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

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What's Inside:

Board of Scientific Counselors advises NTP on draft concepts and more

By Robin Mackar, reprinted from the Environmental Factor, May 2014

The NTP Board of Scientific Counselors (BSC) met April 17-18 in Rodbell Auditorium to provide input on several draft evaluation concepts and evaluate findings in draft reports recently peer-reviewed.

Topics included Report on Carcinogen (RoC) draft concepts for cobalt, goldenseal root powder, and selected viruses; the peer-review outcome of four draft technical reports; and two draft concepts from the NTP Office of Health Assessment and Translation (OHAT).

Birnbaum provided updates about the budget, strategic plan, and scientific advances. (Photo courtesy of Steve McCaw)

Report on Carcinogens

Ruth Lunn, Dr.P.H., director of the RoC office, summarized the December peer-review meeting on *ortho*-toluidine, used to make rubber, and the wood preservative pentachlorophenol and by-products of its synthesis. The new BSC chair, Lisa Peterson, Ph.D., of the University of Minnesota, attended the peer-review meeting as BSC liaison. "The science NTP presented was strong and discussions among the reviewers and NTP were quite animated and constructive," Peterson said.

Blystone presented four draft NTP technical reports that were peer-reviewed in October. (Photo courtesy of Steve McCaw)

Gloria Jahnke, D.V.M., presented the draft RoC concept on Epstein-Barr virus, human immunodeficiency virus type 1, human T-cell lymphotrophic virus type 1, Kaposi sarcoma-associated herpes virus, and Merkel cell polyoma virus. She noted that NTP will prepare a separate monograph for each virus, but RoC listing, should it occur, would include all the viruses together. The RoC already lists 3 viruses as known to be human carcinogens.

After the presentation by Diane Spencer of NTP on the draft RoC concept for the popular botanical supplement goldenseal root powder, BSC members discussed relevant doses, studies that should be included in the evaluation, and how to consider other ingredients in goldenseal preparations, before offering support for moving forward.

Spencer also addressed the draft RoC concept for cobalt, a naturally occurring metal. NTP and BSC discussed what mechanisms might drive the development of tumors noted in some studies and what forms of cobalt should be evaluated. Overall, the board expressed support for moving forward with this concept, but several reviewers commented that NTP should specify the forms of cobalt to be reviewed.

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RoC's Spencer gave a show-and-tell of goldenseal root powder, which can be easily purchased at local stores. (Photo courtesy of Steve McCaw)

Lisa Peterson, Ph.D., center, of the University of Minnesota, served ably as the BSC chair, with Bucher, left, and NTP Deputy Division Director for Science, Nigel Walker, Ph.D. (Photo courtesy of Steve McCaw)

Technical reports

NTP toxicologist Chad Blystone, Ph.D., updated the board on the October peer-review meeting for the draft technical reports on cobalt metal, vinylidene chloride, tetrabromobisphenol A, and glycidamide.

Richard Miller, D.V.M., Ph.D., of GlaxoSmithKline and BSC liaison to that meeting, gave positive feedback on both the meeting itself and the studies investigating molecular signatures of the tumors.

Draft concept presentations

Kembra Howdeshell, Ph.D., of OHAT, presented the draft concept for evaluating literature on pregnancy outcomes associated with traffic-related air pollution. She described her team's preliminary literature search of nearly 18,000 unique scientific references, pared down to those addressing health effects, and finally to about 300 studies that included pregnancy outcomes. "When we found this good pocket of literature on pregnancy outcomes, we decided to focus our evaluation on the associations between pregnancy outcomes and traffic-related air pollution," Howdeshell said.

David Dorman, D.V.M., Ph.D., of North Carolina State University, and Sonya K. Sobrian, Ph.D., of Howard University College of Medicine, stressed the need to more clearly define what is meant by traffic-related air pollution.

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Upcoming NTP Events

July 31, 2014

Webinar on Lessons Learned in Application of the OHAT Framework for Systematic Review and Evidence Integration to Case Studies
Location: Web-based meeting

http://ntp.niehs.nih.gov/go/41629

August 12, 2014

Peer Review of Draft Report on Carcinogens (RoC) Monograph on Trichloroethylene (TCE)

http://ntp.niehs.nih.gov/go/38853

August 18, 2014

Symposium on Assessing Exposures and Health Effects Related to Indoor Biomass Fuel Burning

http://ntp.niehs.nih.gov/go/41613

September 3-5, 2014

ICCVAM Workshop
Adverse Outcome Pathways: From Research to Regulation

Location: William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

http://ntp.niehs.nih.gov/go/41374

September 16, 2014

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

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

December 9-10, 2014

NTP Board of Scientific Counselors

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

All meetings are held at NIEHS unless otherwise noted:

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

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

Howdeshell presented two draft OHAT concepts at the meeting, receiving an abundance of welcome comments from the BSC. (Photo courtesy of Steve McCaw)

"You are taking on a daunting subject," Sobrian said. Both suggested that OHAT wait until the CDC completes its evaluations on pregnancy outcomes before proceeding too far with this concept.

NIEHS and NTP Director Linda Birnbaum, Ph.D., and NTP Associate Director John Bucher, Ph.D., both thanked the board for their helpful comments on this issue. "Your comments are making us realize how difficult it is to evaluate a project so early in the process. We will give more thought into how to get public input early," Birnbaum said.

Another draft concept Howdeshell presented to the board was to systematically review the scientific evidence for adverse health effects associated with occupational exposure to cancer chemotherapy agents. The BSC strongly supported pursuing this evaluation.

