UPDATE
National Toxicology Program
U.S. Department of Health and Human Services

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Headquartered at the National Institute of Environmental Health Sciences • NIH-HHS

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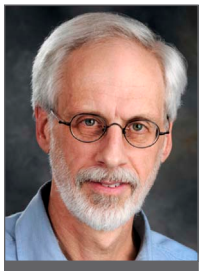
Implementing Systematic Review at the National Toxicology Program: Status and Next Steps

By Linda S. Birnbaum, Kristina A. Thayer, John R. Bucher, Mary S. Wolfe, reprinted from *Environmental Health Perspectives*, 121:a108-a109 (2013), online April 2013

Linda S. Birnbaum

Kristina A. Thayer


John R. Bucher

Mary S. Wolfe

The National Toxicology Program (NTP), an interagency program headquartered at the National Institute of Environmental Health Sciences (NIEHS), carries out a broad range of toxicology research and testing and serves as a resource for identification of substances in our environment that are hazards for human health. One of the ways that the NTP identifies hazards is through carrying out literature-based health assessments. Approximately 2 years ago we began exploring systematic-review methodology as a means to enhance transparency and increase efficiency in summarizing and synthesizing findings from studies in our literature-based health assessments. A systematic review uses an explicit, prespecified approach to identify, select, assess, and appraise the data from studies that focus on addressing a specific scientific question (Institute of Medicine 2011). Although traditionally used to grade the quality of evidence and strength of scientific support for recommendations for clinical practice guidelines and healthcare interventions [Agency for Healthcare Research and Quality (AHRQ) 2012; Guyatt et al. 2011; Higgins and Green 2011], we — and others — were interested in how systematic review methodology might be applied to environmental health questions (Agency for Toxic Substances and Disease Registry 2012; National Research Council 2011; Silbergeld and Scherer 2013; U.S. Environmental Protection Agency 2013; Woodruff and Sutton 2011).

With the establishment of the Office of Health Assessment and Translation (OHAT) in 2011, the NIEHS launched a new problem-solving resource for the NTP, particularly with respect to identification of noncancer hazards in our environment (Bucher et al. 2011). OHAT took the lead in investigating how systematic review methodology might be used by the NTP. We embraced systematic review methodology as a useful approach for providing thorough documentation of the steps, inputs, and decisions in a literature-based evaluation. However, we also recognized the necessity to extend existing systematic review methods to accommodate our need in environmental health to integrate data from multiple evidence streams (human, animal, *in vitro*) and focus on observational human studies rather than on the randomized clinical trials more commonly encountered in the field of health-care intervention (NTP 2012a, 2012b).

In late February 2013, the NTP released the Draft OHAT *Approach for Systematic Review and Evidence Integration for Literature-based Health Assessments – February 2013* [Draft OHAT Approach; Department of Health and Human Services (DHHS) 2013] for public comment; the deadline for receipt of comments is 11 June 2013. The Draft OHAT Approach adopts or adapts guidance from authoritative systematic review groups (AHRQ 2012; Guyatt et al. 2011; Higgins and Green 2011) to handle the breadth of data from human, animal, *in vitro*, and mechanistic studies relevant for

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addressing environmental health questions. In developing a draft approach, OHAT sought advice on systematic review through educational webinars and consultation with technical experts, the NTP Executive Committee, a working group of the NTP Board of Scientific Counselors, the NTP Board of Scientific Counselors, and the public. The draft approach involves a seven-step framework for incorporating systematic review methodology into OHAT literature-based health assessments. In early April of 2013, OHAT will release protocols for two case studies to illustrate application of this framework in specific evaluations. We will test our approach in these case studies to help determine whether additional refinement or revision to the Draft OHAT Approach might be needed. To help the public understand the draft approach and protocols, the NTP will hold a web-based informational meeting on 23 April 2013 to provide an overview of the framework, describe the contents of the case-study protocols, and respond to questions (DHHS 2013). Our intent is to carefully consider all public comments received on the draft approach and to present the Draft OHAT Approach to the NTP Board of Scientific Counselors at its meeting on 25–26 June 2013, with discussion by the NTP of any plans to update the document on the basis of the public's input. Moving forward, our goal is to increase efficiency and provide greater transparency to the rigorous and objective approach that has been the hallmark of OHAT literature-based health assessments.

