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

What's Inside:

Birnbaum presents plenary at meeting of Canadian toxicology group

By Eddy Ball, reprinted from Environmental Factor, January 2014

NIEHS and NTP Director Linda Birnbaum, Ph.D., added an interesting twist on the famous quote from Paracelsus during her plenary talk Dec. 4 in Ottawa, "Does dose make the poison? A current assessment of nonmonotonicity."

Addressing the Society of Toxicology of Canada (STC) 45th Annual Symposium on "Mechanistic Paradigms for Toxicological Regulation," Birnbaum, who was joined by an NTP toxicologist and two NIEHS grantees at the meeting, discussed an emerging paradigm of dose response.

Birnbaum, right, enjoyed an opportunity to talk with STC President Louise Winn, Ph.D., of Queen's University, about environmental health concerns common to people in the U.S. and Canada. Birnbaum's elegant argument for expanding perspective on dose response set the stage for the first session of the meeting, which examined future directions in the areas of carcinogenesis and toxicity. (Photo courtesy of David Josephy)

The quote from Paracelsus (1493-1541), who is acknowledged as the father of toxicology, points to the traditional notion of dose response — that increasing dose increases toxicity in a monotonic pattern. "All things are poison," Paracelsus is quoted as saying, "and nothing is without poison; only the dose permits something not to be poisonous."

Increasingly, toxicologists in the field of environmental health science, such as Birnbaum, are recognizing that for some compounds, especially hormones and hormone-like chemicals, the reverse may hold true. In these cases, a much smaller dose may have a disproportionate impact on toxicity, while greater doses may actually blunt effects through several antagonistic mechanisms, including the saturation of receptors.

Supporting the goals of our colleagues to the north

Joining Birnbaum at the meeting were NTP toxicologist Scott Auerbach, Ph.D., and NIEHS grantees Dean Jones, Ph.D., of Emory University, and Tom Gasiewicz, Ph.D., of the University of Rochester, who is also a member of the National Advisory Environmental Health Sciences Council. Their talks were prominent, among the 11 presentations during the symposium's three themed sessions:

- Auerbach explored "Characterization and application of toxicogenomic perturbation space," and Jones argued for new directions in toxicology with his talk, "Sequencing the human exposome: a call to action." Their talks were part of session two, "Genome, Epigenome, and Exposome: Future Roles in Carcinogenesis and Toxicity."
- Gasiewicz discussed "The Ah receptor in hematopoietic stem cells (HSCs): regulation of signaling pathways associated with HSC function," as part of session three, "Molecular Toxicology: Mapping the Pathways."

One member of the STC board of directors, incoming president David Josephy, Ph.D. had a special reason to appreciate the contributions of NIEHS scientists and grantees at the symposium. An award-winning molecular toxicologist at the University of Guelph since 1983, Josephy completed a postdoctoral fellowship at NIEHS in 1982.

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"The question is no longer whether nonmonotonic dose responses are 'real' and occur frequently enough to be a concern," Birnbaum told her audience. "Clearly these are common phenomena with well-understood mechanisms. Instead, the question is which dose–response shapes should be expected for specific environmental chemicals and under what specific circumstances."

Does dose make the poison?

Birnbaum built the case for her central premise, with examples of essential nutrients, which exercise their beneficial effects at low doses, and hormones, specifically prolactin, which exerts both stimulatory and inhibitory effects upon testicular steroidogenesis. She also outlined eleven mechanisms for nonmonotonic dose response, including tissue-specific shut-off response, biochemical modification of receptors, and endocrine feedback loops.

This complicated and somewhat counter-intuitive concept, Birnbaum noted, has gained increasing acceptance among scientists and regulators. She pointed to a growing body of literature and statements in 2012 and 2013 by The Endocrine Society, U.S. Environmental Protection Agency (EPA), and European Commission Office of the Chief Scientific Advisor. She also referred to an NTP review in 2001 of literature on endocrine disrupting compounds (EDCs).

