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:

NTP achieves division status at NIEHS

by Eddy Ball reprinted from *eFACTOR*, June 2011

In an April 28 Federal Register announcement, NIH Director Francis Collins, M.D., Ph.D., officially announced establishment of the Division of the National Toxicology Program (NTP), which was formerly a program within the NIEHS Division of Intramural Research (DIR). The announcement is the final step in NTP officially becoming a division at NIEHS, and it marks the achievement of an important goal for NIEHS/NTP Director Linda Birnbaum, Ph.D., the first board-certified toxicologist to serve as the Institute's leader.

Linda S. Birnbaum

John Bucher

In addition to NIH approval, the reorganization was approved by HHS Secretary Kathleen Sebelius. Congress was also notified, since this was one of the first reorganizations that occurred under the NIH Reform Act of 2006, requiring a number of additional steps for Institute reorganizations.

In her email message to employees, Birnbaum outlined the benefits of the reorganization. "The new structure will promote greater efficiency at NIEHS, by making a clear staffing and budgetary demarcation between those components of the NIEHS carrying out work dedicated solely to the pursuit of the goals and initiatives of the NTP, and those principal investigator-initiated efforts carried out by staff in the DIR," she wrote.

The new organizational structure, which became effective Feb. 22, retains four of the previous branches – Biomolecular Screening, Cellular and Molecular Pathology, Program Operations, and Toxicology. Newly established is the NTP Laboratory reflecting the important role of targeted in-house research in achieving NTP objectives.

In addition to holding the position of Associate Director of NTP, John Bucher, Ph.D. will now serve as the Director of the Division of the National Toxicology Program.

"I am very pleased to be overseeing the day-to-day activities of this new division," said Bucher. "Having divisional status provides recognition of the unique mission and goals of the NTP within NIH, and the unique capabilities and talents of our staff."

Learn more about the new division by visiting the organizational chart online

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NTP board supports folic acid workshop, nanomaterials program, and more

by Ernie Hood, reprinted from *eFACTOR*, May 2011

The NTP Board of Scientific Counselors (BSC) gave several scientific initiatives the "thumbs up" when it met April 13 at the Rodbell Auditorium on the NIEHS main campus.

The NTP Board of Scientific Counselors reviewed several proposed new programs at its April 13 meeting. *(Photo courtesy of Steve McCaw)*

Among the projects supported by the BSC was a workshop concept proposed by the Center for the Evaluation of Risks to Human Reproduction (CERHR), which is slated to be re-named the Office of Health Assessment and Translation under the impending re-organization of NTP. The workshop, to be held in March 2012 in Washington, D.C., will focus on clarifying the potential adverse health effects of excess intake of folic acid. The event is being developed in conjunction with the NIH Office of Dietary Supplements (ODS).

Workshop on excess folic acid supplementation

While folic acid supplementation to prevent neural tube defects has been one of the major public health success stories of recent years, a growing body of research suggests that folic acid intake over the recommended daily allowance may be associated with adverse health effects in adults and children, including *in utero* exposure developmental and epigenetic effects, cardiovascular disease, cancer incidence and progression, and neurological and psychiatric disorders.

The proposed workshop will gather experts to review and clarify current related human literature, as well as animal and *in vitro* literature as it may apply to humans, and will identify data gaps to help guide future research.

Although the BSC was not unanimously behind the project, overall the panel members were enthusiastic in their support. U.S. Food and Drug Administration liaison Paul Howard, Ph.D., commented that the effort was reminiscent of CERHR's work on bisphenol A. "I think this is an excellent opportunity to do the same thing," he said. "People are making decisions without knowing the full basis of the literature and having vetted it, and this is an excellent service by NTP and NIEHS – to get experts together, vet the literature, and say, "This is what stands up as being good science."

Testing safety of engineered nanomaterials

The BSC also favored another NTP research concept presented at the meeting – a collaboration with the National Institute for Occupational Safety and Health (NIOSH) Nanotechnology Research Center to extend

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Upcoming Events

CANCELLED
July 21-22, 2011

NTP Board of Scientific Counselors

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

Sep 26-27, 2011

Workshop: Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects

Sheraton Chapel Hill
1 Europa Drive
Chapel Hill, NC

October 11-13, 2011

NICEATM Workshop: International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward

U.S. Department of Agriculture
Center for Veterinary Biologics
Ames, Iowa

October 19-20, 2011

Peer Review of Draft NTP Monograph on Developmental Effects of Cancer Chemotherapy during Pregnancy

NIEHS
111 TW Alexander Drive
Research Triangle Park, NC

November 17-18, 2011

Peer Review of Draft NTP Monograph on Low-Level Lead

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

and expand field exposure assessment studies involving engineered nanomaterials. The proposal covers a three-year period, during which NIOSH will conduct exposure assessment surveys at 12 sites involved in the manufacture or use of 16 representative manufactured nanomaterials determined by the Organisation for Economic Co-operation and Development. The materials include well-known and highly used nanoparticles such as fullerenes, single-walled carbon nanotubes, and titanium dioxide, as well as lower-profile or emerging nanomaterials such as graphene platelets and nanocrystalline cellulose.

