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

July 2013

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

What's Inside:

Board advises NTP on critical issues

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

Highlights of NTP Roadmap progress

The NTP associate director's report focused on progress made by NTP since it laid out its roadmap in 2004. Bucher framed his talk around three of the main areas addressed in the plan, with a heavy emphasis on Tox21:

- Refine traditional toxicology assays
- Develop rapid mechanism-based predictive screens for environmentally induced diseases;
- Improve the overall utility of NTP products for public health decision making

Lunn, who leads the RoC effort, made two presentations to the board — one focused on a new draft concept, and the other on progress of two RoC candidate substances. (Photo courtesy of Steve McCaw)

Bucher talked about how, in Phase II of Tox21, a 10,000-compound library had been tested across a set of nuclear receptor and stress response pathway assays, in a small number of assays. He showed data where compounds with similar biological activity patterns, across the different assays, were linked in a connectivity network.

"Using this kind of plot helps us determine if some of the associations we are seeing make sense," Bucher said. "We are just at the beginning stages, but eventually we hope to get to a point where the Tox21 data can be used to better predict the potential for hazard and, thus, protect public health.

A lively discussion followed the presentation, with encouragement from BSC to continue to move forward with testing in human cells. "In every case we can, we're using human cells," Bucher said.

NTP received both praise and input about how to move forward on several important topics, including systematic review, Tox21, and several cancer listings, June 25 at its Board of Scientific Counselors (BSC) meeting.

New BSC Chair Melissa McDiarmid, M.D., from the University of Maryland, started the meeting with a report from NIEHS and NTP Director Linda Birnbaum, Ph.D. Birnbaum updated the board on recent activities, including the NIEHS strategic plan, budget, science findings, and some recently launched big data initiatives, including the NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge that had more than 60 people signed up the first week.

NTP monograph

Kembra Howdeshell, Ph.D., from the NTP Office of Health Assessment and Translation (OHAT), provided an overview of the NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy. Howdeshell made her presentation by

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McDiarmid, left, seemed right at home taking on her new role as BSC chair, shown with Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy, and Review. (Photo courtesy of Steve McCaw)

phone, since she was also presenting the monograph in a symposium on cancer and pregnancy at the Teratology Society annual meeting, co-chaired by Howdeshell and Michael Shelby, Ph.D., also of OHAT.

Howdeshell said that 457 observational studies were included in the evaluation, which was developed to serve as a tool for physicians and patients making clinical decisions about cancer treatment during pregnancy.

McDiarmid, who served as the BSC liaison during the peer review of the monograph in October 2012, told the board that NTP did a good job given the limitations of the data. NTP and the board identified the need for greater participation in registries, and improvements in the quality of reporting in case reports.

Contracts approved

The BSC also unanimously approved two contract concepts — quality assessment support and global pathology support.

Report on Carcinogens

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens (RoC) shared where NTP was in the development of the next RoC. After presenting a schematic of how the NTP reaches its level of evidence conclusions, she focused on the substances 1-bromopropane and cumene, which were peer reviewed at a public meeting in March 2013. Lunn summarized the comments from the panel and shared NTP's response. The peer review panel concurred with NTP to list both substances as reasonably anticipated human carcinogens.

BSC member Dale Hattis, Ph.D., of Clark University, who served as BSC liaison for the peer review meeting, commented on how thorough he felt the discussions were at the meeting and how receptive NTP was to the comments provided.

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Upcoming Events

September 24-25, 2013

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

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

October 7-8, 2013

Peer Review of NTP Report on Carcinogens Monographs

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

October 10-11, 2013

NICEATM/EPA Workshop on Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk

http://www.niehs.nih.gov/about/visiting/events/highlight/cardiovascular-toxicity-workshop/

October 29, 2013

NTP Technical Reports Peer-Review Panel

http://ntp.niehs.nih.gov/go/36051

December 18-19, 2013

NTP Board of Scientific Counselors

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

June 17-18, 2014

NTP Board of Scientific Counselors

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

All meetings are held at NIEHS unless otherwise noted:

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

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

Systematic review

Andrew Rooney, Ph.D., deputy director of OHAT, presented on the implementation of systematic review and evidence integration for literature based health assessments. Rooney focused his attention on some areas that have received the most input and questions during public comment periods and webinars recently hosted by NTP, including study quality and risk of bias. He discussed how NTP planned to approach these topics and how the public comments would inform these issues moving forward.

OHAT deputy director Rooney addressed some of the ways NTP is revising its systematic review process based on public input.

Thayer, who leads OHAT, talked about next steps for systematic review. (Photos courtesy of Steve McCaw)

OHAT Director Kristina Thayer, Ph.D., then presented next steps for the systematic review process. "We expect to complete our case studies during the next calendar year. These will help us better assess the performance of our methodology and fine tune our processes," Thayer said. Given the public interest, Thayer said, NTP is helping support the development of a free software tool that will facilitate harmonization of information collected on studies included in systematic reviews. "We're pretty excited about what this tool will do," Thayer said. Beta testing begins this summer.