A central issue in environmental health science, Birnbaum continued, is the low-dose effect of exposure to endocrine disruptors, which the World Health Organization defined in 2002 as exogenous, or external, substances or mixtures that alter the function of the endocrine system. Disruptors include the obvious players — natural and synthetic hormones — but also plasticizing compounds, fire-retardant chemicals, and some pesticides.

A new conversation about endocrine disruption

EDCs can have immediate effects, but their most harmful impacts are often masked or delayed — with exposures during sensitive developmental windows triggering alterations that cause disease in later life, especially in vulnerable individuals and sensitive subpopulations. "Low-dose exposures that seem insignificant may have biological meaning if persistent, bioaccumulative, and/or if exposure is continuous or repetitive," Birnbaum said in her conclusion. "It is not only the dose that makes the poison, but also the timing [of the exposure]."

Auerbach is a molecular toxicologist in the NTP Biomolecular Screening Branch. His primary role is the analysis and interpretation of multivariate data sets. (Photo courtesy of David Josephy)

Referring again to the EPA statement on nonmonotonic dose response earlier this year, Birnbaum reinforced her call for action. "It is time to start

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Upcoming NTP Events

April 16-18, 2014

NTP Board of Scientific Counselors

This meeting was postponed from December 18-19, 2013

http://ntp.niehs.nih.gov/go/165

June 17-18, 2014

NTP Board of Scientific Counselors

http://ntp.niehs.nih.gov/go/165

September 16-17, 2014

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

http://ntp.niehs.nih.gov/go/32822

December 9-10, 2014

NTP Board of Scientific Counselors

http://ntp.niehs.nih.gov/go/165

*All meetings are held at NIEHS unless otherwise noted:

Rodbell Auditorum
NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

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

the conversation between environmental health scientists, toxicologists, and risk assessors," she said, "to determine how our understanding of low-dose effects and nonmonotonic dose responses influence the way risk assessments are performed for chemicals with endocrine-disrupting activities."

During the question-and-answer portion of her presentation, Birnbaum fielded a range of questions about high-throughput screening of potentially bad actors; replacement chemicals, such as bisphenol S; and applications, as well as implications, of the precautionary principle.

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NTP shares new toxicology approaches with international colleagues

By Robin Mackar, reprinted from Environmental Factor, January 2014

It's not every day scientists get invited to give a presentation in the same place where the Nobel Prize in Physiology or Medicine has been chosen since 1901, but three NTP members did exactly that this fall at the Advancing Risk Assessment of Environmental Agents Conference.

At the request of the Karolinska Institutet in Sweden, NTP Associate Director John Bucher, Ph.D., delivered the keynote lecture Nov. 20 on new approaches in toxicology research and testing and how they are being applied to advance the health risk assessment process in the U.S.

Bucher's talk nicely set the tone for the next session led by two other NTP invited guests, Kristina Thayer, Ph.D., director of the NTP Office of Health Assessment and Translation (OHAT), and Andrew Rooney, Ph.D., OHAT deputy director, who discussed the NTP framework for systematic review.

All of the talks were given in the new state-of-the-art lecture hall, Aula Medica, which, as of Dec. 7, became the venue for scientific presentations by all Nobel laureates in physiology or medicine, before receiving their medals from the King of Sweden. "A very impressive, if not intimidating, environment to give a science talk in," Bucher noted upon his return.

Under Bucher's leadership, NTP has forged several new partnerships, internationally and domestically, including the Tox21 interagency consortium. (Photo courtesy of Steve McCaw)

Advancing Risk Assessment

The two day conference, "Advancing Risk Assessment of Environmental Agents," was hosted by the Institute of Environmental Medicine (Institutet för Miljömedicin or IMM), an interdisciplinary research department at the Karolinska Institutet. The IMM invited leading researchers from the U.S., Italy, Holland, and Sweden, to discuss how to take research findings and modern technologies and apply them to advance the health risk assessment process.

Anders Ahlbom, Ph.D., director and chair of IMM, kicked off the meeting by welcoming the international speakers, presenting them with a brief overview of health risk assessment at IMM, and laying out some of the major challenges that all government agencies face when conducting environmental health risk assessments. One of the major goals of the conference was to figure out how to move forward with the integration of toxicological, epidemiological, and mechanistic research studies into the risk assessment process.