With the economic importance and use of engineered nanomaterials rapidly increasing, many questions about their impact on health and safety remain unanswered, particularly in occupational settings, where human exposure is most likely. The proposed NTP/NIOSH nanotoxicological studies will target dermal and inhalation exposures in the workplace, examining endpoints such as inflammation, oxidant stress, fibrosis, and translocation. The investigations will increase the overall body of knowledge on the characterization, volume, and specific applications being developed for nanomaterials intended for commercialization, and will help guide future decisions about which nanomaterials to test and how to test them.

Some BSC members felt that the scale of the proposed program was too limited given the scope of the issues involved, but were reassured when NIEHS/NTP Director Linda Birnbaum, Ph.D., reminded them that it was just one part of the much wider NIEHS/NTP efforts in nanosafety research. "This is just one piece of a much larger puzzle," she said.

Dori Germolec, Ph.D., briefed the BSC on the contract recompetition for investigation of agents that may induce immunotoxicity. *(Photo courtesy of Steve McCaw)*

In other business

At its April 13 meeting, the board also voted in favor of a contract concept for recompetition of an existing contract for research into chemicals, drugs, or other environmental agents that are potential hazards affecting the human immune system. The new contract will increase emphasis on evaluation of developmental immunotoxicity. The BSC was also updated on NTP's modified one-generation reproduction study design, statistical methods used in NTP Technical Reports, and a proposed new network of biospecimen repository resources.

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

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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NTP Peer Review Panel weighs in on Aloe vera extract, other compounds

Don't throw out the aloe plant you keep to treat burns, but it might be time to reconsider if you consume certain commercial products containing Aloe vera, such as drinks, concentrates, capsules, powders, and flavorings.

by Ernie Hood reprinted from *eFACTOR*, May 2011

In its April 5, 2011 meeting at NIEHS, the NTP Technical Reports Peer Review Panel agreed with the conclusions reached from two-year drinking water bioassays in rats and mice as presented in the draft NTP Technical Report, which said, "There was *clear evidence* of carcinogenic activity of a non-decolorized whole leaf extract of *Aloe* vera in male and female F344/N rats based upon increased incidences of adenomas and carcinomas of the large intestine." *Clear evidence* is the highest designation in the four-point scale used by NTP to characterize levels of evidence for carcinogenic activity in the substances it evaluates.

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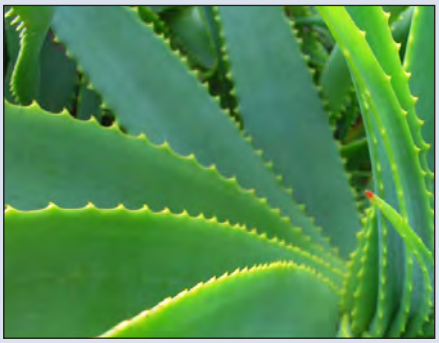

There are at least 420 different plant species of Aloe. Aloe vera specifically refers to the Aloe barbadensis Miller plant, which is the most common form used in Aloe-based products. An organic component in the outer leaf pulp of Aloe leaves, known as the latex, contains aloin.

Mary Boudreau, Ph.D., NCTR study scientist for the Aloe vera technical report, briefed the Peer Review Panel on the toxicology and carcinogenesis studies of Aloe vera administered in drinking water to rats and mice. *(Photo courtesy of Steve McCaw)*

Families can reduce their exposure to acrylamide by adopting a healthy, balanced eating plan that includes fruits and vegetables, lean meats, fish, and high-fiber grains.

While previous NTP studies of dermal exposures to Aloe vera in mice did not find a strong link with skin cancer, these newer studies showed that exposure via chronic ingestion in the water was associated with a high incidence of colon cancer in the rat. The rat colon cancer shared morphological and molecular features with human colon cancer, the fourth most commonly diagnosed cancer and the second-leading cause of cancer-related deaths of people in the United States. In its oral form, Aloe vera is commonly marketed as an "herbal remedy" that is claimed to alleviate a variety of conditions, including cancer, arthritis, constipation, and gastrointestinal disorders. Since the Aloe vera extract is a dietary supplement, it has not been subjected to the same U.S. Food and Drug Administration (FDA) regulations as apply to drugs.

In collaboration with the FDA's National Center for Toxicological Research (NCTR), the NTP studied the non-decolorized extract processed from the whole leaf of the plant. That extract contains an anthraquinone called aloin, which may give the plant its laxative qualities. Some anthraquionones have previously been shown to be carcinogenic. Many commercial preparations, it should be noted, run the whole leaf extract through a filtration process, decolorizing it and removing much of the aloin. However, according to the nomination of Aloe vera to the NTP testing process by the National Cancer Institute, the non-decolorized extract is still widely available, leading to potentially widespread exposure to aloin in the U.S. population.

