EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

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An Era of Transformation

–by National Research Council staff

Phenomenal advances in tools and techniques to understand biological processes down to the molecular level are resulting in a deeper understanding of biology. At the forefront of this new understanding, is an increased appreciation for the interdependent connectivity of molecular processes and the complexity of biological systems. The new molecular approaches and resulting advances in biological knowledge have birthed a new field of science, systems biology.

Now that systems biology has arrived, what can we do with the knowledge it provides? Research scientists, doctors, and public health experts believe systems biology may revolutionize both medicine and public health practice. In terms of environmental health, systems biology has the potential to predict toxicological risks of chemicals in our environments and develop personalized medical

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Advancing Risk Assessment with Systems Biology

–by Kellyn Betts, edited by National Research Council staff

On June 14 and 15, 2012, the National Academy of Sciences Standing Committee on Use of Emerging Science for Environmental Health Decisions held a public meeting, System Biology-Informed Risk Assessment, to discuss how advances in molecular and cellular biology may revolutionize chemical risk assessment. These advances are resulting in a deeper understanding of biology that is prompting a new look at how biological data can augment, extend, or replace traditional data used in risk assessment. Meeting presenters highlighted how new systems biology approaches and thinking are generating new insights into the way chemical exposures may be affecting human health. For example, recent research suggests that testing with low levels of specific chemicals—in the range of everyday exposure - may have different outcomes from conventional tests of the same chemicals at high exposure levels. New techniques also promise to help scientists identify how individual biological differences may affect people's susceptibility to environmental stressors and thereby predict how environmental exposures are likely to affect the entire population.

Keynote speaker, Kim Boekelheide of Brown University, provided an overarching definition for systems biology. Systems biology is "an interconnected network of events predictive of emergent properties," said Boekelheide, which creates a new framework for thinking about what happens when the body is perturbed by an environmental

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This newsletter and additional information about the committee and its activities can be found at http://nas-sites.org/emergingscience/. The newsletter is prepared by National Research Council staff to keep you informed of activities of the Standing Committee on Emerging Science for Environmental Health Decisions. The views expressed in the newsletter are those of the meeting presenters and participants. The newsletter does not represent either formal consensus conclusions of the attendees or positions necessarily endorsed by the National Research Council.

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ADVANCING RA, *cont. from page 1*

exposure. Biological responses to chemical exposure are not a static—Boekelheide emphasized that the systemic biological response changes over the course of seconds, minutes, hours, and days. Cell receptors can be activated, which in turn can activate nuclear receptors. That triggers DNA transcripton that produces enzymes in one or more organs to break down the chemical that initiated the sequence. During the chemical's biotransformation, intermediary metabolites which are potentially harmful may be formed via a process known as metabolic activation. Each of the actions in this series influences the events that follow it, and considered together the interactions may be predictive of a physiological change. When these series of events lead to adverse health outcomes they are often called toxicity pathways.

Scientists' ability to detect these events transforms biology from a phenomenological science to a quantitative science, Boekelheide said. This shift is being driven by expanded understanding of the molecular processes underlying physiological changes, and the results support the vision outlined in the NRC's 2007 Toxicity Testing for the 21st Century report. Meeting speakers presented

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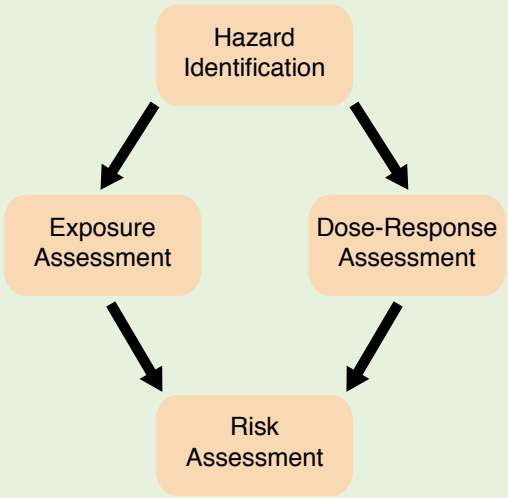
What is Risk Assessment?