Bucher's talk focused on the proactive approach by NTP to address challenges in environmental health. He discussed the progress made since the release of the NTP Roadmap in 2005, along with recent advances in toxicology testing and analysis approaches.

His discussion set the stage for Thayer and Rooney to illustrate how Roadmap progress has helped NTP establish a systematic review process for health assessments that focuses on the integration of data. OHAT develops literature-based evaluations to frame its investigations of potential human health hazards and examine the state of the science.

Thayer leads OHAT efforts to examine emerging issues in toxicology, such as obesity and diabetes, that may be triggered by exposures to endocrine-disrupting chemicals (see story). She also contributes to the NTP and NIEHS green chemistry initiative, which evaluates and compares the relative toxicity of chemicals proposed as safer replacements for other toxic chemicals. (Photo courtesy of Steve McCaw)

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Learning from one another

Thayer talked about steps 1-4 of the OHAT framework for systematic review, which focuses on the critical aspects of developing the protocol, managing data, and assessing study quality. Thayer also dazzled the 200 attendees with the data entry and analysis tools that NTP is using to conduct the evaluations. All the tools will eventually be made available to the public free of charge.

Rooney focused on steps 5-7, which guide the integration of epidemiological, toxicological, and other relevant data. "There was a lot of interest in the methods we're sharing," Rooney said. "They liked the clear, step-by-step process of how we are integrating different lines of evidence to develop conclusions."

Attendees were especially interested in the data entry tools and the possibility of holding training sessions, so others can use the NTP process, and everyone can begin entering and storing information in the same way, Thayer noted.

"No one has the resources to keep reinventing the wheel," Thayer said. "Other agencies, nationally and internationally, are looking to the NTP to take an active role in developing and evaluating approaches for bringing systematic review methods into environmental health science."

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

In addition to his work on the theoretical framework of systematic review, Rooney was instrumental in the OHAT evaluation of literature on the potential health effects of low-level exposures to lead (see story) in 2011. (Photo courtesy of Steve McCaw)

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NTP panel peer reviews substances for potential listing as carcinogens

By Ernie Hood, reprinted from Environmental Factor, January 2014

A panel of experts peer-reviewed the two most recent NTP draft Report on Carcinogens (RoC) documents, known as monographs, at a public meeting Dec. 12-13 at NIEHS.

The panel was charged with reviewing the draft monographs for ortho-Toluidine and pentachlorophenol and by-products of its synthesis. The monographs contain the rationale and background information to support NTP listing recommendations for inclusion in the RoC. The panel voted on whether the scientific evidence supports the listing recommendations, which can characterize a substance as either "known to be human carcinogens" or as "reasonably anticipated to be human carcinogens."

After thoughtful discussions, the panel chaired by Kenneth McMartin, Ph.D., a professor in the Department of Pharmacology, Toxicology, and Neuroscience at Louisiana State University Health Sciences Center, recommended listing *ortho*-Toluidine as a known human carcinogen and pentachlorophenol and by-products of its synthesis as reasonably anticipated to be a human carcinogen.

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens, briefed the peer review panel on the process for preparing the draft monographs, and presented much of the information on *ortho*-Toluidine. (Photo courtesy of Steve McCaw)

Monograph on *ortho*-Toluidine

The substance *ortho*-Toluidine is used to make dyes, rubber chemicals, herbicides, and the local anesthetic prilocaine. It has been listed in the RoC since 1983 as reasonably anticipated to be a human carcinogen. Since then, several cancer studies have been published in peer-reviewed literature, and the International Agency for Research on Cancer (IARC) has concluded that the compound is carcinogenic to humans. For these reasons, it was selected for a reevaluation and a possible change in RoC listing status.

NTP staff highlighted studies, presented in the draft monograph, showing credible evidence of an association between urinary-bladder cancer and exposure to *ortho*-Toluidine, based on consistent findings across human studies. Evidence from studies in experimental animals and on mechanisms of carcinogenicity also supports that finding. The peer-review panel unanimously concurred with the NTP's preliminary listing recommendation that *ortho*-Toluidine is known to be a human carcinogen.