The panel also agreed with the draft Technical Report conclusions reporting clear evidence of carcinogenic activity in male and female mice and rats exposed to acrylamide in drinking water, with tumors formed at multiple sites. Acrylamide is a chemical widely used in the manufacturing of papers, dyes, and other industrial products. It can be formed when certain foods are cooked at high temperatures, such as potatoes and grains processed to make French fries, toast, or potato chips. Cigarette smoke also contains acrylamide. To aid in its risk assessment concerning the compound, including potential actions to reduce human exposures, it was nominated by the FDA's Center for Food Safety and Applied Nutrition for study by the NTP and NCTR.

Finally, the panel also concurred with draft Technical Report conclusions on two other reports: toxicology and carcinogenesis studies of senna, the active ingredient in frequently used over-the-counter laxatives and also as a flavoring agent, and toxicology and carcinogenesis studies of transplacental exposure of several antiretroviral agents used singly or in combination to treat HIV.

The reviewers agreed that there was no evidence of carcinogenic activity of senna in the transgenic mouse models exposed to the compound. They also agreed with the variety of conclusions reached regarding transplacental exposures in mice to the drugs 3′-azido-3′-deoxythymidine (AZT), lamivudine (3TC), nevirapine (NVP), and nelfinavir nesylate (NFV). AZT was tested singly, in combination with 3TC, and both were used in combination with NVP or NFV, reflecting current "cocktail" HIV therapies. Among these combinations, there was some evidence of carcinogenic activity in male mice exposed to the mixture of AZT, 3TC, and NVP. ●

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

The Office of Health Assessment and Translation: A Problem-Solving Resource for the National Toxicology Program

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John R. Bucher


Kristina A. Thayer


Linda S. Birnbaum

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in 1998. CERHR served as an environmental health resource providing in-depth scientific assessments of effects on reproduction and development caused by agents to which humans are exposed. To our knowledge, CERHR was the only resource of its kind, producing evaluations that considered toxicity findings in the context of current human exposures to derive "level-of-concern" conclusions. This qualitative integration step is what distinguished CERHR documents from more traditional hazard evaluations prepared by other agencies.

When CERHR was established, the focus on reproduction and development was appropriate because of a strong interest in these health outcomes by the public, regulatory and health agencies, and the scientific community. In addition, a rationale for creating CERHR was the sense of a lack of uniformity across state and federal agencies in interpreting experimental animal studies of reproduction and development. CERHR was envisioned as a mechanism to apply a consistent strategy for interpreting these data. Although this need remains, we believe that the approaches used for CERHR evaluations should also be extended to other important health outcomes. Many chemicals display more than one type of toxicity, that is, carcinogens are often immunotoxicants, and reproductive and developmental toxicants may influence many endocrine-sensitive systems. A strict focus on reproductive and developmental end points evaluated in the context of current human exposures may not result in the most health protective levels of concern, and could be confusing to the public. From a public health perspective, understanding the implications of current human exposures should include consideration of all relevant health effects. Also, the NTP and the broader toxicology community need to confront the challenging scientific questions involved in utilizing information from the Toxicology in the 21st Century initiative (Collins et al. 2008). To do this we need a mechanism to systematically explore linkages between "toxicity pathways" and disease outcomes. To provide this, CERHR has spent the last 2 years in transition, laying the groundwork to become a more flexible scientific analysis program, while continuing to be grounded and recognized as a unique and important public health resource for the interpretation of reproductive and developmental hazards to humans.

This evolution of CERHR is a response to the changing and increasing demands on both the NTP analysis and research programs. "What does it mean?" is a question we increasingly want to answer, as our research and testing tools become more sophisticated and mechanistically based. A change in CERHR's scope will also bring its work more in line with two recent initiatives established within the NTP that have mandates to address a broad range of health effects (Bucher 2008). In 2007 the NTP established a biomolecular screening program to administer its High Throughput Screening (HTS) Initiative in collaboration with our Tox21 partners (Schmidt 2009). This program takes advantage of technological advances in molecular biology and computer science to screen for mechanistic targets or "toxicity pathways" considered critical to adverse health effects. The host susceptibility program was also established in 2007 to study the genetic basis for differences in susceptibility that may lead to a better understanding of how substances in our environment may be hazardous to some individuals and not to others.

On 11–13 January 2011, CERHR launched its expanded role by convening a diverse group of experts in toxicology, epidemiology, bioinformatics, and endocrinology to assess the strength of the literature linking selected environmental agents and exposures with diabetes and obesity (NTP 2011). Consideration was given to an array of information ranging from epidemiological findings and experimental animal and mechanistic data to screens of toxicity and disease pathways using HTS and literature curation methodologies. The use of several new analysis tools revealed novel linkages between a number of environmental agents and obesity or diabetes. These exciting findings are now being collated for publication.