Risk assessment is a process for characterizing the nature and magnitude of health risks to humans (e.g., residents, workers, recreational visitors) and ecological receptors (e.g., bird, fish, wildlife) from chemical contaminants and other stressors that may be present in the environment. Risk assessment involves four major steps:



1. ***Hazard Identification****—an examination of whether a stressor has the potential to cause harm to humans or ecological systems*
2. ***Dose-Response Assessment****—an examination of the numerical relationship between exposure and effects*
3. ***Exposure Assessment****—an examination of what is known about the frequency, timing, and levels of contact with a stressor*
4. ***Risk Characterization****—an examination of what is known about the frequency, timing, an levels of contact with a stressor*

TRANSFORMATION, *cont. from page 1*

interventions to individuals exposed to harmful chemicals. Systems biology may strengthen our chemical risk assessment practices, ultimately preventing common or widespread introduction of harmful chemicals into the environment. Systems biology may even enable chemical and material manufacturers to develop safer products. Although scientists are studying these possibilities, it remains to be seen what will come to fruition.

Systems biology is ushering in an era of transformation for research, medicine, and public policy. This newsletter provides a glimpse into some of the new science and thinking revolving around the application of systems biology to environmental health research and risk assessment. New knowledge is prompting scientists and risk assessors alike to look anew a how biological data can better inform risk assessment, but many questions are still yet to be answered. The shared hope is the integration of systems biology into environmental health will improve our ability to protect human health and the environment.

ADVANCING RA, *cont. from page 2*
examples showing that the new technologies are already providing important new information about the effects of exposure to relatively low levels of environmental chemicals. These levels are generally much lower than what scientists can evaluate using conventional toxicological testing with animals.

New Insights into Exposure

Systems biology is even producing new insights into the effects of exposure to chemicals that have been well-studied with the conventional techniques. For example, Robert Devlin of the US Environmental Protection Agency shared new results generated from his work on cell-based systems biology tests with ozone, an air pollutant that the agency has studied extensively for over three decades. The research shows that different toxicity pathways are activated in response to different concentrations of ozone exposure. His findings correlate with work conducted in humans and animals which documents that different effects, or apical endpoints, result from exposure to higher ozone concentrations than lower ones. "One of our take-home messages is that the [exposure] concentration really matters," Devlin said.

Justin Teeguarden of Pacific Northwest National Laboratory discussed his group's efforts to use a systems biology approach to investigate the mode of action underlying how vinyl acetate may cause olfactory and respiratory tumors. EPA's definition of a mode of action for carcinogenesis recognizes the potential for some chemicals to have a threshold below which they do not cause cancer. Teeguarden's work capitalizes on the availability of a massive amount of data on the chemical collected via conventional toxicology. Studies on rats have shown that exposure to high doses of vinyl acetate causes degeneration of the animals' respiratory and olfactory epithelium, followed by regenerative cell proliferation which leads to development of

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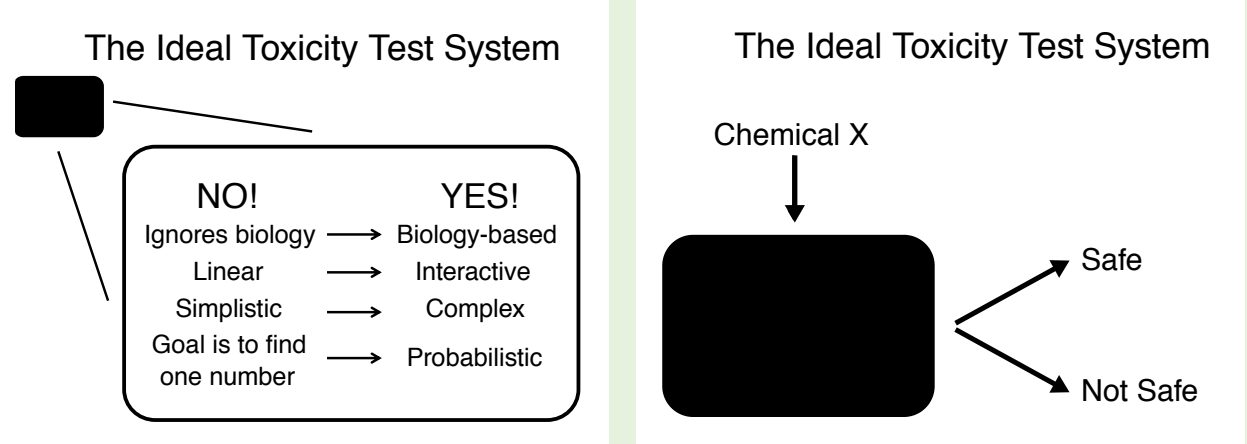
Envisioning the Ideal Toxicity Testing System