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

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Peer review panel evaluates draft NTP technical reports

By Ernie Hood, reprinted from the Environmental Factor, June 2014

Draft NTP technical reports evaluating the carcinogenicity and toxicity of two dietary supplements, a water disinfection byproduct, and a metalworking fluid were peer reviewed May 22 by an expert scientific panel.

NTP, an interagency program, conducts rodent toxicity and cancer studies on agents of public health concern to identify potential human health hazards. The technical reports describe the methods, results, and NTP conclusions regarding levels of evidence for carcinogenic activity under the specific conditions of each study.

During the discussion of the draft NTP technical report on bromodichloroacetic acid, Robert Sills, D.V.M., Ph.D., chief of the Cellular and Molecular Pathology Branch, noted that brain tumors such as gliomas are rare in rodents, and that their contribution to the overall cancer burden is similar to humans, about 1-2 percent. (Photo courtesy of Steve McCaw)

Green tea extract

Green tea extract (GTE) is a commonly used dietary supplement in the U.S., marketed for its potential health benefits, such as increasing metabolism, fighting cancer, boosting the immune system, and promoting cardiovascular health. A component of GTE, epigallocatechin gallate, was originally nominated by the National Cancer Institute (NCI) for testing due to the lack of available chronic toxicity and carcinogenicity data. Ultimately, NTP chose to study GTE because there is more human exposure to the extract than to the nominated component. After analyzing several lots of commercially available GTE, NTP selected one GTE preparation for testing.

The panel accepted the draft NTP conclusions of no evidence of carcinogenic activity of GTE in male and female rats and in male mice. They also recommended a conclusion of no evidence of carcinogenic activity in female mice, instead of the draft NTP conclusion of equivocal evidence.

Indole-3-carbinole

Indole-3-carbinole is a dietary supplement sold alone or in combination with other herbals or vitamins. It is marketed as a cancer prevention agent, as well as for its health benefits, such as detoxifying the liver and boosting the immune system. NCI nominated indole-3-carbinole for study based on its occurrence in natural products such as cruciferous vegetables, including broccoli, Brussels sprouts, cauliflower, and kale, and its potential use as a breast cancer chemoprotective agent, to protect healthy tissue from the toxic effects of anticancer drugs.

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The panel accepted the draft NTP conclusions of no evidence of carcinogenic activity in male rats and female mice, some evidence in female rats, and clear evidence in male mice.

Cimstar 3800

Cimstar 3800 is a semi-synthetic metalworking fluid used in machining automotive parts and other materials. The National Institute for Occupational Safety and Health nominated it for study based on a high potential for occupational exposures and the absence of toxicity or carcinogenicity studies.

The panel accepted the draft NTP conclusions of equivocal evidence in male and female rats, no evidence in male mice, and some evidence in female mice.

Bromodichloroacetic acid

Bromodichloroacetic acid (BDCA) is a member of the haloacetic acid family of drinking water disinfection by-products, formed when disinfectants such as chlorine or ozone are used in water treatment plants. It was nominated for study by the U.S. Environmental Protection Agency and the American Water Works Association Research Foundation, based on widespread human exposure in drinking water and lack of toxicity and carcinogenicity studies.

The panel accepted the overall draft NTP conclusions of clear evidence of carcinogenic activity based upon a variety of neoplasms occurring in male and female rats and male and female mice.

For the benefit of those new to the NTP peer-review process, NTP toxicologist Chad Blystone, Ph.D., provided background information on the technical reports and the overall process, including the format of the peer review. (Photo courtesy of Steve McCaw)

NTP pathologist Susan Elmore, D.V.M., explained the differences between the older and newer methods used by NTP pathologists to review uterine tissue sections. While the original transverse sectioning method remains in use, the newer residual longitudinal sectioning method has been used in six NTP studies so far, including three of the four studies being peer reviewed at the meeting — green tea extract, indole-3-carbinol, and Cimstar 3800. (Photo courtesy of Steve McCaw)

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

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NTP board green lights research concepts and predictive toxicology efforts

By Robin Mackar, reprinted from Environmental Factor, July 2014

Birnbaum, left, presented NIOSH representative Gayle DeBord, Ph.D., with a certificate of appreciation for her many years of service to NTP. (Photo courtesy of Steve McCaw)

NTP received the go-ahead June 17-18 to pursue six research concepts, ranging from bisphenol S to xylenes, from its Board of Scientific Counselors (BSC). Predictive toxicology efforts underway by NTP and its federal partners were also presented and well-received by BSC.

NIEHS and NTP Director Linda Birnbaum, Ph.D., and NTP Associate Director John Bucher, Ph.D., kicked off the meeting with brief updates on activities going on at NIEHS and NTP. Scott Masten, Ph.D., who heads the NTP Office of Nominations and Selection, provided a brief introduction to the research concepts to be presented.

Bisphenol S and triclocarban

Vicki Sutherland, Ph.D., a relatively new NTP staff member in the Toxicology Branch, presented the first two concepts. Bisphenol S (BPS) and some of its derivatives are chemicals being used to replace Bisphenol A, a chemical used in many consumer products, including thermal paper and food packaging.

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Paules, left, who provides his expertise to both NTP and the NIEHS Division of Intramural Research, joined Tice to update BSC about predictive toxicology efforts at NTP. (Photo courtesy of Steve McCaw)

Stout responded to questions from BSC about xylenes. (Photo courtesy of Steve McCaw)

Sayers, right, presented on C9 alkylbenzenes and responded to questions from BSC. Nigel Walker, Ph.D., NTP Deputy Division Director for Science is seated to his left. (Photo courtesy of Steve McCaw)

Sutherland said there is limited toxicological data on the effects of BPS. NTP proposed looking at the endocrine activity and other endpoints, using *in vitro* and *in vivo* studies, to predict adverse health effects associated with BPS and other bisphenols.

