UPDATE
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U.S. Department of Health and Human Services

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What's Inside:

NTP workshop investigates links between chemicals and obesity

Article by by Thaddeus Schug reprinted from *eFACTOR*, February 2011

While dietary excess and lack of exercise are well established factors fueling the obesity epidemic in the United States, new research is emerging that suggests that environmental exposures may also play a significant role in the risks associated with developing diabetes and obesity.

These linkages were the focus of an intensive three-day workshop — "Role of Environmental Chemicals in the Development of Diabetes and Obesity" — sponsored by the National Toxicology Program (NTP) January 11-13 at the Marriott at Crabtree Valley in Raleigh.

(L-R) Shown, left to right, Gallo, Thayer, and Bucher, are all smiles following three days of intense debate.

The workshop brought together more than 135 scientists, representing fields ranging from molecular biology to epidemiology, to examine the science associating exposure to certain chemicals with the development of diabetes and obesity in humans. Participants also provided input on potential testing strategies, data gaps, and future research needs to address these associations. Breakout sessions were arranged to cover six particular chemical classes — arsenic and other metals, bisphenol A, organotins and phthalates, nicotine, pesticides, and persistent organic pollutants.

Smoking linked to childhood obesity

There is "good, qualitative evidence" to link maternal smoking and arsenic and persistent organic pollutants (POPS) exposure to such health conditions, according to workshop chair Michael Gallo, Ph.D., director of the Toxicology Division and the NIEHS Center of Excellence at the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey. "Some of these associations are pretty strong," Gallo added.

"Perhaps less recognized is the consistent association of maternal smoking with increased risk of offspring being overweight or obese later in life," said workshop organizer Kristina Thayer, Ph.D., director of the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR).

According to Thayer, this pattern is initially detectable in young children and continues through adulthood. It is supported by laboratory findings that monitor animals that are treated with nicotine during development.

Data plausible, but more research needed

"Like many complex diseases, it is likely that many factors contribute to the development of diabetes," explained Thayer. "It is unknown to what extent environmental chemicals may be contributing to the current epidemics of diabetes and obesity, but it is clear that additional research is warranted to follow-up on the reported associations."

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After working in their breakout groups, participants reconvened Jan. 13 for summaries and a look at next steps.

Gallo agreed, adding, "We don't have good animal models, and we need to deal with the human population. These data really show us that there is biological plausibility to some or all of these chemical groups."

In concluding remarks, Jerry Heindel, acting chief of the Cellular, Organs, and Systems Pathobiology Branch of the NIEHS Division of Extramural Research and Training, said agency staff will evaluate the data needs and research strategy suggestions made by participants, and present the meeting results to its advisory group in February. The feedback will help to develop a research strategy and guide the awarding of related grants, Heindel said. "The goal is to stem the tide of the obesity and diabetes epidemic."

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction and a regular contributor to the Environmental Factor. He is currently on detail as a program analyst in the NIEHS Division of Extramural Research and Training.)

A potential role for predictive toxicology

Significant discussion at the workshop centered on which types of studies, *in vitro* cell studies or whole animal *in vivo* assays, are best structured to examine the effects of environmental contaminants on metabolic disorders. Development and use of new testing methods was backed in a major National Research Council (NRC) report as a way to replace costly animal tests. However, a major hurdle pointed out by several researchers lies in how to incorporate findings from cell-based assays into reliable human risk assessment models.

According to John Bucher, associate director of the National Toxicology Program, one of the key objectives for the U.S. Environmental Protection Agency (EPA), NIEHS and the U.S. Food and Drug Administration in obesity and diabetes research is to identify new toxicity pathways and biological targets for assays that may be relevant to diabetes and obesity health outcomes and could be incorporated into EPA's ToxCast computational toxicology database.

The ToxCast program has identified a link between a number of endpoints relevant to diabetes and obesity, such as islet cell function and insulin sensitivity, and toxicity pathways believed to be key mechanisms in metabolic disorders. "High throughput screening was not developed with this workshop in mind, but we can take advantage of ToxCast," noted Bucher.

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Upcoming Events

April 13, 2011

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

June 16-17, 2011

Scientific Advisory Committee on Alternative Toxicological Methods

Hilton Arlington
950 North Stafford Street
Arlington, VA

July 21-22, 2011

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

August 29-30, 2011

CERHR
Developmental Effects of Cancer Chemotherapy during Pregnancy

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

December 15-16, 2011

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

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

Request for Information (RFI): Needs and Approaches for Assessing the Human Health Impacts of Exposure to Mixtures

The Division of Extramural Research and Training (DERT) and the National Toxicology Program (NTP) seek input for identification of key research areas in mixtures. Information provided will be used in planning a workshop for late summer 2011 to help inform the development of intramural and extramural research efforts that address the combined health effects of multiple environmental exposures ("mixtures"). This request for information (RFI) is for planning purposes only and should not be construed as a funding opportunity or grant program. Input from all interested parties is welcome, including the lay public, environmental health researchers, health professionals, educators, policy makers, industry, and others. Please respond on-line at the Mixtures Request for Information webpage (http://ntp.niehs.nih.gov/go/rfimix) by April 15, 2011.