Boekelheide outlined his vision for an ideal toxicity testing system to support risk assessment. He described the current risk assessment methods, a step-by-step process that includes hazard identification, exposure assessment, dose-response assessment, as a simplistic approach that lacks biological basis and the flexibility to incorporate data produced from advancing or changing scientific approaches. A new testing paradigm, based in-part on systems biology, needs to be "interactive, pliable, and responsive". Boekelheide contends that with a better understanding of biological complexity, scientists will be able to develop more simplistic approaches for risk assessment.

ADVANCING RA, *cont. from page 3*
olfactory and respiratory tumors. Other research has identified some of the pathways through which vinyl acetate is metabolized and established that the compound is rapidly transformed into acetaldehyde in human blood and animal tissues.

Do Thresholds Exist?

Systems biology tools can already be used to support understanding of the doses associated with various biological transitions, such as levels of exposure associated with cellular stress, inflammation, cell proliferation, DNA damage, and apoptosis. Teeguarden said that in vitro tests with vinyl acetate have demonstrated clear evidence of a threshold. However, he acknowledged that it is unclear whether the evidence is sufficient to convince EPA that a threshold exists. Efforts to determine whether a specific chemical has a threshold dose or if exposure to any quantity has the potential to cause cancer can be controversial, said Teeguarden. Maurice Whelan, of the European Commission's Joint Research Centre, noted that a major debate is beginning to emerge regarding whether there is such a thing as a threshold. The debate focuses on our understanding of what happens in response to a perturbation, such as by a chemical, and how the cell's system of homeostasis can enable it to rebound from perturbations. Answering this question will aid in addressing important scientific issues such as endocrine disruption, Whelan said, noting his belief that system biology may provide a solid grounding to consider such issues.

A Changing Landscape in Risk Assessment

With the advances in systems biology, the landscape of risk assessment is also changing. As noted by John Balbus, senior advisor for public health for the National Institute of Environmental Health Sciences (NIEHS), the transformation of risk assessment has been "a long deliberate march." Risk assessment is shifting from a process that relies primarily on interpretation and extrapolation of rodent bioassays to a predictive process that takes advantage of the speed and high-throughput of both in vitro (molecular and cellular studies) approaches as well as in vivo approaches with lower-order organisms. Balbus emphasized that more modern biological and toxicological techniques have real potential for efforts "to create a better system of public health protection from chemical hazards." However, to move forward, Balbus stressed that we need to align scientific research with public health practice.

The shift to incorporate more detailed biological information based upon systems biology research into risk assessment comes with a cultural challenge for practicing scientists. Ila Cote, director of NexGen program at the United States Environmental Protection Agency (EPA), told attendees that when she was first offered the opportunity to research how molecular biology could inform risk assessment she was reluctant because she believed it was "way too early." However, once Cote started reading the literature, she found that "the world of biology had changed dramatically."

Cote pointed out that incorporating systems biology into the risk assessment process will require re-education of the existing risk assessment community and an infrastructure that supports collaborations between senior scientists and younger, well trained scientists " to infuse the risk assessment community" with new knowledge. Dr. Cote told meeting attendees that she believes that the next generation of scientists is well-positioned to adapt to the new approaches, which she predicts will also be informed by personalized medicine as it develops. She encouraged meeting participants to engage in proactive and collaborative endeavors to merge systems biology, clinical knowledge, and existing toxicological expertise. Cote is convinced, "the time to begin to incorporate these new insights into risk assessment is now."

Metabolomics: Re-shaping Risk Assessment?