BSC member Robert Chapin, Ph.D., of Pfizer, said, "No one can do this kind of project better than the NTP. I give it three thumbs-up." All board members agreed it was a high priority project for NTP to pursue, especially given widespread use of BPS and efforts currently underway by NTP on related chemicals.

Sutherland also presented a research concept on triclocarban, an antibacterial chemical used in soaps and skin care products. NTP proposed studies to evaluate developmental and reproductive outcomes, and the board deemed it a moderate to high priority.

"This product has been in use a long time but has not been thoroughly assessed for endocrine activity," Sutherland said.

C9 alkylbenzenes and xylenes

Brian Sayers, Ph.D., also of the NTP Toxicology Branch, presented the concept of C9 alkylbenzenes, a group of eight chemicals that occur naturally in crude oil and used as additives for gasoline blending. Sayers said NTP would conduct a series of short-term and chronic inhalation studies to determine reproductive, developmental, neurotoxic, and carcinogenic potential. After a fruitful discussion on the appropriate scope of the testing effort, BSC Chair Lisa Peterson, Ph.D., of the University of Minnesota, said the board supports this project.

Matthew Stout, Ph.D., from the NTP Program Operations Branch, presented the approach NTP would take to characterize the toxicity and carcinogenicity of xylenes, high volume chemicals produced from petroleum and used to make solvents, paints, and coatings. Stout explained NTP would likely test a high purity mixture of three isomers. As with the prior concept, the board had much discussion on the relative merits of testing mixtures versus individual compounds and considered it a moderate priority.

Health and translation concepts

Kyla Taylor, of the NTP Office of Health Assessment and Translation (OHAT), presented a concept that would involve collaborating with EPA to assess the accuracy of questionnaires used in epidemiological studies as they relate to exposure information about personal care products. BSC gave the overall concept a moderate to high priority.

Andrew Rooney, Ph.D., also of OHAT, presented a concept that would use a two-pronged approach for a literature-based evaluation — a systematic review and the development of an adverse outcome pathway. NTP would examine the evidence that environmental substances contribute to inflammation that ultimately leads to health effects. NTP also would identify biomarkers of the inflammation involved.

NTP would restrict its evaluation to a single health effect, in this case, atherosclerosis, a disease in which plaque builds up in arteries. Board member David Dorman, D.V.M., Ph.D., of North Carolina State University, pointed out that the comorbidity issues related to atherosclerosis could complicate the evaluation. BSC member Iris Udasin, M.D., of Robert Wood Johnson Medical School, also raised concern about comorbidities, but gave the concept a thumbs-up and said the evaluation would be extremely relevant to clinicians.

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

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Predictive toxicology efforts

BSC members also had a chance to hear about efforts underway in the area of predictive toxicology. Raymond Tice, Ph.D., head of the NTP Biomolecular Screening Branch (BSB), provided an update on Tox21, a federal collaboration aimed at improving hazard identification of substances. He provided a timeline and talked about some accomplishments made in the first two phases of the program. He also noted how they are working on improving their biological coverage and relevance in phase III. Tice said there will be more focus on physiologically relevant *in vitro* cell systems, and more emphasis on developing computational models. They also plan to focus on high content screens and high throughput gene expression platforms.

Tice's talk set the stage for Richard Paules, Ph.D., also of BSB, who talked about a Tox21 phase III activity called the S1500 Genes High Throughput Transcriptomics Project. The project builds off information gathered at a workshop in fall 2013, and will develop a Tox21 sentinel gene set comprised of 1,500 genes, to be used for determining the effects of environmental toxins on cells or tissues. The initial focus is on a human gene set, with a similar approach to be used to identify gene sets for rats, mice, zebrafish, and *Caenorhabditis elegans*.

Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), presented the role his group plays in evaluating the applicability of new alternative methods for regulatory use. Casey focused his talk on adverse outcome pathways, which attempt to link exposure to a chemical with a health event or an adverse outcome. He described the role the Organisation for Economic Co-operation and Development plays in processing and publishing information about adverse outcome pathways, and also talked about the role NICEATM plays in helping federal regulatory agencies develop testing strategies to do risk assessments using Bayesian networks, a mathematical approach.

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Small fish may offer big opportunities for future toxicity testing

By Catherine Sprankle, reprinted from Environmental Factor, June 2014

Workshop organizing committee

NIEHS: Casey; Christopher Weis, Ph.D.; Mamta Behl, Ph.D. (contractor); Jonathan Hamm, Ph.D. (contractor)

NCSU: Seth Kullman, Ph.D.; Carolyn Mattingly, Ph.D.; Antonio Planchart, Ph.D.

Duke University: David Hinton, Ph.D.

Environmental Protection Agency: Tamara Tal, Ph.D.

National Center for Toxicological Research, U.S. Food and Drug Administration: Jyotshna Kanungo, Ph.D.

Casey provided an overview of how small fish might provide an alternative model for toxicity testing. (Photo courtesy of Catherine Sprankle)

Scientists from around the world met May 5-6 at North Carolina State University (NCSU) in Raleigh, to consider the key role small fish and fish embryos may play in toxicity testing. Thousands of chemicals are used in industry, agriculture, and consumer products every day, and hundreds more are being developed every year. Yet little is known about how they affect human health. Scientists typically use mice and rats to identify potential health risks of chemicals, but researchers are now considering using other species that would make testing quicker and easier.