The NIEHS mission is to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease. To accomplish this, the NIEHS supports research and professional development in environmental health sciences, clinical research, and public health.

DERT plans, directs and evaluates the NIEHS grant program, which supports research and research training in environmental health. It develops program priorities and recommends funding levels to assure maximum utilization of available resources in attainment of NIEHS objectives. Through cooperative relationships with NIH and with public and private institutions and organizations, DERT maintains an awareness of national research efforts and assesses the need for research and research training in environmental health.

The NTP is an interagency program whose mission is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology. The NTP designs and conducts laboratory studies and testing programs and analyzes its findings to assess potential hazards to human health from exposure to environmental substances. The NTP also carries out formal review and literature analysis activities.

The evaluation of human health effects from multiple environmental exposures represents a special challenge to the research community due to the inherent complexity of the topic. The term "mixture" can be broadly interpreted and can refer to a substance with variable composition or to mixtures resulting from combined exposures. For the purposes of this RFI, "mixtures" pertains to any set of multiple environmental exposures (chemical or non-chemical) that may contribute jointly to adverse human health outcomes, irrespective of whether people are exposed to the substances at the same/different times or through similar/distinct sources or routes.

Continuous human exposure to complex and dynamic mixtures precludes directly testing the toxicity of each possible exposure combination. Therefore, predictive models of mixture toxicity must be developed and validated in order to characterize the hazard associated with complex exposures. In order to develop these models, a better understanding is required of both the composition of real-world exposures and the fundamental principles of chemical interactions. Combinatorial or statistical approaches are needed to address the potential interactions of complex exposures. Moreover, these approaches should be used to move beyond assessment of individual chemicals and further our understanding of the impacts of realistic exposures.

Information gathered through this RFI will be used in planning a workshop on mixtures to be held in late summer 2011. The date and location have not yet been determined, but when set, will be announced in the NIH Guide. The overarching goals of this workshop are to foster discussion on the approaches, infrastructure, and resources needed to make progress and to identify new scientific opportunities by applying innovative tools to the field of mixtures research. Additionally, the workshop should provide opportunities for development of collaborations and foster multidisciplinary interactions among the mixtures scientific community. The workshop will bring together experts from multiple disciplines including, but not limited to, exposure assessment, risk assessment, biostatistics, toxicology, biology, regulatory science, and epidemiology.

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Information requested

DERT and the NTP request information on the challenges and potential solutions in mixtures research. Responses to any or all of the questions below are invited from interested individuals/groups, including, but not limited to, the environmental health research community, health professionals, educators, policy makers, industry, and the public.

- What are the underlying scientific knowledge gaps for assessing the effects of mixtures on human health?
- What are the scientific issues encountered in performing risk assessments of mixtures that can be addressed by new research?
- What types of scientific data (e.g., mechanistic, epidemiological) are needed to address these underlying knowledge gaps?
- What are the new technologies and innovative approaches that could be leveraged to address these underlying knowledge gaps?

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Peer review panel deliberates NTP Technical Reports

Article by Ernie Hood reprinted from *eFACTOR*, March 2011

Shown left to right, NIEHS/NTP Director Linda Birnbaum, Ph.D., panel chair Raymond Novak, Ph.D., corporate director of research at Shriners Hospital for Children in Tampa, Fla., and Walker gave careful consideration to the Technical Report presentations.

The National Toxicology Program (NTP) convened a peer review of draft NTP Technical Reports by an external scientific panel at a meeting January 26 at NIEHS. Assessing the daylong consideration of technical report documents, NTP Deputy Program Director for Science Nigel Walker, Ph.D., said, "We were very pleased with the depth and breadth of the comments."

The gold standard in observational toxicology

The Technical Reports describe the results of two-year bioassays of nominated substances in male and female mice and rats. They reflect considerable effort on the part of NTP scientists and contractors – often involving 50-70 people and many years worth of work. Draft reports are prepared by an internal team led by NTP pathologist David Malarkey, D.V.M., Ph.D., and NTP toxicologist Michelle Hooth, Ph.D., and are reviewed by NTP scientists before they are released to the public and presented to the external peer review panel.

The conclusions reported are seen by regulatory agencies as authoritative sources in their decision-making. "Part of the NTP mission is providing information on hazardous substances to the stakeholders in the community, and to me, the Technical Reports meetings are where the rubber meets the road for that part of our mission," says Walker. "They exemplify everything NTP is about."