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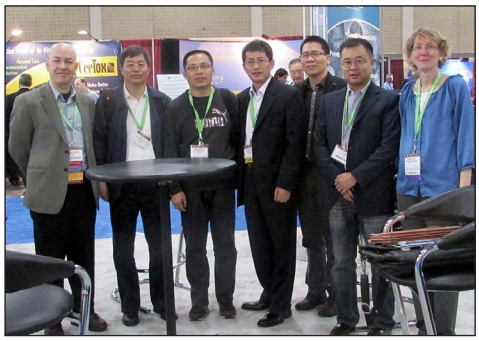
Smaller presence at SOT, but big enthusiasm for science

By Robin Mackar, reprinted from *eFACTOR*, April 2013



Nigel Walker, Ph.D. , NTP deputy division director for science, left, and Mary Wolfe, Ph.D., NTP deputy division director for policy, right, set time aside to talk to a delegation from China about NTP key activities and how NTP is organized. (Photo courtesy of Denise Lasko)

Although the NIEHS and NTP presence at this year's Society of Toxicology (SOT) annual meeting March 10-14 was much smaller than usual due to budget concerns, enthusiasm for science was still in abundance.

San Antonio was the place to be for those who wanted to hear the latest toxicology findings, learn about funding and training opportunities, and personally meet some of the NIEHS and NTP staff attending and participating in the meeting.

Before the official meeting even kicked off, staff members were busy serving on committees planning for next year's conference, setting up posters and exhibits, and teaching continuing education courses.

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Upcoming Events

April 23, 2013
12:00–4:00 p.m. EDT

Web-based Informational Meeting:

Overview of the Draft OHAT Approach
February 2013

June 25, 2013

NTP Board of Scientific Counselors

Rodbell Auditorium
National Institute of
Environmental Health Sciences (NIEHS)
111 TW Alexander Drive
Research Triangle Park, NC 27709

October 29, 2013

NTP Technical Reports Peer Review Panel

Rodbell Auditorium
National Institute of
Environmental Health Sciences (NIEHS)
111 TW Alexander Drive
Research Triangle Park, NC 27709

September 24 - 25, 2013

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

Rodbell Auditorium
National Institute of
Environmental Health Sciences (NIEHS)
111 TW Alexander Drive
Research Triangle Park, NC 27709

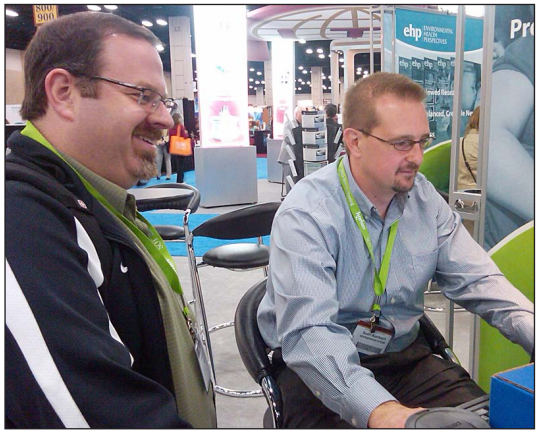
December 18 - 19, 2013

NTP Board of Scientific Counselors

Rodbell Auditorium
National Institute of
Environmental Health Sciences (NIEHS)
111 TW Alexander Drive
Research Triangle Park, NC 27709

http://ntp.niehs.nih.gov/go/calendar

Abee Boyles, Ph.D., center, demonstrated some of the Web-based tools that the NTP Office of Health Assessment and Translation (OHAT) has brought forward for systematic review. Boyles and Andrew Rooney, Ph.D., also of OHAT, presented the tools and concepts of systematic review, at a well-attended exhibitor-hosted session on March 12. (Photo courtesy of Robin Mackar)