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Monograph on pentachlorophenol and by-products of its synthesis

Studies evaluating the carcinogenicity of pentachlorophenol and by-products of its synthesis were discussed in great length and detail among the peer-review panel and RoC staff, to determine if there was sufficient evidence to support NTP's preliminary listing recommendation of known to be a human carcinogen, with non-Hodgkin lymphoma as the primary cancer endpoint of concern in these studies.

Pentachlorophenol is a chlorinated aromatic compound that was used in the U.S. as a commercial and residential wood preservative and multipurpose biocide, until its was restricted in the mid-1980s to non-residential use. Today, it is limited to commercial wood preservation in items such as utility poles, fence posts, and railroad ties.

The panel members stated that overall the evidence of carcinogenicity from the studies in human cancer was limited. They agreed that there was one very good study that found an association between exposure to pentachlorophenol and by-products of its synthesis, but thought the evidence from the other studies was much more limited, due to their small size and potential for confounding factors.

The panel also struggled over whether the candidate substance should be pentachlorophenol itself or pentachlorophenol and the byproducts of its synthesis. Technical-grade pentachlorophenol is a mixture, with up to 10 percent of the substance being by-products of its synthesis, many of which are dioxin-like compounds that may contribute to its carcinogenicity.

NTP Health Scientist Gloria Jahnke, D.V.M., presented most of the information on pentachlorophenol and by-products of its synthesis to the panel. (Photo courtesy of Steve McCaw)

At the end of the day, the panel voted to recommend changing the NTP preliminary listing decision of known to be human carcinogen, to reasonably anticipated to be a human carcinogen, based on limited evidence from studies in humans. The listing recommendation also took into consideration the sufficient evidence of carcinogenicity of pentachlorophenol, and pentachlorophenol and by-products of its synthesis, from studies in experimental animals and supporting mechanistic evidence.

Next Steps

The NTP will consider the panel's comments and public comments, as it makes revisions to the draft monographs. The updated monographs will be presented to the NTP Board of Scientific Counselors at the next meeting in April 2014.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Expert panel concurs with conclusions in draft NTP technical reports

By Ernie Hood, reprinted from Environmental Factor, December 2013

An expert panel, convened by NTP Oct. 29, peer reviewed four draft technical reports and agreed with the NTP conclusions on the carcinogenicity and toxicity of the substances tested. The proceedings were webcast, and included presentations of study findings, public comments, peer-review comments, and panel discussions for each report.

The meeting kicked off with a briefing from NTP toxicologist Chad Blystone, Ph.D., who provided background information on the reports and the peer review process. The reports summarize NTP rodent toxicity and cancer studies on substances in our environment of public health concern to identify potential hazards for human health. They describe the methods, results, and draft NTP conclusions as levels of evidence — clear evidence, some evidence, equivocal evidence, no evidence or inadequate study — of carcinogenic activity under the specific conditions of the studies.

The peer reviewers were charged with evaluating the scientific and technical elements of each study, as presented in the draft technical report, and determining whether the study's experimental design, conduct, and findings support the conclusions. For each report, the peer-review panel provided their comments and discussed the study's findings and conclusions. NTP staff acknowledged the comments and responded to points raised by the panel. The panel voted to accept the draft conclusions, as written, in all four reports.

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Vinylidene chloride

Vinylidene chloride is a high production volume chemical used to make common household products, artificial turf, pipes, lacquer resins and latex, and flame-resistant carpet backing. It was nominated for NTP study by the Agency for Toxic Substances and Disease Registry, primarily due to occupational exposure. Under the conditions of the two-year inhalation study, the NTP concluded that there was clear evidence of carcinogenic activity in male rats, some evidence in female rats, and clear evidence in male and female mice.

Cobalt metal

Cobalt metal was nominated by the Cobalt Development Institute, as well as the International Union, United Automobile, Aerospace and Agricultural Implement Workers of America, better known as the United Automobile Workers, based on widespread occupational exposure and occurrence of hard metal disease associated with exposure to cobalt and its compounds. More than one million U.S. workers are potentially exposed to cobalt, primarily through skin or inhalation exposures. It is also present naturally in soil, groundwater, and sediments, and is an essential trace element found in vitamin B12. The panel agreed with the NTP draft conclusions of clear evidence of carcinogenic activity of cobalt metal in male and female rats and mice.