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International gathering meets local collaboration

The Collaborative Workshop on Aquatic Models and 21st Century Toxicology drew nearly 150 scientists from the U.S., Canada, Europe, and Asia to discuss the use of small fish or fish embryos in testing to assess chemical safety. A diverse group of scientists from the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) NCSU, Duke University, the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration (see text box), organized the workshop.

Daniel Solomon, Ph.D., dean of the NCSU College of Sciences, welcomed attendees to the new and technologically advanced James B. Hunt Jr. Library on the NCSU campus. Solomon noted the large number of Research Triangle, N.C., area attendees at the workshop in his opening remarks. "Despite the athletic rivalries that exist between our local universities, there are strong collaborations among the researchers, including those working with zebrafish," he said.

NICEATM Director Warren Casey, Ph.D., also welcomed the attendees and remarked that this gathering was part of a larger effort to rethink traditional approaches to toxicology. "We now have the technology to make substantial changes in the way toxicology testing is conducted."

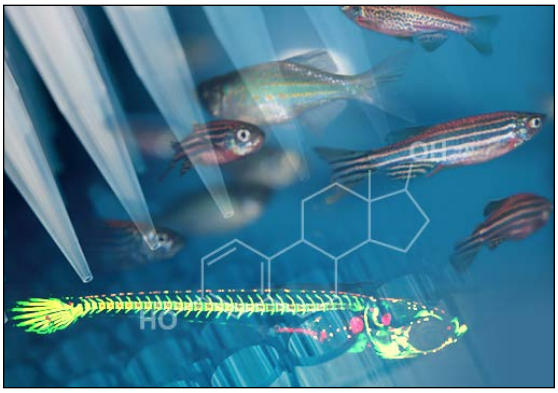
Organizing committee members Mattingly, left, and Behl found a moment to relax during a break. (Photo courtesy of Catherine Sprankle)

Research, practical advice, data use, and awards

More than 20 scientific talks were given during the two-day workshop, many of them by NIEHS grantees. Presentations included descriptions of research studies and results, practical advice on conducting toxicity studies using small fish and fish embryos, and use of toxicity data derived from aquatic species in drug development and regulatory compliance.

A poster session May 5 allowed attendees to interact informally and learn about other research being conducted. The organizing committee recognized junior researchers from NCSU, Oregon State University, and the University of South Carolina for outstanding presentations.

Participants highlight next steps



The conference concluded May 6 with a discussion session. Workshop participants noted that the suitability of small fish species for toxicity testing, particularly their practical advantages, needs to be brought to the attention of other audiences, including industry, regulators, scientists in other disciplines, and the general public.

Topics identified for further exploration included the effective application of fish study data for better understanding of chemical safety, and integration of fish data with complementary information from other types of toxicity studies. Other needs included clarification of the relationship between chemical treatment, uptake and metabolism, and the observed effects in fish models.

Attendees agreed that the research presented at the workshop was important and of high quality, and that the event provided a valuable opportunity for researchers within and outside the field of toxicology to share insights on the potential role of small fish and fish embryos in the future of toxicology.

A summary and full report of the workshop will be developed and posted on the workshop Web page, along with presentations and poster abstracts.

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

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High-throughput toxicity screening produces human-relevant results

By Thomas Burns Jr., reprinted from Environmental Factor, June 2014

Using *in vitro* and *in silico* testing in primary human cell systems, scientists reported in the May issue of the journal Nature Biotechnology bioactivity profiles for 776 unique and diverse chemicals with potential for human exposure. The use of a human-relevant system may provide a rapid and accurate screening method to prioritize chemicals for further toxicity testing or to identify new pharmaceutical activities.

"This is the first data manuscript in the field of high throughput toxicity screening [HTS] on such a large number of chemicals to be published in one of the Nature journals," said Nicole Kleinstreuer, Ph.D., the paper's lead author, who is now a contractor supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). "It demonstrates the utility of HTS assays that use human primary cells to elucidate mechanisms of action and predict toxicities for a diverse set of chemicals."

Limitations of traditional toxicity testing

Toxicity data on many chemicals do not exist. The study's authors point out that it is difficult or impossible to test these chemicals for toxicity using traditional animal testing methods, because of the expense, time required, ethical concerns about animal testing, and problems with species extrapolation.

The researchers wanted to examine whether *in vitro* and *in silico* high throughput test methods, especially those using human cell and gene targets, could provide a viable alternative to such testing.

In vitro testing can provide human-relevant results

Scientists from the U.S. Environmental Protection Agency (EPA) tested 776 unique environmental and industrial chemicals, including pesticides, food additives, and pharmaceuticals. The researchers chose eight human primary cell systems, based on their sensitivity to specific drug mechanisms and adverse effects, and recorded 87 different measurements, resulting in 306,240 individual data points.

Pharmaceuticals and pesticides were the most active chemicals, while fragrances and colorants, used in cosmetics and as food additives, proved to be the least active. Only eight percent of the chemicals were uniformly inactive, including a few known to be pharmaceutically active in humans — a finding that highlights both areas for further research as well as the potential need for additional endpoints of study.

Identifying chemicals with previously unknown mechanisms of action

The study's authors reported intriguing results of the cluster analysis. Researchers grouped chemicals that showed a similar endpoint profile, so that specific mechanisms of action could be inferred for each group. For example, analgesics, such as aspirin and the non-steroidal anti-inflammatory drugs Indomethacin and Celecoxib showed similar endpoint profiles, a finding that helped validate this approach.