–by Kellyn Betts, edited by National Research Council staff

Dean Jones of Emory University described a completely different approach to identifying environmental risk factors based on metabolomics. Metabolomics, the systematic study of cellular metabolites (small-molecules), employs advanced biochemical tools to identify and quantify metabolites that are produced when cells break down chemicals. Cellular metabolism produces energy and materials needed for growth and reproduction as well as removes toxic substances. Metabolomics is a key technology for systems biology, and scientists from a variety of disciplines have used such techniques to discover previously unsuspected risks for major diseases, including cardiovascular disease and colon cancer. Jones contended that metabolomics has the potential to overcome many of the problems associated with the current approach to risk assessment, including identifying exposures.

Through metabolomics, researchers can collect information that reflects an individual's diet, microbiome (the collection of microbes that live in the gut and other areas of the body), and environmental exposures—all of which can impact people's susceptibility to disease. The technologies for detecting metabolites have improved dramatically since the first diagnostic test was created in 1957. Metabolomics generally uses gas or liquid chromatography coupled to mass spectrometry equipment to identify small-molecular-weight metabolites in biological samples such as blood or urine. Many of the unprecedented improvements over the past few years have resulted from a NIEHS grant to increase the number of metabolites that could be measured. As a result technology advances have enabled detection to increase from around 300 metabolites in 2007 to 1,500 by 2013.

The initial goal was met by 2009, thanks mainly to technology improvements in the mass spectrometry equipment. Additional technology enhancements now permit the measurement of over 45,000 ions in a single, 10 minute assay; with some of the most sophisticated equipment, the number jumps to 95,000 ions. Ions aren't exactly equivalent to metabolites; they are individual isolated chemicals in ion form and there's some redundancy. Jones said that his metabolite measurements are done in triplicate to produce very precise results and ensure reproducibility.

Jones predicted that, in time, the approach could prove useful for defining the risks of exposure and collecting specific information on biological pathways that are impacted. Based on the data collected thus far, Jones' group has identified metabolites in 146 pathways. By identifying the pathways perturbed by a chemical exposure, the technology can aid in understanding mechanisms of toxicity, he said.

Metabolomics research using human samples has the possibility to turn risk assessment upside down, Jones contended. Rather than making presumptions regarding what chemicals are causing risk, as the current approach to assessing risk requires, metabolomics enables researchers to investigate which chemicals are associated with risk. Because the associations do not prove anything by themselves, researchers must follow up by mechanistically testing the resulting hypotheses. "From the standpoint of discovery, it can tell us in the human population, which chemicals are actually associated with whatever risk factor you want to look at," Jones said. In addition, work published earlier this year by one of Jones' colleagues points to significant differences

> ***It's not a stretch of the imagination that we could incorporate this into human health care....into annual physical exams.***
>
> **—Dean Jones**

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Linking Chemistry and Systems Biology

Chihae Yang of Altamira LLC discussed how chemical inherency can aid in the interpretation of the vast amount of data arising from systems biology**.** Chemical inherency combines insights that chemists can glean from a chemical's intrinsic properties, such as its structure and physical and chemical properties, with information about chemical interactions including chemical reactivity and metabolic potential. The concept also incorporates insights from biology, including predictions made by Quantitative Structural Activity Relationship (QSAR) models and exposure data.

Using data from the National Toxicology Program's Toxcast program, the National Institutes of Health's Chemical Genomics Center (NCGC), and the EPA's High Production Volume (HPV) programs, Yang and her colleagues assembled a database of more than 8,200 compounds. It includes pharmaceuticals, biocides, food chemicals, cosmetics, and general and industrial chemicals with a diverse array of structures. Yang's group used the database's wide range of chemical structures, target interactions, pathways, and modes of action (MoA) to create what she termed a structural fragment library.

The researchers used principal component analysis to group the compounds into clusters based on different features and look for possible correlations. For example, they evaluated links between toxicity endpoints and the physical and chemical properties of the structural fragments in the database.

The chemistry and the biology both have their own pathways, and they meet in the cell, Yang explained. Yang's group combined data on biological pathways known to be associated with the developmental effects with data on chemical classes linked to disruptions in key biological events that lead to birth defects. The group evaluated biological data linked to the malformation of the cleft palate with data on chemical classes can affect closure of the palate using a weight-of-evidence approach. This singled out groups of chemicals likely to be associated with cleft palates, including retinoids, conjugated dienes, dioxolanes, and triazoles.