Scott Auerbach, Ph.D. , right, of the NTP Biomolecular Screening Branch, gave hands-on demonstrations of the DrugMatrix® database and ToxFX® reporting system, at the exhibit space. (Photo courtesy of Robin Mackar)

Funding issues

At the Meet the Director symposium on March 11, Linda Birnbaum, Ph.D., director of both the NIEHS and NTP, updated SOT attendees on the current federal budget scenario, which she acknowledges is something that has been changing on an almost daily basis.

Birnbaum talked about steps being taken at NIH to prepare for the sequestration. "As of March 1, the federal government is operating under a sequestration, which means a 5 percent cut for NIH," Birnbaum said. She discussed how the payline for grants at NIEHS would likely have to drop, resulting in fewer new grants being funded. Birnbaum encouraged attendees to continue their conversations with NIEHS program staff to keep abreast of available funding announcements and opportunities.

Birnbaum also used her time to update attendees on happenings at the Institute, including progress toward developing cross-cutting implementation plans to help NIEHS reach its overall strategic goals.

Resource room

One of the most popular spots for new investigators, as well as long-standing grantees, was the centrally located NIH resource room.

"The funding room was always busy," said Annette Kirshner, Ph.D., program administrator in the NIEHS Cellular, Organ, and Systems Pathobiology Branch of the Division of Extramural Research and Training (DERT). Kirshner and others in DERT, including Janice Allen, Ph.D., from the Scientific Review Branch, worked with SOT to host the room and a brown bag luncheon, so new investigators could become familiar with the NIH peer review grant process. DERT staffed the room for two days, providing one-on-one consultation time with researchers who had questions about NIH funding and training opportunities.

Another popular session was the symposium chaired by Paul Foster, Ph.D., of NTP, and Earl Gray, Ph.D., of the U.S. Environmental Protection Agency. It was standing room only for the "Nonmonotonic Dose-Response Curves and Endocrine-Disrupting Chemicals: Fact or Falderal?" session, which also featured Birnbaum. ●

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

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First two substances peer reviewed for listing in new Report on Carcinogens

A panel of experts concurred with the National Toxicology Program's preliminary decision to list 1-bromopropane and cumene as reasonably anticipated human carcinogens, based on sufficient laboratory animal data.

These are the first two chemicals to be peer reviewed as part of a new process for evaluating substances for the 13th Report on Carcinogens (RoC).

In an open meeting that was also webcast, the panel, which met March 21-22, was charged with reviewing the draft documents, referred to as monographs, and voting on whether the scientific evidence presented supports the NTP's listing decisions. The RoC can list substances in one of two categories — known to be human carcinogens or reasonably anticipated to be human carcinogens.

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Lunn provided an overview of the RoC process at the peer review panel meeting. (Photo courtesy of Steve McCaw)

Consultant Stephen Nesnow, Ph.D., right, an organic chemist by training, and a well-known expert on chemical carcinogenesis, offered many thoughtful comments on both the cumene and 1-bromopropane draft monographs. Nesnow was seated next to Bucher. (Photo courtesy of Steve McCaw)

Lunn, left, and Jahnke responded to questions from the panel about the cumene literature. Spencer joined Lunn the next day to present on 1-bromopropane. (Photo courtesy of Steve McCaw)

Each RoC monograph is comprised of a cancer evaluation component, which lays out all the information used to make a listing decision, and a substance profile, containing both the NTP's listing recommendation and a summary of the scientific information considered key to reaching that recommendation. The development of the draft monograph is one of the newer additions to the RoC evaluation process.

"We wanted to create a document that clearly illustrates how we came to our conclusions about listing a substance," said NTP Associate Director John Bucher, Ph.D.

The panel appeared to like the draft monographs. "This is about the third time I've served on a peer review committee for the NTP, and I must say you really hit your target in the way you are developing your documents and getting public input," said panel member Wayne Sanderson, Ph.D., of the University of Kentucky.