Review panel outcomes

At the January meeting, the panel reviewed draft NTP Technical Reports on kava kava extract, a botanical product used widely as a dietary supplement; retinoic acid/retinyl palmitate, a formulation of vitamin A widely used in cosmetic products; methyl trans-styryl ketone, a compound used as a synthetic flavoring or fragrance agent; styrene-acrylonitrile (SAN) trimer, a chemical byproduct suspected to be associated with childhood cancers; and alpha, beta-thujone, a compound found in herbal medicines, food and beverage flavorings, cosmetic products, and repellants.

The panel accepted the draft conclusions as written for methyl trans-styryl ketone and alpha, beta-thujone, but recommended changes for the conclusions for the other compounds, including changing the draft conclusion for SAN trimer from "equivocal evidence of carcinogenic activity" in male F344/N rats to a finding of "no evidence."

Due to time constraints, consideration of the draft Technical Report for senna, an herb used as a stimulant laxative, was postponed until the peer review panel in April.

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

Intramural paper is highlighted as a science brief in the News and Observer

Two pesticides, rotenone and paraquat, have been linked to Parkinson's disease by researchers at the National Institute of Environmental Health Sciences in Research Triangle Park.

Their research shows that people who used either pesticide developed Parkinson's disease approximately 2.5 times more often than nonusers.

Use of paraquat, a weed killer, has long been restricted to certified applicators, largely due to health concerns. Rotenone is now primarily used as a pesticide to kill invasive fish species; it was previously used as an insecticide to kill garden pests.

"Rotenone directly inhibits the function of the mitochondria, the structure responsible for making energy in the cell," said Freya Kamel, a researcher in the intramural program at NIEHS and co-author of the paper appearing online in the journal Environmental Health Perspectives. "Paraquat increases production of certain oxygen derivatives that may harm cellular structures."

The authors studied 110 people with Parkinson's disease and 358 other people to investigate the relationship between Parkinson's and exposure to pesticides or other agents that are toxic to nervous tissue.

"This may have important implications for the treatment and ultimately the prevention of Parkinson's disease," said Dr. Caroline Tanner, clinical research director of the Parkinson's Institute and Clinical Center and lead author of the article.

http://www.newsobserver.com/2011/03/07/1034517/science-briefs.html.

(Freya Kamel is a Staff Scientist with the NIEHS Epidemiology Branch and National Toxicology Program.)

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Woychik talks about NIEHS and the 2012-2016 Strategic Plan

Article by Ernie Hood reprinted from *eFACTOR*, March 2011

NIEHS Deputy Director Richard Woychik, Ph.D. responded to questions from the Environmental Factor about his presentation February 16 on the NIEHS 2012-2016 Strategic Plan and his first two weeks at the Institute working closely with NIEHS/NTP Director Linda Birnbaum, Ph.D.

FACTOR: Why is it so important for the Institute to formulate a new strategic plan?

WOYCHIK: A strategic plan gives everyone associated with the Institute — internal, external, the environmental health sciences community — a sense of where we are going. As part of the process, you do an evaluation of your strengths and weaknesses. What are the real opportunities and the threats that are out there in the biomedical environment? So, it gives you a chance every five years to really look at how the world community has changed, and then to evaluate what we have done, at what parts of the previous strategic plan are still applicable or unfinished business and are important to help guide the future directions of the Institute — and the new opportunities and new areas we want to be moving in over the course of the next five years.

First impressions

FACTOR: You've only been here at NIEHS a couple of weeks now, but you certainly seem to have hit the ground running. What are your first impressions?

WOYCHIK: My first impressions are very positive. First of all, starting with an institute that has a focus that is so much in alignment with my own personal passions is something I am very excited about, and the first two weeks on the job confirm that all of my due diligence about the interests of the Institute was in fact spot on. So it's great to be amongst groups of people [like this], certainly Linda, with her passions and interests; I'm clearly in the right place relative to scientific focus. The other thing I've been struck by is the quality of the people here. It's a place where I'm amazed at how much you can get done in a relatively short period of time. Plus, as I've been getting to know people throughout the organization, I've been exceedingly impressed with the quality of the work that we've done, and I'm very encouraged by the quality of the work and the impact that we can have over the next five to ten years.

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Positive responses from Council

FACTOR: Following your briefing to Council about the process and timelines for the Strategic Plan, you seemed very pleased with the members' comments.

WOYCHIK: First of all, I'm encouraged that they were so supportive of the process, and supportive of us doing this now. There really weren't any negatives about what we're proposing to do and the timeframe in which we're doing it. What didn't get captured in the public discussion were the many very positive statements that many Council members made to me personally at the coffee break.