A seemingly unrelated chemical, propyl gallate, a common cosmetic and food additive, also clustered with this group, suggesting that propyl gallate might have a similar mechanism of action as do the known analgesics. This finding illustrates the potential of this approach to shed light on as yet unrecognized toxicities or mechanisms of action for chemicals, based on profile similarities.

This work was conducted as part of the EPA ToxCast Program, which is a member of Tox21, a federal consortium that includes NIEHS, NTP, EPA, the National Center for Advancing Translational Sciences, and the U.S. Food and Drug Administration. The goal of Tox21 is to develop predictive toxicity models and prioritization schemes based on data from alternative testing methods. ●

Citation: Kleinstreuer NC, Yang J, Berg EL, Knudsen TB, Richard AM, Martin MT, Reif DM, Judson RS, Polokoff M, Dix DJ, Kavlock RJ, Houck KA. 2014. Phenotypic screening of the ToxCast chemical library to classify toxic and therapeutic mechanisms. Nat Biotechnol; doi:10.1038/nbt.2914 [Online 18 May 2014].

(Thomas Burns Jr. is a contract writer with Tekrighter Scientific and Medical Writing Services in Wendell, North Carolina.)

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Predictive toxicology faculty rallies around new directions

By Eddy Ball, reprinted from Environmental Factor, July 2014

Tice led off the agenda of division reports with a summary of Tox21 activities. (Photo courtesy of Steve McCaw)

Putting the strategic plan into action

NIEHS is using the concept of cross-divisional faculties and overarching themes to unite efforts to implement the strategic plan and advance research and public health in eight key areas of interest and concern:

- Epigenetics
- Exposome (see story)
- Global Environmental Health
- Inflammation (see story)
- PT&D
- Stem Cell Biology
- Website and Social Media
- Scientific Data Management

The Predictive Toxicology and Disease (PT&D) faculty meeting June 2 attracted some fifty scientists from across the three research divisions at NIEHS. The meeting provided historical perspective on the PT&D initiative and activity updates, and solicited ideas from the audience for implementing the Institute's 2012-2017 strategic plan.

PT&D is one of eight crosscutting themes in the strategic plan. The faculty concept is an effort to marshal resources developed in the various labs, sections, and groups where science is being conducted, into a unified effort.

"The implementation teams were the obvious next step for the strategic plan," said NIEHS planning and policy lead Sheila Newton, Ph.D., in her opening talk on historical perspective. Since the themes are ones that all the divisions independently identified as priorities, she continued, "[Leaders proposed] we should have the planning process be one that involves all of the divisions working together, rather than [having each division] independently come up with a plan."

Deconstructing silos

Representatives of the three divisions — the Division of Intramural Research (DIR), Division of Extramural Research and Training (DERT), and Division of the National Toxicology Program (DNTP) — took turns at the podium, describing their respective programs and resources, in a demonstration of the kind of proactive communication the faculty concept is working to inspire. As speakers shared the details of their predictive toxicology and disease programs, they also attempted to identify intersections among their divisions' efforts.

Paules, who holds a joint appointment in DIR and DNTP, was a leader in the former National Center for Toxicogenomics, which played an important role in inspiring the now firmly established relationship between bioinformatics and computational toxicology. (Photo courtesy of Steve McCaw)

Maull is one of the heavy lifters for the PT&D faculty. Her experience with DERT and BSB, prior to joining NICEATM, has been instrumental in highlighting the connections among NIEHS divisions, as well as external agency and private sector programs. (Photo courtesy of Steve McCaw)

DNTP Tox21 lead and Biomedical Screening Branch (BSB) head Raymond Tice, Ph.D., helped set the tone with his report on the federal partner consortium formed in 2008 to address the development of next-generation high-throughput toxicology testing for thousands of chemicals. Colleague Stephen Ferguson, Ph.D., joined in to discuss progress in Phase III of the Tox21 program now underway.

"We're actively seeking the opportunity for cross-division collaborations," Tice told the group, "and one of the purposes of the faculty is to provide a forum for the free exchange of information."

In her report, DERT representative Claudia Thompson, Ph.D., briefly discussed a database that coded all the epidemiology projects supported by NIEHS. She said the database could be used as a resource to identify potential sources of biological samples, to address questions of concern for the PT&D initiative.

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Casey heads the NTP center that promotes federal agencies' adoption of testing methods to reduce the use of animals in safety testing, through advancing predictive toxicology. (Photo courtesy of Steve McCaw)

DIR toxicogenomics veteran Richard Paules, Ph.D., described a leadership-sponsored, cross-division effort to develop a high-throughput transcriptome platform using approximately 1,500 genes that could be used to greatly expand our understanding of the relationship between chemicals, genes, pathways, and disease.

DERT program lead Daniel Shaughnessy, Ph.D., offered a preview of the stem cell development meeting June 3-4 and its significance for PT&D implementation efforts.

DERT representative Kimberly McAllister, Ph.D., pointed to an upcoming workshop on collaborative cross and diversity outbred mice models.

Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), reviewed his group's work in adverse outcome pathway research using *in vitro* testing, as well as alternative animal models, including zebrafish, and noted the added benefit of an integrated predictive toxicology program, with the reduction of the number of animals used in testing.

Facilitator Elizabeth Maull, Ph.D., of DNTP, closed the meeting with a look at next steps, including a possible PT&D lecture series. By specifically describing itself as a faculty activity, such a series might lure scientists away from their silos of specialization and into the broader arena of communication, and help people perceive, more acutely, activities across the divisions.