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To fulfill its mission, the NTP is developing more innovative and flexible approaches for information and data integration, both across different programs within the NTP and across the different types of data that are generated and utilized (i.e., mechanistic or high throughput; "hypothesis-driven" animal studies of the type undertaken by National Institute of Environmental Health Sciences (NIEHS)-funded extramural grantees; and toxicology studies conducted for the purpose of safety assessment). Recent experience with bisphenol A highlights the public's confusion and the waste of scientific resources that can occur when these different types of scientific literature are developed on parallel, but separate, paths (Bucher 2009). The evolution of CERHR is an important part of this information integration effort, and CERHR's new role calls for a new name: the Office of Health Assessment and Translation. Under the leadership of Kristina Thayer, the Office of Health Assessment and Translation will be the NTP focal point for the thoughtful and deliberative integration of relevant information of all types in health assessments for the protection of public health.

The authors declare they have no actual or potential competing financial interests.

John R. Bucher
Kristina A. Thayer
Linda S. Birnbaum
National Institute of Environmental Health Sciences
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, North Carolina
E-mail: bucher@niehs.nih.gov

John R. Bucher is the Associate Director of the NTP, an interagency program headquartered at the NIEHS. Along with participating programs at the National Center for Toxicological Research, Food and Drug Administration, and laboratories of the National Institute for Occupational Safety and Health in Morgantown, West Virginia, and Cincinnati, Ohio, the NTP is the nation's principal comprehensive toxicology analysis, research, and testing effort. Bucher holds a Ph.D. in pharmacology from the University of Iowa, an M.S. in biochemistry from the University of North Carolina, and a B.A. in biology from Knox College, and he was an NIH Postdoctoral Fellow in biochemistry and environmental toxicology at Michigan State University. He is a Diplomate of the American Board of Toxicology and a Fellow of the Collegium Ramazzini.

Kristina A. Thayer, Director of the NTP Office of Health Assessment and Translation, holds a Ph.D. in biological sciences from the University of Missouri–Columbia. She has been with the NIEHS since 2003, serving in the NTP Office of Liaison, Policy, and Review and the NIEHS Office of Risk Assessment Research prior to assuming her current position. She has authored numerous NTP reports and manuscripts on the toxicological potential of environmental substances.

Linda S. Birnbaum, Director of the NIEHS and the NTP, oversees a budget that funds multidisciplinary biomedical research programs and prevention and intervention efforts that encompass training, education, technology transfer, and community outreach. She recently received an honorary Doctor of Science from the University of Rochester, the distinguished alumna award from the University of Illinois, and was elected to the Institute of Medicine. She is the author of > 700 peer-reviewed publications, book chapters, abstracts, and reports. Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois, Urbana. A board-certified toxicologist, she has served as a federal scientist for 31 years, 19 with the U.S. EPA Office of Research and Development, preceded by 10 years at the NIEHS as a senior staff fellow, a principal investigator, a research microbiologist, and a group leader for the institute's Chemical Disposition Group.

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New substances added to HHS Report on Carcinogens

by Robin Mackar reprinted from *eFACTOR*, July 2011

The U.S. Department of Health and Human Services added eight substances to its latest Report on Carcinogens, a science-based document that identifies chemicals and biological agents that may put people at increased risk for cancer. The report was officially announced by NIEHS during a press briefing June 10.

The industrial chemical formaldehyde and a botanical known as aristolochic acids are listed as *known human carcinogens*. Six other substances – captafol, cobalt-tungsten carbide (in powder or hard metal form), certain inhalable glass wool fibers, o-nitrotoluene, riddelliine, and styrene – were added as substances that are reasonably anticipated to be human carcinogens. With these additions, the 12th Report on Carcinogens now includes 240 listings.

"Reducing exposure to cancer-causing agents is something we all want, and the Report on Carcinogens provides important information on substances that pose a cancer risk," said Linda Birnbaum, Ph.D., NIEHS/NTP director. "The NTP is pleased to be able to compile this report."

John Bucher, Ph.D., associate director of the NTP added, "This report underscores the critical connection between our nation's health and what's in our environment."

The Report on Carcinogens is a congressionally mandated document that is prepared for the HHS Secretary by the NTP. The report identifies agents, substances, mixtures, or exposures in two categories - known to be a human carcinogen and reasonably anticipated to be a human carcinogen. A listing in the Report on Carcinogens does not by itself mean that a substance will cause cancer. Many factors, including the amount and duration of exposure, and an individual's susceptibility to a substance, affect whether a person will develop cancer.

Once a substance is nominated by the public or private sector and selected for consideration, it undergoes an extensive evaluation with numerous opportunities for scientific and public input. There were at least six opportunities for public input on each substance. The NTP used established criteria to evaluate the scientific evidence on each candidate substance under review. The NTP drew upon the scientific expertise of several federal agencies, including the National Institutes of Health, Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry, U.S. Food and Drug Administration, U.S. Environmental Protection Agency, U.S. Consumer Product Safety Commission, and Occupational Safety and Health Administration.

"The strength of this report lies in the rigorous scientific review process," said Ruth Lunn, Dr.P.H., director of the NTP Office of the Report on Carcinogens. "We could not have completed this report without the significant input we received from the public, industry, academia, and other government agencies."

A detailed description of each substance listed in the Report on Carcinogens is included in the new report. NTP has posted the report and other materials, such as fact sheets and frequently asked questions, online.