So I think there's a real sense of interest, that the timing is right to take a look at mission and vision, and to develop the strategic goals for the next five years. I was also very encouraged just by the engagement. It's clear that there's a lot of passion out there around issues in environmental health science.

FACTOR: Another large theme that emerged in the Council meeting was the current budget atmosphere, and the uncertainties that are being faced over the near term. Will that have any effect on the strategic planning process?

WOYCHIK: I think that when you have budgetary challenges, it's all the more reason to be doing a strategic plan, because the plan will also lay out your priorities as you move forward. So, if there are budgetary shortfalls, then one knows exactly, based on the grassroots input, where the interests are, and where the funds should be placed, as the highest priorities, and the second-highest priorities. Another thing that I was very encouraged with was the idea several members articulated of making sure that NIEHS is partnering and collaborating with other institutes and other agencies.

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

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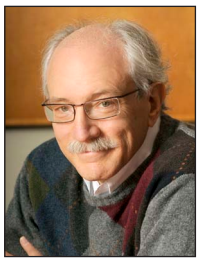
Strategic planning process emphasizes transparency and inclusion

Asked about the Strategic Planning process, Woychik pointed to the combination of Web-based tools and stakeholder meetings designed to promote participation in the development of the final product.

> Linda and I feel very strongly that we want to structure the process in such a way that all stakeholders understand — we want to hear from you. So we've developed both a Web-based system and an in-person, large group meeting that is scheduled far enough in advance so that anyone and everyone who is interested in having input into this process will have an opportunity to contribute. We're going to be publishing the process, when the time periods are when you'll have a chance to give us input, and in what format the input will be provided. So pay attention to those things, and then follow the progress, and anyone in the community will have a chance to comment on the progress that we make. I hope that at the end of this process, fifteen months later, the entire environmental health sciences community will feel that we have a plan that really provides a roadmap and guidance on what we can be doing to impact the quality of human health and human suffering.



During his first days on the job, Woychik made it clear to all that he plans to be a deputy director who is accessible to employees and stakeholders and involved in all aspects of the Institute's operations.
Photo courtesy of Steven McCaw

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Dedication of new Tox21 robot system to test 10,000 chemicals for toxicity

Article by Robin Mackar reprinted from *eFACTOR*, April 2011

The lead program staff from each of the four agencies involved in Tox21 take a break from their busy schedule to enjoy the robot cake. Shown left to right are Tice, Bob Kavlock, Ph.D., from EPA, Austin, and David Jacobson-Kram, Ph.D., from FDA. (Photo courtesy of NCGC)

Key players involved in the Tox21 effort gathered March 10 at the NIH Chemical Genomics Center (NCGC) in Rockville, MD to dedicate a new high-speed robot screening system. The addition of this robot system will enable the screening of a 10,000 chemical library for potential toxicity and marks the beginning of a new phase of the ongoing Tox21 collaboration that is working to protect human health by improving how chemicals are tested in the United States.

NIEHS/NTP Director Linda Birnbaum, Ph.D., joined fellow institute director Eric Green, M.D., Ph.D., of the National Human Genome Research Institute (NHGRI), representatives from the U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA), and key Tox21 staff to dedicate the new system and provide a tour to about 40 invited guests. Tox21 includes a memorandum of understanding between the four agencies to more effectively predict how chemicals will affect human health and the environment. Among the guests were representatives from the U.S., European, and Korean committees for alternative testing methods.

Birnbaum and many of the other guests who came to the dedication immediately after the 50th anniversary meeting of the Society of Toxicology (SOT) held in Washington D.C., commented on how the ceremony added to the SOT experience.

"I can't think of a better way to conclude SOT," Birnbaum said. "This robot truly exemplifies a remarkable collaboration effort between four federal organizations that showcases how we can all bring our strengths and resources to the table to build the framework for a new predictive toxicology."

Getting ready to cut the ribbon for the new dedicated robot are Green, Birnbaum, Woodcock, and Lek Kadeli, acting deputy assistant administrator for management in EPA's Office of Research and Development. (Photo courtesy of NCGC)

The 10,000 chemical library to be screened by the robot system include compounds found in industrial and consumer products, pesticides, food additives, and drugs. A thorough analysis of more than 200 government and non-government databases of chemicals and drugs used in the United States and abroad was conducted to select the chemicals in this library. Testing results will provide information useful for evaluating whether these chemicals have the potential to disrupt human body processes enough to lead to adverse health effects.

In his remarks at the dedication, Green said, "Tox21 has used robots to screen chemicals since 2008, but this new robotic system is dedicated to screening a much larger compound library."

The director of the NCGC at NHGRI, Christopher Austin, M.D., provided an overview of Tox21 efforts and added, "The Tox21 collaboration will transform our understanding of toxicology with the ability to test in a day what would take one year for a person to do by hand."