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Toxicology trainee honored for translational research

By Eddy Ball, reprinted from Environmental Factor, May 2014

Macon's study of PFOA was selected as a 2011 NTP paper of the year. (Photo courtesy of Steve McCaw)

For most graduate students, the Ph.D. is the highest point of the academic experience, but for NTP trainee Madisa Macon, Ph.D., the degree comes with an added distinction. Even before she officially received her diploma, Macon took home a prestigious award for research that generates knowledge and innovative solutions to address critical societal needs — in her case, the public health impact of human exposure to endocrine-disrupting chemicals.

Along with the degree in toxicology she'll receive May 10 during graduation ceremonies at the University of North Carolina at Chapel Hill (UNC), Macon is one of 20 graduate students presented a 2014 Impact Award from the UNC Graduate Education Advancement Board during the 16th Annual Graduate Student Recognition Celebration April 24 in Chapel Hill, N.C.

Macon is a trainee in the Reproductive Endocrinology Group of the NTP Laboratory, headed by her Intramural Research Training Award mentor and dissertation advisor, Suzanne Fenton, Ph.D. Macon studies the mechanistic basis of health effects following prenatal exposure to perfluorooctanoic acid (PFOA) in mice (see text box).

As the award committee wrote in its announcement of the winners, "Published data from Macon's studies have already been used by two agencies in their human health assessment of PFOA toxicity. Her research has the potential to further inform regulatory agencies in North Carolina and beyond in their risk assessment of PFOA."

Moving insights at the bench into public health

In keeping with the NIEHS and NTP public health mission, Fenton's group is deeply concerned with the potential public health impact of its studies of human disease, using mice and rat models, translating internal dose in animal models to known exposure levels in U.S. residents.

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"Madisa has worked very hard for the sake of public health. She has performed her studies to help us understand the potential effects of children's exposure to this harmful chemical," Fenton explained. "Importantly, she has discovered modes of action for effects of PFOA in the breast, which seems to be a particularly sensitive target tissue. She is very deserving of this award."

Advancing a career with support from NIEHS and NTP

After completing her undergraduate work at Xavier University of Louisiana and a Master of Public Health degree at Drexel University, Macon joined Fenton's group, at NIEHS, in 2009 as a predoctoral fellow, as she pursued her Ph.D. from the UNC School of Medicine Curriculum in Toxicology. Fenton is one of eight NIEHS lead researchers who serve as members of the curriculum, and currently serves on its executive committee.

In addition to her doctoral degree and award, Macon was first author on two peer-reviewed publications by Fenton's group. She has been active in the Society of Toxicology (SOT) nationally, and at the state level as a North Carolina Chapter representative. Her future plans include continuing as a postdoctoral fellow in the Tumor Biology Program at Georgetown University, as she works toward toxicology certifications, including the Diplomate of the American Board of Toxicology, and sharpens her career focus in the field of cancer.

"I am very grateful for the opportunities I've enjoyed at NIEHS and in the NTP Laboratory," Macon said, "and I can't say enough about how much Sue has helped me as mentor and advisor. I'm especially proud that UNC has recognized the public health impact of my work on PFOA, and I am grateful for Sue's guidance during my research."

Citations:

Macon MB, Fenton SE. 2013. Endocrine disruptors and the breast: early life effects and later life disease. J Mammary Gland Biol Neoplasia 18(1):43-61.

Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. Toxicol Sci 122(1):134-145.

PFOA and human health

Fenton's group is interested in the developmental effects of high-use or high-exposure environmental compounds, such as PFOA, also known as C8.

PFOA was a natural choice for research by the group. It is a long-chained perfluorinated chemical that does not occur naturally in the environment, and has special properties and hundreds of manufacturing and industrial applications, most notably in coatings for nonstick cookware. It meets the requirements as a chemical of interest for environmental scientists, because of its persistence in the environment and in the blood of the general U.S. population, as well as its demonstrated developmental and other adverse effects in laboratory animals.

Although regulatory action on PFOA currently resides at the state level, the U.S. Environmental Protection Agency (EPA) is working with major companies to reduce emissions and product content of PFOAs, with the goal of eliminating production and use of the chemical by 2015. In 2009, EPA issued Provisional Health Advisories that included PFOA, to protect against potential risk from exposure to the chemical through drinking water.

EPA nominated PFOA for NTP study in 2003. Since then, NTP scientists and contractors have performed short-term toxicity, long-term carcinogenicity, and a range of special studies on the compound. In a Sept. 20, 2013 announcement in the Federal Register, NTP listed PFOA among twenty new substances nominated for possible review for future editions of the Report on Carcinogens.

The C8 Science Panel, organized to research the potential health effects of PFOA in industry-contaminated parts of West Virginia and Ohio, has determined that PFOA may have a probable link to kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, hypercholesterolemia, and pregnancy-induced hypertension, including preeclampsia, in humans.

Research by Macon and her colleagues in Fenton's group is making significant contributions toward understanding how exposure to PFOA, and other chemicals of interest, may also impact early life human development and lifelong health more subtly through modifications in gene expression triggered by low-dose exposures during critical windows of development.

NIEHS employees honored at NIH Director's Awards Ceremony

By Eddy Ball, reprinted from Environmental Factor, July 2014

Winners from the DREAM Toxicogenetics Challenge team are, from left, are Tice, Woychik, Boyles, Witt, and Dearry. (Photo courtesy of Steve McCaw)

NIEHS Tox21 group winners also came together for a group photo. Seated, from left, are Bucher, Tice, Birnbaum, and DeVito. Standing, from left, are Hsieh, Shockley, Witt, Fostel, and Waidyanatha. (Photo courtesy of Steve McCaw)

Director Linda Birnbaum, Ph.D., and 13 employees of NIEHS and NTP (see text box) were among recipients of National Institutes of Health (NIH) Director's Awards. They were presented at a ceremony June 12 in Bethesda, Maryland, organized around the theme, "Why I Love NIH." The employees were recognized for their outstanding contributions to trans-NIH initiatives in the DREAM Toxicogenetics Challenge, the Tox21predictive toxicology consortium, remote support technology, and organization of a geroscience summit.