Yang said that she and her colleagues are using the same approach to analyze links to other developmental defects associated with the eye, kidneys, and the urinary tract. Yang concluded by suggesting that the features of the approach, such as its transparent rationale and use of a quantitative weight of evidence assessment, may make its results appealing to regulators—in other words, chemical inherency may propel systems biology data into regulatory acceptance.

METABOLOMICS, *continued from page 5*

between how humans and seven different mammalian laboratory species metabolize environmental compounds. This highlights the problems associated with trying to extrapolate across the species that are required for conventional toxicology testing, said Jones. Biomonitoring with metabolomics also has the potential to help scientists evaluate the combined effects of the mixtures of chemicals that people are exposed to, he added.

The pace of recent advances in metabolomics and the relatively reasonable cost of analysis have convinced Jones that the technology sets the stage for universal biomonitoring. The technology has the potential to cost-effectively biomonitor 500,000 agents simultaneously, and it can be used to determine the concentration of exogenous substances in test samples, he said. Jones envisions a future when samples are collected regularly during annual physicals and compared with earlier samples in support of personalized risk assessment. Jones says he believes that the necessary steps to use metabolomics could be completed relatively quickly, perhaps within five years.

The Next Generation of Risk Assessment

–by Kellyn Betts, edited by National Research Council staff

Ila Cote discussed EPA's efforts to explore new science and methods that are ripe for incorporation into risk assessment through the NexGen program (http://www.epa.gov/risk/nexgen/). NexGen, which stands for next generation, aims to create a more scientifically robust system for chemical risk assessment that is less expensive and faster than current approaches. The idea is to replace risk assessment defaults and assumptions with systems biology-derived data, Cote said.

Cote highlighted a key piece of advice from the NRC's 2009 *Science and Decisions* report that chemical risk assessment should target the risk management problem that the risk assessment is meant to address. With that in mind, her group is choosing prototype risk assessments for which there exists systems biology data as well as animal toxicology, human exposure, and other data traditionally used to calculate risk. The scientists then try to "reverse engineer" between systems biology and the more traditional data sets in order to determine what kinds of new approaches are needed to generate credible answers. "Without [such] proof-of-concept examples, the wider risk assessment and risk management community will be leery of proceeding," she said.

The agency has made "tremendous progress" in developing assays and applications for tier 1 screening to indicate whether chemicals are likely to cause health effects, Cote told attendees. The work to date makes clear that not all data are created equal. "We are looking for molecular patterns of events that we think will cause a chemical to be more likely to cause an effect," Cote said. The life stage of the organism and type of tissue and species used for such testing can make a big difference in the outcomes, she stressed. Cote added that EPA is also focused on identifying adverse outcome pathways that are indicative of a population-level response and incorporating population variability by building a framework for

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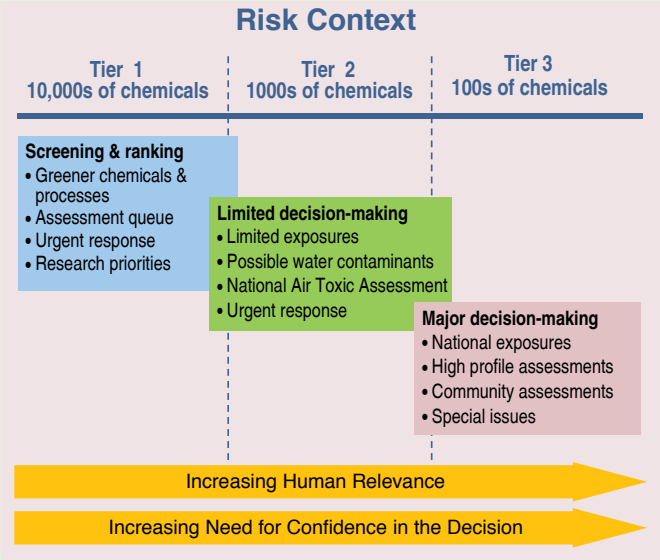
Chemical Tiers: Matching Toxicity Tests to Risk Context