Glycidamide

Glycidamide is a metabolite of acrylamide, the known carcinogen found in certain baked and fried starchy foods, such as french fries and potato chips. When acrylamide is consumed through food, the body converts it to glycidamide. Under the conditions of the two-year drinking water study, NTP concluded that there was clear evidence of carcinogenic activity in male and female rats and mice.

Tetrabromobisphenol A (TBBPA)

Nominated by NIEHS, TBBPA is a high production volume flame retardant widely used in plastics, paper, electronics, textiles, and adhesives. It is present in a variety of household products, such as computers, televisions, and mobile phones. The two-year gavage, or direct oral administration, studies yielded clear evidence of carcinogenic activity in female Wistar Han rats, equivocal evidence in male Wistar Han rats, some evidence in male mice, and no evidence in female mice.

In addition to the standard carcinogenicity studies, molecular characterization of select tumors was included in three of the four draft technical reports. These data separated spontaneous tumors from those in chemical-exposed groups. The panel reviewed the studies positively and encouraged further NTP molecular studies. ●

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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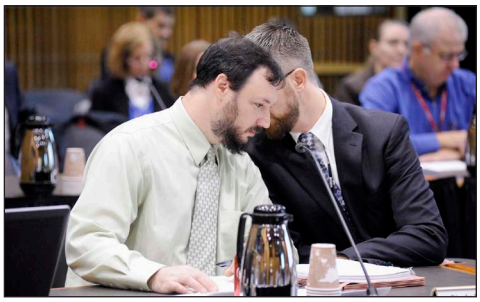
The NTP technical report peer-review meeting included the seven members of the peer review panel, liaisons to the U.S. Food and Drug Administration and the NTP Board of Scientific Counselors, and NTP study scientists and pathologists for each of the four technical reports. (Photo courtesy of Steve McCaw)

NTP Laboratory Animal Management Group lead Angela King-Herbert, D.V.M., detailed changes in the rat models used by NTP in its technical reports studies. (Photo courtesy of Steve McCaw)



Contemplating their response to a reviewer's question, NTP vinylidene chloride study scientist Michael Wyde, Ph.D., left, conferred with study pathologist Mark Hoenerhoff, D.V.M., Ph.D. (Photo courtesy of Steve McCaw)

John Cullen, V.M.D., Ph.D., right, professor of veterinary pathology at the North Carolina State University College of Veterinary Medicine, chaired the peer review panel. He is shown with NTP Associate Director John Bucher, Ph.D. (Photo courtesy of Steve McCaw)

EPA releases chemical screening data and launches challenges

Reprinted from Environmental Factor, January 2014

Researchers gained access to more chemical screening data with the U.S. Environmental Protection Agency (EPA) release of new information Dec. 17 on 1,800 chemicals found in industrial and consumer products, food additives, and drugs.

The data were gathered through advanced techniques, including robotics and high-throughput screening, as part of an ongoing federal collaboration to improve chemical screening. The collaboration, Tox21, includes EPA, NTP, the National Center for Advancing Translational Sciences, and the U.S. Food and Drug Administration.

"Making these data publicly available will help researchers across disciplines to better identify hazardous chemicals," said Raymond Tice, Ph.D., who heads the NTP Biomolecular Screening Branch, in the EPA press release. "We are pleased to be a partner in these collaborative efforts and look forward to further enhancing the amount of Tox21 data available to the public."

The chemical screening data is accessible on EPA's new interactive Chemical Safety for Sustainability or iCSS Dashboard.

That same day, EPA announced a series of challenges inviting the science and technology community to work with the data and provide solutions for how the new chemical screening data can be used to predict the lowest dose that shows adverse effects in animals. Challenge winners will receive awards for their innovative research ideas.

"Today's release marks an important milestone in communicating and improving our understanding of the impact chemicals have on human health and the environment," said Lek Kadeli, acting assistant administrator for EPA's Office of Research and Development.