Contact Information: Dr. Ruth M. Lunn, Report on Carcinogens Center, NIH/NIEHS, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709
T: (919)-316-4637; FAX: (919)-541-0144; lunn@niehs.nih.gov. Courier address: NIEHS, Room 2006, 530 Davis Drive, Durham, NC 27713

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Steady progress reported at SACATM Meeting

by Ernie Hood reprinted from *eFACTOR*, July 2011

SACATM participants gathered to celebrate the increasing acceptance of alternative testing methods. http://www.niehs.nih.gov/news/newsletter/2011/july/science-steady/index.cfm *(Photo courtesy of Ernie Branson)*

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meets only once a year, but with considerable progress during the past year in efforts to reduce, refine, or replace animal use in chemical and product safety testing, there was much to discuss and digest at this year's SACATM meeting June 16-17 in Arlington, Va.

In its advisory role to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods.

NIEHS/NTP Director Linda Birnbaum, Ph.D., in her welcoming remarks to the SACATM members; ICCVAM members, representing the 15 participating Federal agencies; and NICEATM staff in attendance, noted the organizations' successes. "ICCVAM and NICEATM continue to provide an effective process for achieving the regulatory acceptance of new safety testing methods," she said.

"The center and the committee have now contributed to the endorsement or adoption of 42 new alternative methods. 28 of these are *in vitro*, and over half of those *in vitro* methods involve human cells," Birnbaum explained. "Thanks to ICCVAM's continued, focused efforts, there are now approved alternatives for many different types of testing, including five of the six most commonly conducted safety tests." Nine of the 42 new alternative methods were put forward in just the past year, she noted.

Two new nominations to NICEATM and ICCVAM, both of which were unanimously supported by the committee, were also prominent in SACATM's agenda. The first, an *in vitro* pyrogen test method for assessing non-endotoxin pyrogens, is an extension of an existing method to screen for substances that induce fever, which is currently used only to detect gram-negative endotoxin. Validation and adoption of the *in vitro* method for non-endotoxin pyrogens would further reduce the use of rabbits, the current model for detecting fever reactions in various drugs and products prior to their commercial release.

The second nomination involves three types of *in vitro* diagnostic and potency assays for botulinum neurotoxins (BoNTs). The new tests are proposed to detect BoNT in suspected botulism poisonings in people and wildlife, and for testing therapeutic and cosmetic BoNT products, which were used in an estimated five million off-label cosmetic treatments in the U.S. in 2008. Rear Adm. William Stokes, D.V.M., director of NICEATM and executive director of ICCVAM noted, "these methods have the potential for more rapid and accurate public health and product testing, and could significantly reduce the number of mice used for BoNT testing throughout the world."

SACATM chair Steven Niemi, D.V.M., from Massachusetts General Hospital, said it was very appropriate for the nominations to be front and center for the committee's business at the meeting. "They were both obviously very high priority, and will have a big impact on animal welfare as soon as they're adopted."

Meeting participants were also updated by representatives of ICCVAM's international partners. In-person presentations were made by collaborators from the Korean Center for the Validation of Alternative Methods (KoCVAM) and the Japanese Center for the Validation of Alternative Methods, and the panel was briefed by telephone by officials from Health Canada and the European Centre for the Validation of Alternative Methods, both of whom had taken in the meeting's proceedings by webcast.

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Stokes praised the international cooperation ICCVAM and NICEATM have received. "It allows us to leverage resources, so we can share the cost and time that it takes to carry out expensive validation studies, and we can also work together so that we're more likely to be in agreement and can achieve faster acceptance of those methods internationally," he said.

Putting alternative test methods into practice

During the meeting, Stokes updated SACATM members on the groups' recent activities and priorities, as well as what he said was "a lot of progress" in domestic and international regulatory acceptance and adoption of ICCVAM-recommended alternative test methods. Among the past year's significant activities were:

- An international workshop on the state of the science and future directions in vaccine potency and safety testing, where there is enormous potential for reducing, refining or replacing the use of animals
- Two workshops on best practices for regulatory safety testing, covering ocular safety testing and allergic contact dermatitis hazard testing
- An ICCVAM Peer Review Panel meeting to evaluate an *in vitro* endocrine disruptor screening method, the LUMI-CELL ER® (BG1Luc ER TA) test method to identify substances with estrogen agonist and/or antagonist activity

Regarding the endocrine disruptor screening test, Stokes said that "it looks like a very promising method, and recommendations will be forwarded to both the U.S. agencies and to the international agency, OECD [Organisation for Economic Co-operation and Development], in the near future."

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

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Kissling to be honored by American Statistical Association

by Eddy Ball, reprinted from *eFACTOR*, June 2011

During her induction at the awards ceremony, Kissling will be presented with a marble Fellows paperweight.

NIEHS/NTP Staff Scientist Grace Kissling, Ph.D., will join a handful of her colleagues when she is officially inducted as a fellow of the American Statistical Association (ASA) Aug. 2 at a Joint Statistical Meetings awards ceremony in Miami Beach, Fla. Kissling will receive the highest honor in her field for what the ASA described as "outstanding contributions to the statistical profession."