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NTP Biomolecular Screening Branch Chief Ray Tice, Ph.D., a key player in the Tox21 efforts for NIEHS/NTP is enthusiastic about the promise that new tools like this bring to the field. "By screening these chemicals for effects in key cellular pathways, we will gain a much better understanding of the relationship between chemicals, genes, pathways, and disease. This will enable us to better prioritize compounds for more comprehensive testing, to identify mechanisms of action, and ultimately to develop predictive models for adverse effects in humans."

"Understanding the molecular basis of hazard is fundamental to the protection of human health and the environment," said Paul Anastas, Ph.D., assistant administrator of the EPA Office of Research and Development. "Tox21 allows us to obtain deeper understanding and more powerful insights, faster than ever before."

"This partnership builds upon FDA's commitment to developing new methods to evaluate the toxicity of the substances that we regulate," said Janet Woodcock, M.D., director of the FDA Center for Drug Evaluation and Research.

For b-roll clips from the NCGC facility, visit http://www.genome.gov/27543670.

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

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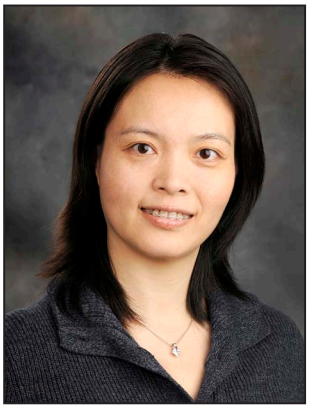
Trainees honored for scholarship and service at SOT

Article by Eddy Ball reprinted from *eFACTOR*, April 2011

Xiaoqing Chang, Ph.D., a visiting fellow in the NTP Biomolecular Screening Branch headed by Raymond Tice, Ph.D., won the Nanotoxicology Specialty Section Outstanding Postdoc Award for her abstract, "A physiologically based pharmacokinetic (PBPK) model of micro- and nano-sized fluorescent polystyrene spheres in rats." Co-authors on the study include her first mentor at NIEHS, former Special Advisor Chris Portier, Ph.D., and NTP scientist Nigel Walker, Ph.D. Her current mentor in the NTP is Michael DeVito, Ph.D., who nominated Chang for her award.



Xiaoqing Chang
(Photo courtesy of Steve McCaw)

According to Chang, the model adequately describes the kinetics of both micro and nano polystyrene spheres and clearly demonstrates that the size of these particles influenced their kinetics. This research provides a general framework for elucidating the kinetics of nanoparticles and should greatly enhance understanding of nanotoxicity and improve risk assessment of nanotechnology in the near future.

Minerva Mercado-Feliciano
(Photo courtesy of Steve McCaw)

Minerva Mercado-Feliciano, Ph.D., an Intramural Research Training Award fellow in the NTP Toxicology Branch headed by Paul Foster, Ph.D., was presented with an award for outstanding service by the Hispanic Organization of Toxicology (HOT) Special Interest Group. She was recognized for her contributions as editor of the official SOT-HOT newsletter, Toxenlaces, which began publication in 2009.

Toxenlaces provides Hispanic toxicologists in the United States and the international Spanish and Portuguese-speaking scientific communities with information about important toxicological events and issues occurring in their countries. The newsletter serves as toxicology forum and disseminates critical dates for events, health perspectives, and funding and training opportunities.

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NTP alternatives center holds workshops on best safety testing

Article by Debbie McCarley and Cathy Sprankle reprinted from *eFACTOR*, February 2011

Stokes, above, also serves as the executive director of ICCVAM. *Photo courtesy of NICEATM.*

Thanks to the recent endorsement of several alternative testing methods, federal public health agencies and regulated industry now have important new tools for assessing the safety of chemicals and products.

The new test methods were the topic of two workshops on Best Practices for Regulatory Safety Testing January 19-20 in Bethesda, MD, organized by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NICEATM and ICCVAM recommended the test methods to agencies after comprehensive review of their scientific validity.

The workshops addressed current best practices for safety testing necessary to determine whether chemicals and products may cause eye injuries and allergic contact dermatitis (ACD). Both types of injuries continue to have a significant impact on public health. For example, household cleaners and other chemical products are the leading cause of consumer-product-related eye injuries in children under 10. Skin diseases, including allergic skin reactions, comprise the most common category of occupational disease, and ACD accounts for an estimated 7 million health care visits each year in the United States.

Since their establishment in 1997, NICEATM and ICCVAM have contributed to the adoption of 40 alternative safety testing methods.