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Scientists at NIEHS earn professional certifications

In November, four NTP scientists were awarded their certification as Diplomate of the American Board of Toxicology (DABT), after much hard work and dedication.

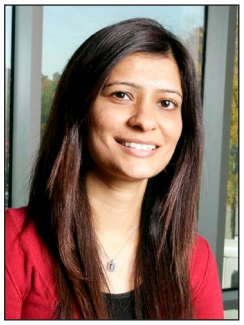
Mamta Behl, Ph.D., is a contract toxicologist in the Toxicology Branch. As a neurotoxicologist, Behl develops testing strategies to assess developmental neurotoxicity and neurotoxicity using in vitro and in vivo models.

Michael Boyle, DVM, DACVP, was a postdoctoral Intramural Research Training Award (IRTA) fellow in the Cellular and Molecular Pathology Branch (CMPB). His work involved the design, implementation, and evaluation of animal studies. He has since moved from the NTP and taken a position in industry.

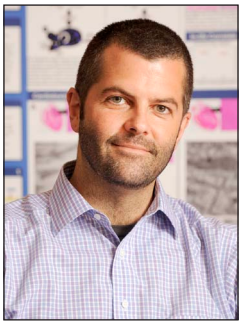
Arun Pandiri, Ph.D., DACVP, is a contract pathologist in the CMPB. His work focuses on chemical-induced tumorigenesis and lung and gastrointestinal pathology.

Sheetal Thakur, Ph.D., is a postdoctoral IRTA fellow in the Toxicology Branch. Thakur is a lead study scientist on non-clinical toxicology studies designed to evaluate toxicity and carcinogenicity of chemicals and herbal and pharmaceutical agents.

The American Board of Toxicology was established in 1979 to advance standards in the field of toxicology and confer recognition upon those members of the profession who, measured against such standards, demonstrate competence. DABT certification requirements include a combination of education and experience and a three-part examination.



Mamta Behl, Ph.D.
Contractor/Toxicologist



Michael Boyle, DVM, DACVP, Postdoctoral IRTA Fellow

Arun Pandiri, Ph.D., DACVP, Contractor/ Pathologist

Sheetal Thakur, Ph.D.
Postdoctoral IRTA Fellow

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In September, Erin Quist, DVM, M.S., received her board certification with the American College of Veterinary Pathologists (DACVP). Quist is a postdoctoral IRTA Fellow within the NTP Laboratory as well as a PhD candidate in Comparative Biomedical Sciences at North Carolina State University. She is examining adverse reproductive or developmental changes associated with environmental exposures to perfluorooctanoic acid and volatile organic compounds.

The American College of Veterinary Pathologists (ACVP) is an organization of board-certified scientists that has been setting the standard for veterinary pathology since 1949. By promoting excellence in veterinary pathology, ACVP improves and protects human and animal health for the betterment of society.

Erin M. Quist, DVM, MS, DACVP
Postdoctoral IRTA Fellow

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Toxicogenetics Challenge winners announced

By Ernie Hood, reprinted from Environmental Factor, December 2013

The winning teams for the NIEHS–NCATS–UNC DREAM Toxicogenetics Challenge, a competition involving crowdsourced computational challenges to find better ways to predict the toxicity of chemicals, were announced in Toronto Nov. 8 at the Sixth Annual RECOMB/ISCB Conference on Regulatory and Systems Genomics, with DREAM Challenges. NIEHS Deputy Director Richard Woychik, Ph.D., chaired the meeting's Challenge session and introduced the speakers from the winning teams.

The competition June 11-Sept. 15 was co-sponsored by NIEHS, the National Center for Advancing Translational Sciences (NCATS), the Carolina Center for Computational Toxicology at the University of North Carolina at Chapel Hill, DREAM (Dialogue for Reverse Engineering Assessments and Methods), and Sage Bionetworks.

The sponsors provided data for two related subchallenges — (1) to develop a model that accurately predicts individual responses to compound exposure based on genomic information, and (2) to develop a model that accurately predicts how a particular population will respond to certain types of chemicals. Teams were free to submit to one or both of the subchallenges.