Kissling is a member of the NIEHS Biostatistics Branch (BB) headed by Chief Clare Weinberg, Ph.D. Working with scientists across the Institute, Kissling provides statistical advice and assistance for the toxicology and carcinogenicity studies carried out by the NTP and experimental studies carried out by NIEHS researchers. She collaborates on research at all stages – study design, statistical analysis, and interpretation – and has co-authored more than 125 peer-reviewed studies.

Weinberg, who nominated Kissling and has been an ASA Fellow herself since 1995, described election to the ASA Fellows as "an extremely high honor – one achieved by only a tiny fraction of statisticians in their lifetime of work." Commenting on Kissling's work, Weinberg added, "As the person tasked with maintaining the statistical integrity of studies related to the National Toxicology Program, Grace has displayed an outstanding level of creative productivity. It's gratifying to see our 'unsung hero' get this well-deserved recognition!"

According to ASA rules, no more than one-third of one percent of the ASA membership may be elected each year to become new ASA Fellows. Fewer than 3,000 members have been so honored since the society began electing fellows in 1914. In addition to Kissling and Weinberg, NIEHS BB Principal Investigator Shyamal Peddada, Ph.D., who was elected in 2005, and BB Staff Scientist David Umbach, Ph.D., named in 2009, are also ASA Fellows.

ASA, which was founded in Boston in 1839, is the second oldest, continuously operating professional society in the United States. The organization serves statisticians, quantitative scientists, and users of statistics across a wealth of academic areas and applications. With an international membership of 16,000, ASA applies its expertise to many diverse tasks – from assessing environmental risk factors and assuring quality measures in industry, to examining social issues and establishing statistical standards used at all government levels.

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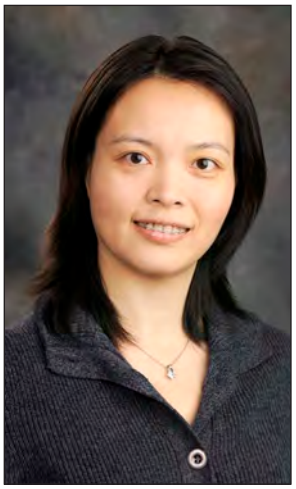
NTP fellow wins NIH research excellence award

Article by Eddy Ball



Chang's abstract also won her recognition in March from the Society of Toxicology with the Nanotoxicology Specialty Section Outstanding Postdoc Award. *(Photo courtesy of Steve McCaw)*

NTP Fellow Xiaoqing Chang, Ph.D., was one of the 21 NIEHS trainees who received 2012 NIH Fellows Awards for Research Excellence (FARE). Chang is a member of the NTP Biomolecular Screening Branch headed by Raymond Tice, Ph.D.

Chang received a FARE for her abstract, "A Physiologically Based Pharmacokinetic Model of Micro- and Nano-Sized Fluorescent Polystyrene Spheres in Rat." 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.

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.

The abstract was selected through peer-review by the Pharmacology and Toxicology/ Environmental Health special study section. FARE awards reflect the scientific excellence of the winners, the quality of the NIEHS/NTP training and career development program, and the superior mentoring that takes place in the Institute's labs.

The FARE program is sponsored by the FelCom, Offices of the Scientific Directors, the NIH Office of Research on Women's Health, and the NIH Office of Intramural Training and Education, and is funded by the Scientific Directors and the Office of Research on Women's Health.

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NTP fellow wins travel award

Article by Eddy Ball

NTP Toxicology Branch Research Fellow Mamta Behl, Ph.D., received a $1000 travel award from the Society of Toxicologic Pathology to attend the annual meeting held June 19-23 in Denver, CO.

Behl presented a poster on NTP research on "Peripheral Neuropathy in Rats Exposed to Styrene Acrylonitrile (SAN) Trimer." SAN Trimer is a by-product of the production of acrylonitrile styrene plastics and is created in specific manufacturing processes for polymers of acrylonitrile and styrene. NTP conducted two-year chronic feeding studies exposing rats to SAN Trimer in a perinatal-postnatal exposure design. Findings from the NTP studies on SAN Trimer were peer-reviewed at a public meeting Jan. 26, (see story).

Other members of the research team included lead NTP Toxicologist Rajendra Chhabra, Ph.D., NIEHS biostatistician Grace Kissling, Ph.D., lead NTP Pathologist Susan Elmore, D.V.M., former NTP Research Fellow Deepa Rao, BVSc, Ph.D., now of Integrated Laboratory Systems, Inc., James Morrison, D.V.M. of Charles River Pathology Associates, and Amy Brix, D.V.M, Ph.D., of Experimental Pathology Laboratories. Dr. Chhabra is Behl's current mentor.

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

Peer Panel Report Available on a New Method to Identify Potential Endocrine Active Substances

In a public meeting on March 29-30, 2011, at the National Institutes of Health, an independent international peer review panel agreed with draft test method recommendations developed by the Interagency Coordinating Committee on the Validation of Alternative Methods, 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 U.S. Federal regulatory agencies attended. The meeting was organized by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), as part of the ICCVAM test method evaluation process.