Leading off the ceremony was NIH Director Francis Collins, M.D., Ph.D., who praised employees for their persistence and creativity in making fiscal year 2013-2014 a successful year for the organization, despite fiscal restraints and operational interruptions. He pointed to a long list of achievements, including a record number of Nobel prizes awarded to grantees, the BRAIN (Brain Research Through Advancing Innovative Neurotechnologies) Initiative, and the cooperation established with the family of Henrietta Lacks, source of the famous HeLa cell line.

"NIH was able to avoid almost all delays in the scientific review process [despite the shutdown in October 2013]," he said, noting also that patients at the NIH Clinical Center continued to receive quality care, despite the interruption of operations elsewhere. "[But] we're not out of the woods, yet," he warned.

Collins joined emcee NIH Associate Director for Communications and Public Liaison John Burklow, and NIH Deputy Director for Extramural Research Sally Rockey, Ph.D., on stage for an original song written to the tune of the Beatles' "We Can Work It Out." Addressed to Congress, the song reinforced the NIH message that advancing biomedical research is a national priority that deserves nonpartisan support.

Collins had to leave to make a meeting with President Obama before introductions of Institute and Center (IC) leaders seated on stage and presentation of awards. In his absence, the awards were presented by NIH Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., and representatives of the lead IC for each initiative.

DNTP Biomolecular Screening Branch (BSB) Chief Raymond Tice, Ph.D., and Genetic Toxicology Group lead Kristine Witt each received two awards. BSB research fellow Jui-Hua Hsieh, Ph.D., was the youngest NIEHS scientist honored and the sole trainee.

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And the winners were …

NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge Team

In recognition of significant contributions to the NIEHS-NCATS-UNC Dream Challenge (see story), the first crowdsourcing collaboration for analysis of high content data — Rebecca Boyles; Allen Dearry, Ph.D.; Tice; Witt; and Richard Woychik, Ph.D.

Tox21 Team, led by the National Center for Advancing Translational Sciences (NCATS)

In recognition of extraordinary vision, effort, creativity, and scientific leadership during the implementation of the Toxicology in the 21st Century (Tox21) interagency effort — Linda Birnbaum, Ph.D.; John Bucher, Ph.D.; Michael DeVito, Ph.D.; Jennifer Fostel, Ph.D.; Hsieh; Keith Shockley, Ph.D.; Tice; Suramya Waidyanatha, Ph.D., and Witt.

Remote Support Working Group, led by the National Institute of Dental and Craniofacial Research

For the evaluation and piloting of a remote support technology at NIH — Jack Field.

Geroscience Summit Organizing Committee, led by the National Institute on Aging

For dedication and commitment in promoting geroscience, specifically in organizing the multi-disciplinary scientific summit "Advances in Geroscience: Impact on Healthspan and Chronic Disease" — Xiaoling Li, Ph.D.

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Seventeen trainees join FARE winners' circle

By Eddy Ball, reprinted from Environmental Factor, July 2014

Robinson authored "Assessing early developmental and pubertal effects in CD-1 mice following *in utero* exposure to bisphenol (BP) analogs." She is a member of the NTP Laboratory Reproductive Endocrinology Group, headed by Suzanne Fenton, Ph.D. (Photo courtesy of Steve McCaw)

When the results of the 2015 Fellows Award for Research Excellence (FARE) were announced in June, 17 NIEHS trainees joined the elite group of young scientists so honored by NIH.

In his June 13 announcement of the winners, NIEHS Deputy Scientific Director and Training Director Bill Schrader, Ph.D., wrote, "Congratulations to all these FARE awardees, for their ability to carry out exciting science, and to describe it succinctly in abstract form."

The FARE award program is sponsored by the NIH Fellows Committee, scientific directors, and Office of Intramural Training and Education, and is funded by the scientific directors. Earlier this year, fellows submitted their research abstracts, which were then placed in study sections for review by postdoctoral fellows and senior scientists. Abstracts in the top 25 percent of each study section were selected for FARE awards, based on scientific merit, originality, experimental design, and overall quality and presentation.

Distinction that comes with a cash award

Winners of FARE awards receive a $1,000 stipend to attend a scientific meeting of their choice, where they present their research. They are also invited to present a poster at the annual NIH Research Festival; attend the FARE awards ceremony held on the NIH Bethesda, Maryland, campus in October; and participate in judging the following year's FARE competition. Recipients will also be recognized at the NIEHS Director's Awards ceremony in 2015.

Winning, in its own right, recognizes the exceptional scientific research of trainees and the quality mentorship of the lead researchers involved. In addition, however, there are other notable facts about the winners and their mentors.

Four fellows were repeat winners — Percy Tumbale, Ph.D., and Senthilkumar Cinghu, Ph.D., also won in 2013; Erica Ungewitter, Ph.D., was a 2014 winner; and Qingshan Wang, M.D., won in 2013 and 2014.

One of the winners, Deirdre Robinson, is a doctoral candidate in the NTP Laboratory. No more than one or two predoctoral fellows achieve a FARE in any given year.

Lead researchers with more than one FARE winner from their group included Raja Jothi, Ph.D., with three winners, and John Cidlowski, Ph.D., and Humphrey Yao, Ph.D., with two each.