Winners and representatives of some of the sponsoring organizations of the Toxicogenetics Challenge posed for a celebratory photo at the conference. Left to right: Ivan Rusyn, M.D., Ph.D., UNC; Wang; Federica Eduati, Ph.D., European Bioinformatics Institute; Woychik; Xie; Fred Wright, Ph.D., North Carolina State University. (Photo courtesy of Lisa Murzin)

Subchallenge 1 generated 99 submissions from 34 teams. Subchallenge 2 received 85 submissions from 24 teams.

The envelopes, please

Teams from the Quantitative Biomedical Research Center (QBRC) at the University of Texas Southwestern Medical Center (UTSW) were named best performer in both of the subchallenges. Team Yang Lab, represented in Toronto by Ph.D. student Tao Wang, took the honors for subchallenge 1. Team QBRC, also represented in Toronto by Tao Wang, on behalf of assistant professor Hao Tang, Ph.D., came in first in subchallenge 2. Associate professor Yang Xie, Ph.D., was also there to accept the award. The second best performer for subchallenge 1 was Team Cassis from the Centre for Computational Biology in Paris, which was represented at the conference by team member Elsa Bernard, a Ph.D. student at the Institut Curie, one of the Centre's joint laboratory member institutions.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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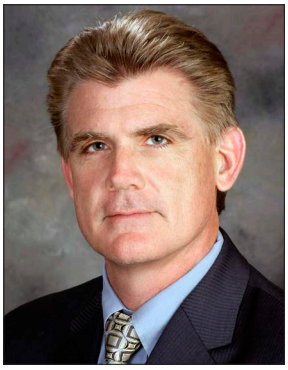
NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

By Catherine Sprankle, ILS, Inc./Contractor supporting the NICEATM

New NICEATM Director Named



Warren Casey, Ph.D., DABT

For the past year, Dr. Warren Casey has served as Acting Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) within the Division of the NTP at NIEHS. He has done an outstanding job. Dr. Casey has now been appointed to serve as the permanent NICEATM Director where he will continue his leadership in moving forward alternative methods and achievement of the 3Rs.

NICEATM provides scientific and administrative support to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The 15 federal research and regulatory agencies that comprise ICCVAM are working together to advance the acceptance of scientifically valid alternative test methods. NICEATM also provides bioinformatics and computational toxicology support for Tox21, the multiagency collaboration aimed at improving the human hazard characterization of chemicals.

NICEATM Launches New Website

In an effort to make information on NICEATM activities more accessible to stakeholders, NICEATM launched a new website in December. The site includes a section describing past and current activities of the ICCVAM, which NICEATM supports. The new website condenses summaries of past and current NICEATM and ICCVAM activities into a reduced number of webpages for easier navigation and highlights ongoing NICEATM activities that support new approaches to toxicological testing.

The new NICEATM website is available at http://ntp.niehs.nih.gov/go/niceatm.
ICCVAM activities are available at http://ntp.niehs.nih.gov/go/iccvam.

ICCVAM Requests Information on Skin Sensitization Testing Activities

ICCVAM is developing a plan of action to advance alternative test methods and testing strategies for skin sensitization. As part of this process, ICCVAM invites its stakeholders to comment on the proposed activities. ICCVAM is interested in receiving information on the state of the science of test methods and testing strategies for skin sensitization and about activities on this topic of which ICCVAM may not be aware. ICCVAM also invites input on the role ICCVAM should play in the development and evaluation of alternative skin sensitization test methods and testing strategies, as well as the potential contributions that regulated industries or nongovernment organizations and other interested parties might make toward these efforts.

Activities under consideration by ICCVAM include: organizing workshops; developing guidance documents; collaborating with international organizations that are conducting relevant validation studies or preparing relevant guidance; providing support to NICEATM's efforts in this area; and providing information about funding resources and agency priorities to test method developers. To coordinate these efforts, ICCVAM recently established a skin sensitization working group of scientists from relevant Federal agencies.

ICCVAM will consider all information received as it develops plans to augment and support activities that will advance the state of the science for alternative skin sensitization test methods and testing strategies.