The panel, which included 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. Also known as the LUMI-CELL® ER assay, this method was developed by Xenobiotic Detections Systems, Inc., with support from a Small Business Innovation Research grant from the NIEHS.

The panel's peer review report was made available in May for public comment, and was discussed by the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at its June meeting (see story page 8). ICCVAM will consider the peer review panel's report, and public and SACATM comments as it develops final test method recommendations, which will be forwarded to U.S. Federal agencies later this year.

Exposure to substances that interfere with the normal function of hormones in the endocrine system can lead to abnormal growth, development, or reproduction. The U.S. Environmental Protection Agency 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.

The peer review panel report is available on the NICEATM-ICCVAM website at: http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm.

Information about the NICEATM-sponsored validation study of the BG1Luc ER TA test method is available at: http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm.

ICCVAM Working Group Proposes Test Guideline Changes to Improve Animal Welfare

Despite recent progress toward developing alternative test methods that do not use live animals, regulatory testing for ocular hazard identification often still uses the rabbit eye test. However, U.S. Federal agencies have now accepted ICCVAM recommendations on pain management procedures that eliminate pain and distress associated with the *in vivo* test when it is determined necessary to conduct this test for regulatory safety assessments.

NICEATM and the ICCVAM Interagency Ocular Toxicity Working Group (OTWG) recently proposed that an internationally accepted test guideline for *in vivo* ocular safety testing be updated to incorporate the ICCVAM-recommended pain management procedures. This would allow these procedures to be used worldwide, resulting in improved animal welfare in cases where *in vivo* testing must be used for ocular safety testing.

The current test guideline for *in vivo* ocular safety testing, "Acute Eye Irritation/Corrosion," was issued in April 2002 as Test Guideline 405 by the Organisation for Economic Co-operation and Development (OECD). OECD test guidelines represent internationally agreed-upon testing methods, which can be used by government, industry, and independent laboratories in the 34 OECD member countries, to determine the safety of chemicals and chemical preparations.

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The ICCVAM recommendations include protocols that describe how to use topical anesthetics (similar to those used in human eye surgeries) and systemic analgesics prior to and after test article administration in order to avoid animal pain and distress. They also identify specific clinical signs and lesions that can be used as humane endpoints to allow an investigator to end a study early in order to alleviate animal pain and distress.

A draft revised Test Guideline 405 was circulated to OECD member countries for comment, and will be considered by the international Working Group of National Coordinators of the OECD Test Guidelines Programme at their meeting in Spring 2012.

More information about the ICCVAM recommendations on the use of anesthetics, analgesics, and humane endpoints in ocular safety testing may be found on the NICEATM–ICCVAM web site at: http://iccvam.niehs.nih.gov/methods/ocutox/pretreat.htm.

NICEATM and ICCVAM Will Convene Workshop on Rabies Vaccine Testing

NICEATM and ICCVAM will convene an "International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward" on October 11-13, 2011, at the U.S. Department of Agriculture Center for Veterinary Biologics in Ames, Iowa. This workshop will bring together international scientific experts from government, industry, and academia to review available methods and approaches that reduce, refine (decrease or eliminate pain and distress), and replace animals used in human and veterinary rabies vaccine potency testing. Participants will then develop an implementation strategy to achieve global acceptance and use of these alternatives.

Rabies in humans is a uniformly fatal disease, with infections killing over 55,000 people worldwide each year. Rabies vaccines serve a vital role in preventing further deaths and controlling the disease in certain animal populations. According to the World Health Organization, an estimated 15 million people receive post-exposure vaccine prophylaxis annually due to actual or suspected exposures to the rabies virus. In the United States and other developed countries, rabies vaccines have effectively eliminated domestic canine rabies virus strains. However, determining the safety and effectiveness of rabies vaccines requires large numbers of laboratory animals and involves significant pain and distress. New methods and approaches are sought that: (1) are more humane and use fewer or no animals, (2) are faster, cheaper, and more accurate, and (3) are safer for laboratory workers.

A recent international workshop organized by NICEATM, ICCVAM, and its international partners identified rabies vaccines as one of the three highest priorities for future research, development, and validation of alternative test methods that could further refine, reduce, and ultimately replace animal use for potency and safety testing. One of the highest priority implementation activities was organization of an international workshop on alternative methods for rabies vaccine potency testing. Based on recent scientific and technological advances, several alternative approaches have been proposed or are currently available.

Participants in the October workshop will review these approaches and define efforts necessary to achieve global acceptance and implementation. The workshop will identify critical components of manufacturing processes necessary to demonstrate batch-to-batch consistency and how monitoring these components can be used with *in vivo* and *in vitro* potency tests in an integrated approach to reduce and replace animal use for rabies batch release. Participants will also identify the most appropriate source(s) for reference reagents to ensure standardization of *in vitro* rabies potency testing methods.

Along with NICEATM and ICCVAM, the workshop will be cosponsored by the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, the Korean Center for the Validation of Alternative Methods, and Health Canada.