Ensuring worker and consumer safety

In his opening remarks, Rear Admiral William Stokes, D.V.M., NICEATM director, emphasized the important role of ICCVAM and NICEATM in translating new science from the bench into accepted and standardized test methods, such as those discussed at the workshops. "These methods can now be used as public health tools to help prevent diseases and injuries to consumers and workers by ensuring appropriate labeling of hazardous chemicals and products," Stokes said. "The methods also minimize or avoid animal use and improve animal welfare where it is still necessary to use animals."

More than 70 scientists from industry, academia, and federal research and regulatory agencies gathered at the National Institutes of Health (NIH) campus for each workshop. Both workshops, which were also webcast, were co-sponsored by the Society of Toxicology and the Society for Risk Analysis.

An interagency research initiative

Stokes also highlighted the NIH and U.S. Food and Drug Administration (FDA) joint regulatory science research initiative launched last year by NIH Director Francis Collins, M.D., Ph.D., and Margaret Hamburg, M.D., FDA commissioner (see press release). The initiative seeks to accelerate the development of new tools and approaches to more efficiently and effectively evaluate product safety, efficacy, and quality. Four initial grants were awarded, including one to develop an *in vitro* test battery to determine the potential for chemicals and products to cause eye injuries.

Applying new methods — a case study approach

Eugene Elmore, Ph.D., a scientist from the University of California, Irvine and member of the federal advisory committee for NICEATM and ICCVAM, noted, "The workshop not only provided an important opportunity to explain how the new methods can be used for regulatory safety decisions, but also provided important information on how to properly conduct and interpret the assays. The successful conduct of *in vitro* assays requires careful adherence not only to all aspects of the protocol, but also to all aspects of good cell culture practices."

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Each workshop featured several case studies to allow participants to gain experience in selecting appropriate test methods and interpreting results from actual studies. Each workshop also included roundtable discussions with regulatory agencies and concluded with presentations on promising *in vitro* and *in chemico* methods in the validation pipeline. They were also the focus of many of the 35 poster presentations available for viewing throughout both workshops.

Shown, left to right, are the speakers and staff at the Jan. 20 workshop on allergic contact dermatitis: Stokes; Darrell Boverhof, Ph.D., The Dow Chemical Company; Michael Woolhiser, Ph.D., The Dow Chemical Company; ICCVAM Vice Chair Joanna Matheson, Ph.D., Consumer Product Safety Commission; Abby Jacobs, Ph.D., Food and Drug Administration; ICCVAM Chair Jodie Kulpa-Eddy, Ph.D., Department of Agriculture; David Allen, Ph.D., principal investigator, ILS, Inc. supporting NICEATM; Judy Strickland, Ph.D., toxicologist, ILS, Inc., supporting NICEATM; Hitoshi Sakaguchi, Ph.D., Kao Corporation; Eleni Salicru, Ph.D., toxicologist, ILS, Inc. supporting NICEATM. *(Photo courtesy of NICEATM)*

Responses from participants were overwhelmingly positive. One commented that the workshop was "an extremely helpful mechanism to bring industry and regulators up to speed and on the same page regarding what [test methods] are available, how they work, and to what extent regulators are willing to consider them."

Presentations from the workshops are available on the NICEATM-ICCVAM Website. Plenary session presentations were webcast and are available for viewing as archival webcasts on the NIH videocast home page; a link to the archived webcast will also be available on the NICEATM-ICCVAM Website.

(Debbie McCarley is the Special Assistant to Rear Admiral William Stokes, D.V.M., D.A.C.L.A.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

The NICEATM-ICCVAM Five-Year Plan issued in 2008 included the promotion of the regulatory acceptance and use of scientifically sound alternative test methods as a major objective. The Best Practices Workshops implement this objective by creating awareness and encouraging consideration and use of newly available accepted alternative safety testing methods. The two workshops are the first in a series on Best Practices for Regulatory Safety Testing, sponsored by NICEATM and ICCVAM, an interagency committee administered by NICEATM.

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Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) will meet on June 16-17, 2011, at the Hilton Arlington, 950 North Stafford Street, Arlington, VA. The meeting will be announced in the Federal Register and will be open to the public with opportunity for presentation of oral comments or submission of written comments. Materials for the meeting will be posted on the SACATM webpage (http://ntp.niehs.nih.gov/go/7441). SACATM provides external advice on activities of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).

Preliminary agenda topics include: (1) an update on NICEATM/ICCVAM activities, (2) a report on regulatory acceptance and availability of ICCVAM-recommended alternative test methods, (3) the March 29-30 peer review panel meeting – *Evaluation of an* In Vitro *Estrogen Receptor Transcriptional Activation Test Method for Endocrine Disruptor Chemical Screening*, (4) recent NICEATM/ICCVAM workshops, and (5) updates on activities by international liaisons from Health Canada, the European Centre for the Validation of Alternative Methods, the Korean Center for the Validation of Alternative Methods, and the Japanese Center for the Validation of Alternative Methods.