Cumene

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens (RoC), outlined the process for developing the documents. Next, Mary Wolfe, Ph.D., director of the NTP Office of Liaison Policy and Review, identified scientific issues in the written public comments on the substance, and asked the panel to carefully consider the public comments.

NTP health scientist Gloria Jahnke, D.V.M, gave the presentation on cumene. Cumene is a colorless liquid, primarily used to make other chemicals, including acetone and phenol. It is also found in fossil fuels, such as blended high octane gasoline and kerosene.

The panel spent time discussing whether or not a significant number of persons in the United States were exposed to cumene. Chair Lucy Anderson, Ph.D., summed up the panel conversations by saying the committee thinks that the occupational and environmental exposure data presented qualifies as significant.

The panel voted to concur with NTP to list cumene as a reasonably anticipated human carcinogen. The panel's conclusions were based on tumors found in lung and liver, but, since there was not consensus about the renal tumors, the panel decided to recommend adding renal tumors as supporting evidence for the listing.

1-Bromopropane

NTP health scientist Diane Spencer walked the panel through the science of 1-bromopropane, which is a solvent used as a cleaner to degrease electronics and metals, and may be used in some dry cleaning operations. The panel agreed that the chemical is significant to public health.

Because there were no human studies to consider, Spencer presented the animal data showing the substance caused skin tumors in male rats, large intestine tumors in male and female rats, and lung tumors in female mice.

Reviewer Terry Gordon, Ph.D., of the New York University Langone Medical Center, agreed with the data presented, saying he felt the rodent data were biologically relevant to humans, but remained puzzled by the different gender effects.

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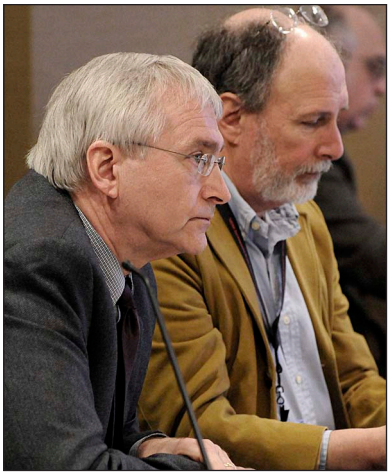

Peer reviewer Michael Elwell, D.V.M., Ph.D., left, from Covance Laboratories Inc., and Gordon provided comments on the draft documents. (Photo courtesy of Steve McCaw)

Although there were few mechanistic data available, the panel generally agreed with NTP conclusions on the genotoxicity data. They felt the overall evaluation was an effective synthesis of integrating the metabolic, genotoxic, and mechanistic data with the carcinogenicity results.

The panel also discussed the role that immunosuppression may play in tumor development in animals. "Immunosuppression needs to be mentioned and emphasized more in the document," said Paul White, Ph.D., of Health Canada, with concurrence from MaryJane Selgrade, Ph.D., of ICF International.

The panel unanimously voted to list 1-bromopropane as reasonably anticipated to be a human carcinogen, based on the animal studies presented by NTP.

The documents will be revised based on comments, placed on the public website, and shared at a public meeting with the NTP Board of Scientific Counselors. ●

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

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NTP postdoc wins top award at SOT

By Robin Mackar and Martha Lindauer, reprinted from *eFACTOR*, March 2013

Award-winning postdoctoral researcher Xu. (Photo courtesy of Steve McCaw)

Yuanyuan (Laura) Xu, Ph.D., of the National Toxicology Program (NTP) Laboratory, will be honored with the Best Postdoctoral Publication Award as part of the Society of Toxicology (SOT) Annual Meeting March 10-14 in San Antonio. Xu, a third-year postdoctoral fellow in the NTP Inorganic Toxicology Group, led by Michael Waalkes, Ph.D., is being recognized for her work related to arsenic, stem cells, and cancer.