Please submit comments or information on skin sensitization test method activities to iccvam@niehs.nih.gov.
Additional information is available at http://ntp.niehs.nih.gov/go/40498.

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International Cooperation on Alternative Test Methods Partners Meet

A coordination meeting of the International Cooperation on Alternative Test Methods (ICATM) was held on November 26–27 at the European Commission Joint Research Centre's headquarters in Ispra, Italy. ICATM is an international partnership of government validation organizations that promotes the advancement of replacement, reduction, and refinement alternatives for animal testing. ICATM currently has membership from organizations representing the European Commission, the United States, Japan, Canada, and South Korea.

At the November meeting, ICATM partner organizations presented updates on current activities and discussed opportunities for future cooperation. Specific topics of the meeting included coordination of recommendations, strategic selection and prioritization test method, coordination of validation studies to improve efficiency, and conduct of peer reviews that meet the needs of all member countries. The attendees also toured the *in vitro* GLP laboratory facilities at the Joint Research Centre. A summary of the meeting will be published in January 2014.

One of the ICATM partner organizations, the European Reference Laboratory for Alternatives to Animal Testing, an ICATM partner organization, recently published recommendations on the use of the direct peptide reactivity assay, or DPRA, for identification of potential skin sensitizers. The recommendation and other information about the DPRA can be found on the European Union's Institute for Health and Consumer Protection website a http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/eurl-ecvam-recommendations/eurl-ecvam-recommendation-on-the-direct-peptide-reactivity-assay-dpra.

Workshop on Alternatives for *Leptospira* Vaccine Testing

Proceedings from a September 2012 NICEATM-sponsored workshop on alternative methods for *Leptospira* vaccine potency testing were published in November as a dedicated issue of *Biologicals*. The proceedings are available on the *Biologicals* website at http://www.sciencedirect.com/science/journal/10451056/41/5.

Participants at the workshop reviewed available alternative methods for *Leptospira* vaccine potency testing and defined efforts necessary to achieve their global acceptance and implementation. Specific actions were identified that should be taken by both regulators and industry to facilitate broader use of USDA-validated ELISA antigen quantification methods, which would replace animal use. Where use of the ELISA methods is not appropriate, approaches to reduce and refine animal use were identified. They include use of serological assays, analgesics, and humane endpoints; potential elimination of back titrations for calculation of LD_{50}; and harmonization of regulatory requirements for the number of animals used for testing.

A summary of the workshop, workshop presentations, and a link to the proceedings are available on the NTP website at http://ntp.niehs.nih.gov/go/leptowksp.

Upcoming Workshops on Alternatives

On March 6–7, a workshop titled "Validation and Qualification of New *In Vitro* Tools and Models for the Pre-clinical Drug Discovery Process" will be held at the National Institutes of Health in Bethesda, Maryland. This is the fourth in a series of workshops to create validation guidelines for investigators developing new tools for the preclinical drug development process. The workshop will build upon the results and recommendations of the previous workshops, with emphasis on model systems that may augment or replace animal models in the U.S. drug approval process.

It is being organized by the NIH National Institute for Biomedical Imaging and Bioengineering (NIBIB) and the American Institute for Medical and Biological Engineering. Information and a link to registration are on the NIBIB website at http://www.nibib.nih.gov/news-events/meetings-events/fourth-aimbenih-workshop-validation-and-qualification-new-vitro-tools.

On April 14, the U.S. Food and Drug Administration (FDA) will hold a workshop on methods used for thrombogenicity testing of blood-contacting medical devices. The workshop will take place at the FDA White Oak campus in Silver Spring, Maryland.

Current testing of medical devices for thrombogenicity relies heavily on animal studies. These procedures can produce inconsistent and unreliable results, are expensive, and raise animal welfare concerns. The April workshop will bring together academics, industry professionals, and FDA regulators to discuss the advantages and limitations of both *in vivo* and *in vitro* thrombogenicity test methods. Ideas generated during this workshop will facilitate development of new guidance and standards for thrombogenicity testing.

For information about the workshop, please contact Dr. James Kleinedler at the FDA at James.Kleinedler@fda.hhs.gov.

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