergency response studies to more quickly provide information on potential toxicological hazards of dispersant chemicals. Of potentially greater impact, in 2015 the Endocrine Disruption Screening Program (EDSP) within the EPA's Office of Chemical Safety and Pollution Prevention announced a pivot, away from lower throughput tests to inclusion of newer approaches and updated its strategy on how data from NAMs will be considered.

A case study of computational methods to elucidate effects on the estrogen signaling pathway showed the feasibility of the approach, with similar methods for the androgen and thyroid signaling pathways advancing rapidly. Rather than taking decades to screen all the chemicals covered by the EDSP, this will soon be achieved in a couple of years. And, there are cost savings associated with these new methods. The initial EDSP screening battery has been estimated to cost close to $1 million per chemical, whereas the NAM approach is at least an order of magnitude cheaper. Similarly, a recent industry analysis calculated that approximately 400 animals and $200,000 per chemical could be saved by using read-across and in silico approaches compared with the required Organization for Economic Cooperation and Development test guidelines.

If NAMS have proven useful in national emergencies, in prioritizing chemicals for testing in higher tier assays while saving enormous amounts of time and money, and for saving money for the regulated industry in routine testing, why haven't they seen broader adoption by regulatory agencies? Simply put, transformations are difficult and require the buy-in from numerous stakeholders who have a variety of needs and viewpoints. The parties need to be convinced that any new methodology is at least as good, if not better, than that which it replaces—a high bar to meet. But we shouldn't forget that there are flaws in the existing approaches as noted above. The new TSCA legislation certainly offers an opportunity for expanded use of NAMs, as it calls for development of a strategic plan by June 2018, to promote the development and use of scientifically reliable NAMs that would reduce, refine or replace vertebrate animal testing.

What are the barriers to NAM adoption? Since chemicals do not recognize national boundaries, and gaining acceptance of NAMs will require international cooperation, the EPA recently convened a small group of representatives from international regulatory agencies to provide a forum for discussion on progress in applying the new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.

Workshop participants included those from Health Canada, the European Chemical Agency, the European Food Safety Agency, the Australian NICNAS, France's INERIS, the Netherland's RIVM, the Japanese Ministry of Health, Welfare and Labour, Korea's Ministry of the Environment, Singapore's A*STAR program, the Taiwanese SAHTECH, the EPA's Office of Toxic Sub-

  DEN ISSN 1060-2976

stances, the EPA's Office of Pesticide Programs, the EPA's Office of Research and Development, the National Toxicology Program, the Consumer Products Safety Commission, California's EPA and the OECD. During the workshop, scientific and regulatory needs for the quantitative application of NAMs to risk assessments were identified, and example case studies designed to address them were volunteered by a number of participants to help advance NAM application internationally.

One session of the workshop focused on the barriers faced and potential opportunities in the acceptance of NAMs in chemical risk assessment, particularly for regulatory decision-making. The different regulatory needs for chemical risk assessments was noted early in the discussion. In some regulatory settings, there are specific required testing for decision-making, and the use of NAMs are simply not an option. Here, legislative changes may be needed.

Another significant barrier was the current practice of comparing NAM results to those from laboratory animal studies. It is improbable that NAMs will replace these laboratory animal studies at a one-to-one level, and this notion needs to be dispelled. Indeed, the use of animal tests themselves as the gold standard needs to be reconsidered, given the increasing body of evidence from epidemiological studies that question their predictiveness as well as their limited coverage of significant adverse health outcomes.

Another barrier is the lack of understanding and confidence in applying these NAMs, which requires increased engagement, coordination, and education for decision-makers and the public. More consistent and transparent characterization of NAMs when used will also increase confidence and ideally also increase their acceptance for use in a regulatory setting. A key opportunity for progress includes working together globally to increase data sharing, and do so through a shared data platform such as eChemPortal that can be accessed and updated from multiple sources. Improved access to data and data sharing is likely the most imperative first step to improving chemical risk assessments.

Finally, a number of other barriers to implementation exist, including moving data acquisition of NAMs from the research laboratory to commercial facilities that can be accessed by the regulated industry, obtaining more examples of small successes to build confidence, accelerating in vitro to vivo extrapolation of toxicokinetics to place NAM results in the proper perspective, achieving international agreement on NAM protocols, examining how NAMs can be used in classification of hazard (an important element of many regulatory programs), understanding the significance of negative results, demonstrating that qualitative risk assessments based on NAMs can have utility, and understanding the relative uncertainties and variabilities present in NAM and traditional toxicological studies.

To help inform future use of NAMs in regulatory decision-making, case studies like that described above for the EDSP program need to be used to evaluate how NAMs can and cannot be applied in specific decision contexts. A step in this direction came from this workshop through identification of collaborative case studies, focused on common areas of interest from the multinational group. Topics included how NAMs can be used in the area of exposure evaluation, assessing data poor chemicals, or specific chemical classes, and ecological assessment.

Case study proposals are being drafted, and will ultimately be conducted by multinational groups, including OECD, in the next year. These efforts will be an important step in increasing acceptance of these new alternative methods and tools, and increasing their use and acceptance in regulatory chemical risk assessment. In the U.S., the new TSCA authorization has given us the opening for re-thinking the traditional approach to chemical safety. It is time for us to think boldly, diligently and intelligently on what is needed to bring NAMs into the public health decision making toolbox.