Cote noted that the types of environmental problems that EPA is able to address with toxicity testing are largely driven by the number of chemicals the agency has to deal with. She outlined three chemical tiers and explained how her NexGen group matches the data that can be brought to bear based on the chemical tier. Cote emphasized that high throughput testing makes the most sense for the tens of thousands of tier 1 chemicals that have yet to be analyzed. To evaluate the thousands of tier 2 chemicals, such as possible water and air contaminants which require what she termed "limited decision-making," researchers may have the opportunity to bring in data that takes a bit more time to collect and analyze but may be slightly more robust. Only the high-profile tier 3 chemicals associated with nationwide exposure can be tested via the most realistic scenarios (human relevance).



NEXT GENERATION, *continued from page 7*

collecting population data. By conducting tandem assessments with molecular biology and traditional data, EPA is identifying pathway and network patterns that are useful in hazard identification and potency estimation.

The work has made clear that understanding 'disease fingerprints' is important, Cote stressed. This involves recognizing patterns of responses associated with specific diseases, from a systems biology perspective, together with the supporting proof of concept.

SCIENTIFICALLY SPEAKING

Ila Cote is the former director of EPA's National Center for Environmental Assessment–Research Triangle Park Division, and science advisor to EPA senior management. Her expertise is in public health and environmental risk assessment, and the interface of science and public policy. She shared her views on emerging science, environmental health, and systems-based risk assessment.

Q. Why is it important to study systems-based risk assessment?

A. It's clear that at least some systems biology-level understanding is required for the best interpretation and integration of data to support risk assessment. The greater that understanding, the greater the confidence one can have in the data interpretations—and in the risk management decisions those data support.

Q. What did you find most valuable about this Emerging Science meeting?

A. It is very difficult—almost impossible—to keep up with all the emerging information relevant to environmental decision-making. To have leaders in various disciplines come together to present the state-of-the-science in their field is invaluable, in terms of advancing science. This, I think, is one of the greatest contributions of the Emerging Science Workshops. One example from the Systems Biology-Informed Risk Assessment workshop was Dean Jones' work on predictive metabolomics. I do not follow metabolomic research closely and I was unfamiliar with his work. Jones' presentation changed how I envision metabolomics to be incorporated into risk assessments.

Q. Did the meeting help spur any other research or programs?

A. The workshop drew together a group of individuals that may not routinely interact but have overlapping interests, thus providing invaluable opportunities for "catching up" and potentially developing collaborations. I am aware of a number of important activities that evolved from informal discussions at the workshops.

Q. How as the field progressed since the 2012 meeting?

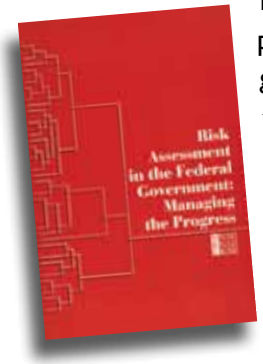
A. Parallel to the Emerging Science workshops EPA was leading a multi-organization effort to characterize new systems biology-informed risk assessment approaches (12 US and European governmental agencies and 12 universities and several private sector organizations). The report was finalized Sept 2014. The thinking expressed in the report was substantially informed by all of the workshops. This report will inform how toxicity testing and risk assessment are conducted within the federal government, and will inform research in general. In particular these new approaches will enable evaluation of data-limited or no traditional data chemicals that are now not evaluated in terms of potential public health risks.

Q. Where do you predict research will head from this point forward?

A. There will continue to be an increasing focus on systems biology-level understanding, including integrating human disease information, animal and in vitro based data. As personalized medicine databases continue to evolve, this will also provide additional useful information.

Historical Perspectives on Risk Assessment

Lauren Zeise of the California Environmental Protection Agency (CalEPA) outlined the history of risk assessment. During the first decade of the federal EPA's existence, both the National Toxicology Program and the National Cancer Institute collected a great deal of information about the effects of exposure to chemicals, said Zeise. However there was no agreement how to interpret what that data meant. In 1983, the debates were ameliorated by the publication of National Research Council's *Risk Assessment in the Federal Government: Managing the Process,* widely known as the "Red Book."