The award is for the paper "Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype," (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3385457/) which appeared in Environmental Health Perspectives last summer (see story) and was selected as an NTP paper of the year (see summary). Publications competing for this award are judged on the basis of scientific innovation, impact of the research on toxicological sciences, and the scientific impact of the publishing journal, among other factors.

Xu's paper was considered to contain seminal scientific findings on how arsenic-transformed malignant human prostate epithelial cells impact neighboring human prostate normal stem cells (NSCs), via a transwell co-culture system (see text box).

This transwell system prevented physical contact between the malignant epithelial cells and NSCs, but did allow them to share secreted factors. The results indicate that arsenic-transformed malignant epithelial cells could drive the nearby, but noncontiguous, NSCs into a cancer phenotype, in effect creating cancer stem cells (CSCs) without any actual physical contact.

"This work is a highly significant step forward in our quest for mechanisms in arsenic carcinogenesis," said Waalkes, who serves as Xu's mentor. "Throughout the work, Dr. Xu employed clever design, elegant experimentation, and outstanding interpretation of data to produce this article. Her work represents a major advance in defining the role of stem cells during arsenic carcinogenesis."

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Xu won a first place Stem Cells Specialty Section Excellence in Research Award in the postdoctoral category at SOT last year. She also won first place for her research at the North Carolina SOT fall meeting in 2010 (see story) and was just elected the group's 2013 postdoctoral representative.

Uncovering a mechanism involved in tumor initiation

Xu found that with arsenic-transformed malignant epithelial cells, CSC recruitment appears to occur by malignant cells sending out tumor microenvironmental factors, potentially including interleukin-6, which alone converted NSCs into CSC-like cells and duplicated most responses induced by malignant epithelial cell co-culture.

This recruitment of NSCs into CSCs by arsenic-transformed malignant epithelial cells potentially constitutes a new phenomenon in tumor growth, invasion, dissemination, or field cancerization.

CSCs are thought to be the source of new malignant cells that allow tumors to grow and spread, and they may well be integral to tumor initiation, progression, and metastasis. Inorganic arsenic is a known human carcinogen, but the precise mechanisms are unknown.

The recruitment of NSCs into CSCs by arsenic-transformed malignant epithelial cells may be a key mechanism in arsenic-induced CSC overabundance previously seen in multiple *in vivo* and *in vitro* model systems

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor. SOT Communications/Media Manager Martha Lindauer wrote the SOT press release on Xu's award.)

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NTP hosts review of endocrine disruptor screening

By Eddy Ball, reprinted from *eFACTOR*, April 2013

Dixon introduced Bucher, who was the first speaker at the meeting. Dixon was a member of the meeting organizing committee and co-leader of the Female Reproductive Assay Breakout Group. (Photo courtesy of Steve McCaw)

To help advance the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program (EDSP), NTP and NIEHS hosted a Society of Toxicologic Pathology (STP) regional working meeting March 21 on pathology endpoints. The meeting attracted some 75 attendees, including NTP scientists Darlene Dixon, D.V.M., Ph.D., and Paul Foster, Ph.D., who participated in breakout sessions, following presentations by representatives of regulatory agencies, sponsors, and contract research organizations currently involved in these studies.

The attendees conducted a critical evaluation of EPA guidelines for conducting pathology assays of pubertal developmental and thyroid function in intact juvenile/prepubertal rats, which are part of the 890 series of endocrine disruptor assays, and developed recommendations that will be made available in 6 to 12 months as a best practices publication in the society's journal, Toxicologic Pathology.

The pubertal developmental and thyroid function assay guidelines are part of a comprehensive program, launched by congressional mandate in 1996, to evaluate the effects of endocrine disrupting compounds (EDCs) in humans and animals, using validated testing, much of it developed specifically for the program (see text box).