Contact Information: Dr. Lori White, Designated Federal Officer, NTP Office of Liaison, Policy and Review,
NIH/NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-9834; FAX: (919) 541-0295; whiteld@niehs.nih.gov

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

U.S. Federal Agencies Endorse ICCVAM Recommendations for New Test Methods to Identify Ocular Toxicity Hazards

NIEHS and other U.S. Federal agencies have endorsed new alternative safety testing methods that can replace animal use for some eye safety testing and provide for pain-free testing when it is necessary to use animals to confirm whether chemicals and products may cause eye injuries. The recommendations were made by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), an interagency committee supported and administered by NICEATM.

ICCVAM made the recommendations after a comprehensive evaluation of the scientific validity of the proposed test methods. The acceptance of the ICCVAM recommendations by regulatory agencies including the Food and Drug Administration, Environmental Protection Agency (EPA), Occupational Safety and Health Administration, and Consumer Product Safety Commission is expected to result in fewer animals being used for eye safety testing, and eliminate discomfort for those animals that are still required for testing according to Federal regulations.

Accurate labeling of chemicals and products for their potential to cause ocular injuries is of clear public health importance. Chemical products such as household cleaning chemicals are the leading cause of consumer product-related ocular injuries in children under age 10. Testing chemicals and products for their potential to cause ocular injuries provides information that allows these products to be appropriately labeled with hazard and first aid information, protecting workers and consumers who use them.

In response to requests from the EPA, NICEATM and ICCVAM evaluated several *in vitro* test methods proposed for classifying ocular hazards without the use of live animals. ICCVAM recommended the Cytosensor microphysiometer (CM) test method as a screening test to identify some types of substances that will not cause sufficient injury to require eye hazard labeling. The CM test method is the first *in vitro* eye safety testing method adopted for use in what is referred to as a bottom-up approach to testing. ICCVAM also recommended that the CM test method can be used to identify some types of substances that may cause permanent or severe eye injuries.

ICCVAM evaluated several other *in vitro* test methods and testing strategies, but concluded that their ability to predict ocular hazard potential needs to be improved before they may be used for the specific regulatory safety testing applications under consideration. Accordingly, ICCVAM made recommendations on future studies that could potentially improve these test methods and testing strategies.

ICCVAM also recommended that pain management procedures should always be used when it is necessary to use animals to determine the eye injury potential of test substances. The procedures include the routine use of topical anesthetics similar to those used for human eye surgeries as well as systemic analgesics. They also include using specific clinical signs and lesions that, if observed during the animal study, can serve as humane endpoints to terminate the study early.

The ICCVAM recommendations also form the basis for proposals to update internationally used existing test guidelines on ocular safety testing issued by the Organization for Economic Co-operation and Development.

Protocols for the CM test method, the pain management procedures for *in vivo* testing, and other ICCVAM-recommended test methods are available on the test method protocols page of the NICEATM-ICCVAM Website at http://iccvam.niehs.nih.gov/methods/protocols.htm.

Information on the September 2010 ICCVAM recommendations on ocular safety testing methods and approaches can be found at: http://iccvam.niehs.nih.gov/methods/ocutox/Transmit-2010.htm.

ICCVAM recommendations on ocular safety testing methods and approaches were presented at a January 2011 workshop, "Best Practices for Regulatory Safety Testing," (see page 7). Materials from this workshop are available at http://iccvam.niehs.nih.gov/meetings/Implement-2011/ImplmtnWksp.htm.

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NTP Director Signs International Agreement During Society of Toxicology Annual Meeting

Dr. Linda Birnbaum, Director of NIEHS and NTP, joined international counterparts last month in signing an agreement that expands international cooperation to reduce the number of animals required for safety testing worldwide. The agreement brings a new country, South Korea, into an existing effort to promote international cooperation that should permit more rapid acceptance of new safety testing methods for chemicals and products. New testing methods can better protect public health and also reduce the number of animals needed for safety testing.

The agreement, known as the International Cooperation on Alternative Test Methods (ICATM), was signed in a ceremony March 8 during the 50th Annual Meeting of the Society of Toxicology (SOT). Birnbaum signed as the U.S. representative on behalf of NICEATM, one of the national organizations participating in the agreement. This update to the April 2009 ICATM Memorandum of Cooperation was also signed by representatives of the European Union and the governments of Canada and Japan.

The ICATM agreement promotes international cooperation on the scientific validation of new test methods. Test methods that are shown to be reproducible based on strong scientific information will be more readily accepted by regulatory agencies worldwide. This will in turn lead to their broader acceptance and use, benefitting both public health and animal welfare.