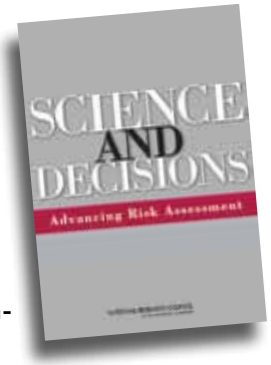


The Red Book provided guidelines for thinking about risk management in an organized fashion. In addition to defining hazard identification, dose-response assessment, and exposure assessments, the book introduced the concept of "inference guidelines" for inferring human risk "from data not fully adequate or not drawn from human experience" to make toxicity decisions. The book's authors recommended that these inference guidelines could be used for indirect evidence such as mutagenicity and structure-activity data.

Zeise explained that the inference guidelines influenced the subsequent creation of the agency's guidelines for evaluating carcinogenicity, neurotoxicity, and reproductive toxicity. Notably, the EPA's 2005 Guidelines for Carcinogen Risk Assessment discussed precursor biological effects, rather than focusing solely on the empirically verifiable outcomes of exposure known as apical endpoints, such as developmental anomalies, breeding behaviors, impaired reproduction, physical changes and alterations in the size and histopathology of organs, and death.

In 2007, the NRC's publication of its landmark *Toxicity Testing for the 21st Century: a Vision and a Strategy* report proposed shifting from a focus on apical end points to *toxicity pathways* as the basis for risk assessment. The report also discussed the value of targeted testing, such as the tests to evaluate which human metabolites are associated with different diseases and environmental exposures.

Next, NRC's 2009 publication *Science and Decisions: Advancing Risk Assessment* emphasized the value of making a greater effort at the problem formulation stage. Widely known as the "Silver Book," the 2009 report provided a methodology for conducting cumulative risk assessment which is important for exposures to chemicals with a common outcome, such as the effect of multiple phthalates on androgen receptor activity. The Silver Book also aims to move away from the current situation where "no traditional test data = no risk" by recommending ways to use probabilistic data for screening, said Zeise.



Access to recorded video and PDF presentations from Emerging Science meetings is available through our website:

http://nas-sites.org/emergingscience/

Moving Forward in Risk Assessment

–by Kellyn Betts, edited by National Research Council staff

Meeting participants shared many ideas for how to move risk assessment even father forward. Integrating insights gleaned through systems biology approaches with data from conventional toxicological assessments has already brought to light cases where scientists were surprised to discover new modes of action for well-studied chemicals, pointed out Lauren Zeise of the California Environmental Protection Agency. She thinks that integrating systems biology tools with tier 3 assessments could provide useful data on human variability and susceptibility. Similarly, the new tools could supplement tier 1 or earlier screening assessments by either confirming what the conventional tools show about mode of action or suggesting that the picture may be a bit more complicated. She also noted that data from the tools could build on the understanding of chemical structure that is propelling green chemists to design chemicals which are inherently safe and non-toxic.

Filling in Gaps

Both Richard Denison of the Environmental Defense Fund and Joyce Tsuji, principal scientist at Exponent, Inc., a scientific and engineering consulting firm, agreed that using systems biology-based assays to evaluate the effects of exposure to low doses of well-known chemicals could be a good way to establish their utility. Denison suggested focusing on well-studied chemicals, where the primary mode of action is known, to see what might have been missed. He pointed out that knowledge is continually changing and some studies may have been conducted at a point in time and under a set of assumptions or inferences that could benefit from being examined more thoroughly. The new evaluations might determine that there are additional types of endpoints that were missed because of the nature of the dosing, or in some cases scientists may detect effects not seen in the original studies.

A near-term activity which could help build support for developing some of these tools, Denison said, would be to show how well the assays that incorporate systems biology, such as the ones used in Toxcast, can help fill in data gaps identified by Derek Knight of the European Chemicals Agency. The U.S. High Production Volume program has charts documenting similar data gaps. The idea would be to identify cases where assays can produce data to either support or raise questions about gaps in categories that are based largely on structure or in some cases system properties. "It seems to me that would be very valuable and would help to bolster confidence in the read-across that we are doing in a lot of these programs," he said.