Part of the evolution to predictive toxicology

NTP Associate Director John Bucher, Ph.D., welcomed workshop attendees with an overview of NTP that helped place the animal testing, being considered in the workshop, within the context of the emerging paradigm of predictive toxicology under development by the Tox21 consortium. Bucher spoke to NTP's major focus on EDC exposure during development, and long-term health effects. Bucher pointed to five-generation estrogenic compound studies, and the bisphenol A clarity study underway in conjunction with the National Center for Toxicological Research (see story).

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Although the main thrust of predictive toxicology is expanding *in vitro* high-throughput screening, Bucher and the speaker who followed him, EPA lead scientist Doug Wolf, D.V.M., Ph.D., emphasized that streamlined rodent pathology studies, based on the principles of good laboratory practices, continue to be critical in decision-making. They agreed, as well, that regulatory agencies need to move forward using best practices achieved through the consensus of expert pathologists.

The devil in the details

STP Education Committee consultant Kevin Keane D.V.M., Ph.D., served as facilitator for the meeting. As he emphasized, "This is an open meeting that is not on behalf of any one stakeholder in these assays, but rather is intended to be a collegial discussion of the science at hand." On a humorous note, Keane described the meeting's goal — "To reach a consensus, as much as you can get a group of pathologists to reach a consensus."

Despite Keane's tongue-in-cheek caveat, and the number of practical matters the group could not agree on, the group reached consensus on many important points, including the value of including the male mammary gland and female vagina as organs to study, as well as the use of humane practices for anesthetizing animals.

In remarks echoed by several of the speakers, Karen Regan, D.V.M., of Regan Path/Tox Services, noted there is also a pressing need for interpathology consistency, standardized methodology, and objectivity. "You don't want to overanalyze these things," she said. "Just describe what you see and interpret later."

At the close of their long day of deliberation, most of the participants gathered on the patio outside the Rall building. (Photo courtesy of Steve McCaw)

In their assessments of the Tier 1 screening, which examines very young animals after 20 to 30 days of exposure to a chemical beginning about three weeks after birth, several speakers pointed to the need for developmental touchstones. "You need to know the normal at this age of animals," said Dianne Creasy, Ph.D., of Huntingdon Life Sciences. "The system needs to be considered as a whole, when you're looking for endocrine disruption."

Because streamlined rodent assays are uncharted territory for many pathologists, presenters and discussants agreed that a number of technical issues will need more discussion, consideration, and specific guidance. As a case in point, in her report on thyroid endpoints, Catherine Picut, V.M.D., J.D., of WIL Research, honed in on one major consideration, as she described the direction in the EPA guidelines to pick a representative area of tissue to describe.

"What does that mean?" she asked attendees. Tellingly, no one seemed to have a ready answer.

After a slow start, EDSP gains momentum

Following careful reviews by experts, in 2009, EPA announced the initial list of chemicals to be screened for their potential effects on the endocrine system, or Tier I testing, and issued requests for data. Testing will eventually be expanded to cover all pesticide chemicals, as well as substances that may occur in sources of drinking water to which a substantial population may be exposed. EDSP involves a battery of *in vivo* and *in vitro* assays of endocrine endpoints in amphibians, fish, rats, and humans.

Through Tier 1 screening, the program hopes to identify chemicals that have the potential to interact with the endocrine system. Tier 2 testing will determine the endocrine-related effects caused by each chemical, and obtain information about effects at various doses.

Endocrine disruptor screening is currently proceeding on three fronts — developing and validating Tier 2 tests; selecting chemicals for screening and testing; and implementing the policies and procedures the agency will use to require screening.

Oil spill researchers tell what they learned

By Christine Flowers, reprinted from *eFACTOR*, February 2013

More than 1,000 scientists gathered in New Orleans Jan. 21-23 to share what they've learned so far about the 2010 Deepwater Horizon oil spill and its effects on the environment and communities. The Gulf of Mexico Oil Spill and Ecosystem Science Conference was sponsored by the BP's Gulf of Mexico Research Initiative (GoMRI), along with 13 other organizations, including NIEHS. The event was the first public presentation of research findings and an opportunity for government agencies, academia, and private industry to build partnerships focused on sustaining long-term environmental health.