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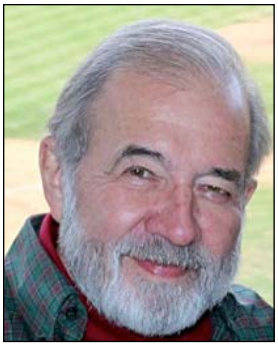
William T. Allaben, Ph.D., ATS, receives the U. S. Food and Drug Administration's (FDA) Lifetime Scientific Achievement Award



William T. Allaben, Ph.D., ATS, who directed the FDA's participation in the National Toxicology Program for over 25 years, received FDA's Lifetime Scientific Achievement Award during honor award ceremonies held on June 6, 2014 at FDA's Headquarters in Silver Spring, Maryland. This scientific achievement award recognizes FDA scientists who have made outstanding contributions to science supporting FDA's mission that resulted in a significant and positive impact on public health. Dr. Allaben was honored for his lasting contributions to the advancement of regulatory science in recognition of his leadership in establishing and managing an interagency agreement (government partnership) with the National Institute of Environmental Health Science/National Toxicology Program that supported the conduct of toxicological assessments on chemicals regulated by the FDA. Through this partnership comprehensive research and testing studies were conducted at NCTR that assessed the safety of FDA high profile chemicals and agents where human health and risk issues existed; under the umbrella of this partnership, Dr. Allaben also established the first federally operated Phototoxicology Research and Testing Laboratory located at NCTR. Since 2009 when the FDA's Lifetime Scientific Achievement Award was established, this is only the second time it has been granted.

Dr. Allaben is Adjunct Professor, Department of Toxicology and Pharmacology, College of Medicine; Adjunct Professor Department of Occupational and Environmental Health, College of Public Health and Associate Professor and Biomedical Advanced Research and Development Authority Program Manager, Division of Radiation Health in the College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR. He was formally the Associate Director for Scientific Coordination at the FDA's National Center for Toxicological Research (NCTR) in Jefferson, Arkansas.

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

By Catherine Sprankle

ICCVAM holds public forum

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) convened a Public Forum on June 25 at the National Institutes of Health in Bethesda, Maryland. NICEATM, which supports ICCVAM, organized the meeting.

The Public Forum provided an opportunity for public interaction with representatives of ICCVAM member agencies. ICCVAM is an interagency committee of representatives from 15 U.S. Federal regulatory and research agencies that generate or use toxicological and safety testing information.

Meeting attendees included 16 ICCVAM Committee members representing 11 ICCVAM member agencies and 13 attendees representing 10 different industry, academic, and animal welfare organizations.

ICCVAM Co-Chair Dr. Anna Lowit, EPA, and NICEATM Director Dr. Warren Casey updated attendees on recent ICCVAM and NICEATM activities, respectively. Dr. Joanna Matheson of the Consumer Product Safety Commission, Co-Chair of the ICCVAM Skin Sensitization Working Group, summarized that group's recent activities. Committee members from five ICCVAM member agencies then provided information about their agencies' activities relevant to development and use of alternative test methods. Five public comments were presented: recurring themes in these comments included appreciation for ICCVAM efforts to improve communication with the public and concern about how validation of high-throughput assays and acceptance of validated methods might be accomplished. Presentations are available on the NTP website.

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ICCVAM plans to hold events similar to the June Public Forum annually. Public comments on ICCVAM activities are also welcome at the meeting of the Scientific Advisory Committee on Alternative Toxicological Methods on September 16 in the Rodbell Auditorium at NIEHS.

NICEATM partners with PCRM to hold adverse outcome pathway workshop

A workshop organized by NICEATM and the Physicians Committee for Responsible Medicine (PCRM) will explore how the concept of adverse outcome pathways can improve regulatory assessment of chemical toxicity. The workshop, "Adverse Outcome Pathways: From Research to Regulation," will be held September 3-5 at the William H. Natcher Conference Center at the National Institutes of Health in Bethesda, Maryland.

The workshop is open to the public free of charge with attendance limited only by the space available, with plenary sessions webcast to remote viewers. Individuals who plan to attend in person or view the webcast should register by August 15. Abstracts for poster presentations will be accepted through July 25.

NICEATM and ICCVAM activities at the Ninth World Congress

NICEATM scientists will present nine posters and three talks at the Ninth World Congress on Alternatives and Animal Use in the Life Sciences (WC9), August 24–28 in Prague, Czech Republic. NICEATM presentations include development of curated reference databases and computational and high-throughput approaches to chemical screening and prediction of toxicity.

ICCVAM committee members from the FDA will present information on photosafety testing and 3Rs considerations in preclinical testing of cellular and gene therapy products.

Information on NICEATM and ICCVAM activities at WC9 is available on the NTP website.

NICEATM requests data on inhalation testing approaches

NICEATM requests available data and information on devices and/or technologies currently used for identifying potential inhalation hazards. Submitted information will be used to assess the state of the science and determine the technical needs for a dynamic nonanimal system to assess the potential toxicity of inhaled chemicals or nanomaterials. Information is requested by July 18.

Information submitted could describe activities relevant to the development or validation of alternatives to *in vivo* inhalation toxicity tests currently required by regulatory agencies, or submission of data from nonanimal tests for identifying acute inhalation hazard potential. If available, corresponding *in vivo* data for substances tested in nonanimal assays are also requested, including data from any ethical human or animal studies or accidental human exposures.

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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

NTP Study Reports and Publications Available at: http://ntp.niehs.nih.gov/go/reports

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