Tsuji agreed, noting that for many of the categories there are "several chemicals that you know a lot about and then you have a whole bunch of them you know nothing about." The effort might show whether the individual chemicals act by similar mechanisms and whether the methods can distinguish differences in toxicity.

To address the reality that people are actually exposed to a multitude of chemicals throughout their lives, Cote said that EPA's NexGen group hopes to eventually develop a fingerprint that is common to multiple chemicals and to get a better sense of mixtures that should be considered as a group. Boekelheide pointed out that a mechanistic approach is also possible by investigating which pathways are stimulated by given individual chemicals and then

> ***Experience is important and cumulative. This will take time, patience, and accepting wrong turns.***
>
> **—Kim Boekelheide**

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looking at combinations and developing a science around the combined exposures. He said he is convinced that this is a viable option with the kinds of systems biology approaches being discussed at the conference.

Collecting the Data

Zeise suggested that it could be a good idea to begin cataloging what we think we know about different toxicological processes. Greg Paoli of Risk Sciences International agreed. He argued that if an agency such as EPA created a space for collecting this data, we would more quickly be able to identify mechanisms of toxicity. Paoli also said that constructing testable hypotheses, perhaps in silico, "will start to bridge the gap between our biotechnology data streams at a very fundamental level of biological organization" and our desire to "understand and prevent disease states." He said that work is going on in many places to try and create those kinds of model simulations and hypotheses.

> ***One of the things that is holding us back at this point is we really don't have any sort of systematic understanding of what the universe of mechanisms for action for toxicity looks like.***
>
> **—Greg Paoli**

John Quackenbush of the Harvard School of Public Health commented that he is excited by the prospect of moving beyond the reductionist approach that has characterized conventional toxicology to really begin thinking about how complex systems work. Rather than being constrained by the need to limit the number of variables that can be considered simultaneously, he stressed that the new technologies enable researchers to begin "putting the pieces together."

Despite the challenges, moving forward is important because our conventional approach to risk assessment basically ignores the mode of action, Tsuji said. It is unclear whether systems biology will inform the existing risk assessment process or whether information gleaned from systems biology research could turn the current risk-assessment paradigm on its head. Either way, Cote accentuated that "change is going to happen." She said that she is convinced that the various disciplines represented at the meeting "can bring a lot to the table," and she exhorted everyone at the conference to play a role in ushering in the new era.

MEETING INFORMATION

Meeting Presentations

Would you like more details about advancing risk assessment or other Emerging Science for Environmental Health meeting topics? Descriptions, agendas, presentations, and newsletters for our meeting topics are available through our Web site. We invite you to subscribe to our Listserv for the latest information about upcoming meetings, available newsletters, and other Emerging Science for Environmental Health activities. For more information, visit:

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Do you have an idea for a meeting topic? We would love to hear it. Please send us an email with your suggestion at eseh@nas.edu.

Previous Meetings

Biological Factors that Underlie Individual Susceptibility to Environmental Stressors — April 18–19, 2012

Emerging Technologies for Measuring Individual Exposomes — December 8–9, 2011

Applying 21st Century Toxicology to Green Chemical and Material Design — September 20–21, 2011

Mixtures and Cumulative Risk Assessment: New Approaches Using the Latest Science and Thinking about Pathways — July 27–28, 2011

Interplay of the Microbiome, Environmental Stressors, and Human Health — April 27–28, 2011

The Use of In Utero and Post-natal Indicators to Predict Health Outcomes Later in Life — October 14–15, 2010

Stem Cell Models for Environmental Health — June 3–4, 2010

The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease — February 25–26, 2010

Computational Toxicology: From Data to Analyses to Applications — September 21–22, 2009

Use of Emerging Science and Technologies to Explore Epigenetic Mechanisms Underlying the Developmental Basis for Disease — July 30–31, 2009

About the Committee

At the request of the National Institute of Environmental Health Sciences, the National Academies forms the Standing Committee on Use of Emerging Science for Environmental Health Decisions to facilitate communication among government agencies, industry, environmental groups, and the academic community about scientific advances that may be used in the identification, quantification, and control of environmental impacts on human health.

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