"It was important for NIEHS to be part of this conference, because research on human health needs to be included in the broad discussion of ecosystem restoration," said Senior Advisor Allen Dearry, Ph.D., who represented NIEHS on the conference steering committee and served as co-chair for the conference sessions on public health impacts of the oil spill.

In total, NIEHS staff and grantees gave 12 presentations and 10 poster sessions on NIEHS-supported recovery efforts, including the GuLF STUDY, the university-community research projects funded by $25 million in NIH grants, the toxicology testing of oil and dispersants, and safety training for cleanup workers.

Prevailing themes

Over the course of the three-day symposium, some common themes prevailed. First, there was broad consensus that emergency response plans should allow research efforts to begin on day one of a disaster. Second, researchers should collect as much data about the people as they do about the biophysical environment. And third, response and research must address the human dimension, including health, economic, and social stressors.

Retired U.S. Coast Guard Adm. Thad Allen, who headed the oil spill Unified Command, gave the opening keynote speech for the conference. "One of the final actions I took was to order the collecting of water samples and oil samples for research … We probably gave up our chance to get baselines," Allen said. "We need to come up with a science response plan, to go along with the disaster response plan. I would endorse creating a science team with the necessary background and security credentials already in place."

National Toxicology Program toxicologist Cynthia Rider, Ph.D., left, gave a presentation on NTP's polycyclic aromatic hydrocarbon research. NTP's Scott Masten, Ph.D., was on hand to answer questions. (Photo courtesy of Christine Flowers)

Maureen Lichtveld, M.D., an NIEHS grantee and chair of the Tulane University Department of Global Environmental Health Sciences, expanded this idea in her plenary talk, saying, "We need upfront approval to do human subjects research — a shovel ready approval — and a plan on the shelf."

A shortage of baseline data posed a serious challenge for all the scientists who presented their research, whether they were studying people, sea life, plants, or water quality. "We need to know the state of the environment, so we can measure change," said John Farrington, Ph.D., scientist emeritus at Woods Hole Oceanographic Institution. "We know that oil spills are one of the multiple stressors on the Gulf of Mexico ecosystems. The next generation of scientists needs to make sure we are better prepared with updated baselines."

The ecosystem includes people too

"The health of the environment and the health of the community are inextricably linked," Lichtveld said. "Let's break down the silos of doing ecosystem research separate from health research."

Michael Orbach, Ph.D., director of the Coastal Environmental Management Program at Duke University, said there is a lack of social science in environmental policy. "We know a lot more about the fish than we know about the fisherman," he said, as he called for more research on socioeconomic impacts. Orbach made the point that economic stress influences

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social behavior and resiliency — a word heard often during the conference, meaning the ability for ecosystems and communities to bounce back after a disaster. "As scientists, we need to document the benefits, as well as the costs, of the oil industry. There is a balance that is not always acknowledged by my friends, the marine biologists."

Local partners

During the conference, NIEHS/NTP Director Linda Birnbaum, Ph.D., and NIEHS Senior Medical Advisor Aubrey Miller, M.D., set aside an evening to meet with state health officials from Louisiana, Alabama, Mississippi, and Florida. NIEHS program staff joined in to answer questions and provide research updates.

"We want to thank you for everything that you've done to support NIEHS studies in your communities," said Birnbaum. "We simply could not do the research without you."

(Christine Flowers, M.P.A., is the Director of the Office of Communications and Public Liaison, Office of the Director, at NIEHS.)

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15 Years Out: Reinventing ICCVAM

By Linda S. Birnbaum, reprinted from *Environmental Health Perspectives* 121:a40-a40 (2013). http://dx.doi.org/10.1289/ehp.1206292 [Online 1 February 2013].