A link to a registration form and other information about the workshop is available on the NICEATM-ICCVAM website at http://iccvam.niehs.nih.gov/meetings/RabiesVaccWksp-2011/RabiesVaccWksp.htm. Those planning to attend the workshop are asked to preregister by October 1, 2011. Please note that U.S. Department of Agriculture security requires that all attendees must preregister for the workshop; late registration on the day of the workshop will not be available.

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A poster session during the workshop will feature presentations on current research, development, validation, and/or regulatory acceptance of alternative methods that may reduce, refine, and/or replace the use of animals in rabies vaccine potency testing. NICEATM and ICCVAM invite the submission of abstracts for scientific posters to be displayed during this workshop; abstracts should be submitted by August 17, 2011. Abstract submission guidelines are available on the NICEATM-ICCVAM web site at the location listed above.

If you have questions about the workshop or would like more information, please contact NICEATM at niceatm@niehs.nih.gov.

Nominations Received for Validation Studies on Four *In Vitro* Test Methods

On behalf of ICCVAM, NICEATM has requested public comment on nominations received for validation studies on four *in vitro* test methods. Comments received by July 7, 2011, will be considered by ICCVAM as it finalizes its recommendations on the priority of these nominations. These test methods may have the potential to reduce or replace animal use for detecting and quantifying botulinum neurotoxins and for identifying non-endotoxin pyrogens. NICEATM also seeks data generated using *in vitro* test methods relevant to the nominations, as well as relevant *in vivo* reference data.

Nomination for the Detection and Quantification of Botulinum Neurotoxins

NICEATM seeks data generated using alternative test methods for detecting and quantifying botulinum neurotoxins (BoNT), including but not limited to three test methods nominated by BioSentinel Pharmaceuticals, Inc. (BioSentinel). Data from the standardized mouse LD50 assay currently used for these endpoints are requested for comparison.

Participants at a 2006 ICCVAM-sponsored workshop on alternative methods for botulinum toxin testing noted that some available methods might be useful as replacements for the standard mouse LD50 assay given additional development and validation efforts. Following appropriate validation and demonstration of adequate performance, the three test methods nominated to ICCVAM by BioSentinel may have the potential to meet regulatory requirements for detection and quantification of BoNTs in a range of applications, thus reducing or replacing animal use in the standard assay.

Nomination for the Detection of Non-Endotoxin Pyrogens

NICEATM also seeks data generated using alternative test methods for identifying non-endotoxin pyrogens, including but not limited to the monocyte activation test (MAT), which was nominated to ICCVAM by Biotest AG. Data on non-endotoxin pyrogens tested in the rabbit pyrogen test are requested for comparison.

In a 2008 report on their evaluation of *in vitro* methods proposed for assessing the potential pyrogenicity of pharmaceuticals and other products, ICCVAM noted that the evaluated test methods, which included the MAT, could be applicable for detection of a wider range of pyrogens than was included in their recommendations. ICCVAM thus recommended future studies that could expand the applicability of the test methods. In response to these recommendations, Biotest AG has nominated a commercialized version of one of these tests for additional validation studies to evaluate its usefulness for identifying non-endotoxin pyrogens.

Public Comment Invited

Based on the information provided by the test method sponsors, ICCVAM proposes that the recently nominated activities are of sufficient interest and applicability to warrant further evaluation. ICCVAM's preliminary recommendation is that both nominations should have a high priority for further discussion to assess what information is needed to adequately characterize the usefulness and limitations of the proposed test methods and any other similar *in vitro* test methods for these endpoints.

As part of the nomination review process, NICEATM invited public comments on these nominations and on the appropriateness and draft relative priority assigned by ICCVAM to the nominated activities. The preliminary ICCVAM recommendations were discussed by the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at its meeting in June. SACATM agreed with ICCVAM that the nominations should receive a high priority for continued activity. ICCVAM will consider public and SACATM comments as it finalizes its recommendations on the priority of these nominations.

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NICEATM Staff Will Present at International Meeting

NICEATM staff and ICCVAM committee members will deliver presentations on recent NICEATM-ICCVAM activities and accomplishments at the Eighth World Congress on Alternatives and Animal Use in the Life Sciences, which will take place in Montreal, Canada, on August 21-25. The World Congress is a biennial meeting that supports progress in the life sciences and application of the ethical principles of animal use embodied in the "three Rs" (reduction, refinement, and replacement of animal use). The specific goal of the Eighth World Congress (WC8) is to bridge the distance between science and policy and to identify opportunities for collaboration.

NICEATM and ICCVAM will deliver five presentations at WC8 summarizing recent ICCVAM recommendations on the use of new versions and applications of the murine local lymph node assay to identify substances with the potential to cause allergic contact dermatitis. Other presentations will highlight recent ICCVAM recommendations on ocular safety testing methods as well as conclusions and recommendations from the 2010 NICEATM-ICCVAM workshop on alternative methods for vaccine potency and safety testing.

More information about WC8 is available at the meeting web site at http://www.wc8.ccac.ca/.

Preregistration for WC8 is open until August 1.

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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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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