More information on the ICATM agreement is available on the NICEATM-ICCVAM Website at http://iccvam.niehs.nih.gov/about/icatm.htm

NICEATM Director Dr. William Stokes co-chaired an information session on ICATM at the SOT Annual Meeting. The goal of the session, which was attended by about 100 people, was to inform SOT members of the important role ICATM plays in facilitating the rapid international adoption of new validated alternative safety testing methods. Dr. Stokes also gave an introductory presentation that described the purposes and goals of ICATM. His presentation outlined the validation process for new test methods and noted the positive impact that the ICATM agreement had on the adoption of international guidelines for chemical safety testing in 2009 and 2010.

Dr. Stokes, NICEATM Deputy Director Dr. Warren Casey, ICCVAM members, and NICEATM contract staff scientists also presented eight posters at SOT summarizing recent NICEATM and ICCVAM test method evaluation activities. The posters described evaluations of new test methods to assess potential eye irritation and allergic contact dermatitis hazards, validation studies for two test methods proposed for identifying substances that may interfere with estrogen activity, and a summary of the 2010 NICEATM-ICCVAM workshop on alternative methods for vaccine potency and safety testing.

Information on NICEATM-ICCVAM activities at the 2011 SOT Annual Meeting can be found at http://iccvam.niehs.nih.gov/meetings/SOT11/sotablst.htm.

ICCVAM Peer Panel Reviews *In Vitro* Test Method for Identification of Potential Endocrine Disruptor Activity

In a public meeting convened last month, an independent international peer review panel agreed with ICCVAM draft test method recommendations stating that an *in vitro* test method may be used as an initial screen to identify substances with the potential to enhance or inhibit activation of the estrogen receptor. Over 40 scientists representing industry, academia, and Federal regulatory agencies attended the peer panel meeting, which was open to the public.

NICEATM and ICCVAM convened the peer review panel meeting on March 29-30, 2011. The panel, which included expert scientists from seven countries, reviewed data from a NICEATM-sponsored validation study to assess the accuracy and reliability of an *in vitro* estrogen receptor (ER) transcriptional activation (TA) test method. This test method, the BG1Luc ER TA, was considered for qualitative identification of substances with *in vitro* ER agonist or antagonist activity. The BG1Luc ER TA test method uses human ovarian cancer cells to measure whether and to what extent a substance induces or inhibits TA activity via ER-mediated pathway.

Endocrine disruptors are substances that interfere with the normal function of hormones in the endocrine system. These interferences can lead to abnormal growth, development, or reproduction. Studies indicating that animal populations

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exposed to high levels of these substances have an increased incidence of reproductive and developmental abnormalities have raised concerns about the potential public health effects of these substances.

In response to these concerns, the EPA initiated the Endocrine Disruptor Screening Program to screen pesticides and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife. The BG1Luc ER TA test method may be appropriate for use as an initial screen of substances tested in this program.

A report of the peer review panel meeting containing a detailed summary of the panel's discussions and conclusions will be published in May and will be available on the NICEATM–ICCVAM Website at: http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm.

Contact Information: Dr. William S. Stokes, Director, NICEATM, NIH/NIEHS, P.O. Box 12233, MD K2-16, Research Triangle Park, NC 27709; T: (919) 541-2384; FAX: (919) 541-0947; niceatm@niehs.nih.gov

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NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC) will meet in the Rodbell Auditorium, Rall Building, NIEHS, on April 13, 2011. The role of the BSC is to provide scientific input on the NTP's activities, centers, and collaborative programs. The meeting was announced in the Federal Register (76 FR 8370) and is open to the public, subject to available space. As available, information for this meeting will be posted on the NTP Website (http://ntp.niehs.nih.gov/go/165). The meeting will be webcast at http://www.niehs.nih.gov/news/video/live/.

Preliminary agenda topics include: (1) reports from the NTP Director and Associate Director, (2) review of a contract concept – *Potential for Environmental and Therapeutic Agents to Induce Immunotoxicity*; (3) NTP's modified one-generation reproduction study design, (4) statistical methods used in NTP Technical Reports, (5) research concepts on nanomaterials exposure assessment and biospecimen repository and analysis capabilities, and (6) a workshop concept – *Clarifying Potential Health Effects of Excess Folic Acid Intake.*

Contact Information: Dr. Lori White, Designated Federal Officer, NTP Office of Liaison, Policy and Review, NIH/NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-9834; FAX: (919) 541-0295; whiteld@niehs.nih.gov

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The NTP website offers electronic files of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports. The PDF files of these reports are available free-of-charge through the NTP website at http://ntp.niehs.nih.gov (see Resources).

Contact Information: NTP Office of Liaison, Policy and Review, NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-0530; FAX: (919) 541-0295; CDM@niehs.nih.gov

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