In 1997, the National Institute of Environmental Health Sciences (NIEHS) established the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), an ad hoc federal interagency committee to address the growing need for obtaining regulatory acceptance of new toxicological test methods. The thought was that simultaneous agency evaluation of new methods that addressed the 3Rs (reduction, refinement, and replacement) of animal testing by an interagency group could greatly speed up and harmonize the cross-agency acceptance and adoption of new methods into federal toxicity testing guidelines. This activity was codified into law in 2000 by passage of the ICCVAM Authorization Act (2000). The Act specified 15 agencies (such as the Food and Drug Administration, U.S. Environmental Protection Agency, Consumer Product Safety Commission, Department of Transportation, Occupational Safety and Health Administration, and U.S. Department of Agriculture) that would constitute ICCVAM. The Act also prescribed specific duties intended to facilitate review and acceptance of test methods, established an external scientific advisory committee, and required the director of the NIEHS to establish ICCVAM under the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which currently exists as a functional unit within the Division of the NTP at the NIEHS.

Over the past 15 years, ICCVAM has successfully evaluated and recommended numerous alternative test methods for regulatory use (NTP 2012). However, the lack of implementation of ICCVAM-recommended methods has been an area of increasing concern. The NIEHS has worked proactively with our ICCVAM partners to identify promising methods, encouraged and aided test developers in building a case for validating their methods, sometimes provided financial support through competitive Small Business Innovation Grants, and held workshops and engaged our federal and international partners to promote acceptance and use of test methods in specific areas of toxicology (e.g., ocular toxicity and skin sensitization). Even so, regulatory use of alternative methods has still lagged behind. Critics have repeatedly pointed out that alternative test methods have not been accepted for regulatory decision making and that the expectations for real reductions in animal use in toxicology testing have always outpaced the documented progress. It has become clear that it is time to change our approach.

The NIEHS is beginning to move forward with a different philosophy toward ICCVAM. Rather than the NIEHS directing the activities of ICCVAM through NICEATM, the interagency agenda will now be driven by the partner regulatory agencies — the agencies that will ultimately implement the ICCVAM-recommended methods. Regulatory agencies are required by statute to use toxicology test information for a variety of purposes, including labeling and registration, and these requirements are not uniform. The ICCVAM Authorization Act acknowledges that some alternative test methods promoted by ICCVAM, while deemed valid, may not meet specific needs of a regulatory agency. With ICCVAM regulatory agencies taking ownership of the process, there should be a better match between the alternative test methods validated and the tests required to meet regulatory guidelines.

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Toxicology testing is shifting from a primary focus on adverse phenotypic observations in animals to mechanism-based biological outcomes *in vitro*, and the NIEHS is embracing this paradigm shift through its participation in the multiagency Tox21 consortium (Collins et al. 2008). NICEATM will expand its scope and concentrate its resources on providing bioinformatic and computational toxicology support to NIEHS Tox21 projects.

With its purpose of transforming toxicology by shifting from *in vivo* animal studies to *in vitro* assays, *in vivo* assays in lower organisms, and computational modeling for toxicity assessments, Tox21 has the real potential to result in dramatic changes in the numbers and types of organisms used for toxicology testing. A stronger interface of NICEATM with Tox21 will better position ICCVAM for addressing how data from these new methods can be integrated into the existing regulatory framework.

We express our deep appreciation to William S. Stokes, who has served as the director of NICEATM since its inception. In December 2012, he retired from the Public Health Service after 33 years of dedicated federal service. His vision, persistence, and direction have been key to bringing NICEATM, ICCVAM, and the International Cooperation on Alternative Test Methods (ICATM) to their current stage of maturity.

We are pleased that Warren Casey, who has served as deputy director of NICEATM, will now serve as the acting director. He is uniquely qualified for this role, having worked in the areas of toxicogenomics, mechanistic toxicology, and biomarker development in the pharmaceutical industry prior to joining the NIEHS.

We look forward to this new approach to promoting the 3Rs — an approach that will be driven by regulatory agency needs while remaining responsive to the test method development community.

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Summary for "International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines" available at: http://iccvam.niehs.nih.gov/meetings/HISTWksp-2012/HISTWksp.htm

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