Draft concept

Bucher encouraged the board to share their thoughts about how the NTP should be moving forward. (Photo courtesy of Steve McCaw)

The final topic discussed at the meeting was something rather new for NTP — getting input on how to define an exposure, light at night, that has been nominated for study.

"We want to define this so it is meaningful to public health," said NTP Associate Director John Bucher, Ph.D. Lunn walked the BSC through the draft concept, shift work at night, light at night, and circadian disruption. She pointed out that those nominating the exposure were concerned that light at night may be a cause of breast cancer among women, and noted that the International Agency for Research on Cancer has classified shiftwork, involving circadian disruption, as a probable carcinogen.

The Board concluded that NTP was in the best position to address this very broad, important topic, but urged it to proceed with caution, consult technical experts, and try to narrow its focus. ●

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

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NTP webinar informs Report on Carcinogens

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

The National Toxicology Program (NTP) successfully used a web-based meeting format April 11 to bring together scientific experts and members of the public for a discussion on pentachlorophenol (PCP) exposure and cancer.

PCP, which is primarily used as a wood preservative in the United States for items such as utility poles, cross arms, fence posts, and railroad ties, is a candidate substance being formally reviewed for possible listing in the Report on Carcinogens (RoC). The webinar created a virtual meeting, allowing more than 70 registered participants to watch, listen, and participate in discussions, by phone and computer, from across the globe.

The half-day session was moderated by epidemiologist Glinda Cooper, Ph.D., from the U.S. Environmental Protection Agency. The meeting included presentations from four outside scientists who have been involved in PCP human studies. The objective of the

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Epidemiologist Cooper, formerly with NIEHS, moderated the RoC webinar on PCP. (Photo courtesy of Steve McCaw)

meeting was to receive scientific input on how best to evaluate the epidemiologic, or human, studies related to PCP exposure. NTP was specifically interested in hearing about PCP components and contaminants, and distinguishing between cancer effects caused by PCP and those that might be caused by other chemicals or contaminants to which workers may have been exposed.

Purpose of webinar

"This webinar is intended to help inform our cancer evaluation of PCP," said Ruth Lunn, Dr.P.H., director of the NTP Office of the Report on Carcinogens, while providing an update on the RoC process. "It is not to receive recommendations from invited speakers or the public on whether or not PCP should be listed in the RoC." The cancer evaluation component, developed by Lunn and her staff, lays out all the information used to make a preliminary listing decision, and is an integral piece of the monograph that NTP prepares as part of its evaluation of a substance.

After some brief introductory comments, Cooper introduced the first panelist, and facilitated a question and answer session among participants after each presentation (see text box).

Discussion and next steps

As discussion leader, Schubauer-Berigan helped clarify what is known about PCP exposure. (Photo courtesy of Mary Schubauer-Berigan)

Mary Schubauer-Berigan, Ph.D., senior research epidemiologist at the National Institute for Occupational Safety and Health (NIOSH), competently served as discussion leader after the talks. She focused on some very straightforward questions, ranging from what is known about how many people are currently exposed to PCP, to asking if all PCP exposure is contaminated or mixed with dioxins or other byproducts, or whether people can be exposed to pure PCP. These types of questions made for a lively discussion between the speakers, NTP staff, and the public.

"Getting scientific and public input using this kind of virtual meeting format is a new way of doing business for us," said Lunn after the meeting. "I was very pleased with how it all came together. We received a lot of good information that will provide a strong foundation as we move forward with our evaluation of PCP."

Following completion of the cancer evaluation component, NTP will prepare the draft substance profile. Both documents will be part of the draft RoC monograph released for public comment and peer review. ●

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

Presentation Highlights

Kevin Dunn, from NIOSH, presented an overview of occupational exposures to PCP. He said PCP was produced in the United States from 1936 to 2006, but since 1984, its use in the U.S. has been restricted to wood preservation and can no longer be used on wood in residential or agricultural buildings. Dunn discussed how exposure for PCP manufacturing workers might occur, including through dust or vapors, depending on the finishing process used to prepare the PCP and exposure in the wood preservative industry. He also identified common PCP contaminants.

Avima Ruder, Ph.D., also from NIOSH, focused on occupational exposure to PCP and other chemicals, while further addressing some of the issues that need to be carefully considered when evaluating human epidemiology studies. She discussed these issues as they relate to what NIOSH recently found in a mortality study that includes 2,122 U.S. PCP production workers, from four large chemical plants operating from 1936-2006. The workers were exposed to other chemicals, as well, while working at the plants.

James Collins, Ph.D., from the Dow Chemical Company, focused his talk on biomonitoring and epidemiologic studies of PCP producers. He talked about how difficult it is to determine exposure assessment for PCP. He shared biomonitoring data on serum dioxins from different types of PCP workers, and suggested that the dioxins, which are long-lived in the body, may serve as an indicator for past exposure to PCP. He discussed findings from an epidemiology study of PCP manufacturing workers at the Dow chemical plant.

The final presentation came from **Paul Demers, Ph.D., a professor at the University of Toronto Dalla Lana School of Public Health and the Cancer Care Ontario Occupational Cancer Research Centre**. Demers focused much of his remarks on a large study he has been involved with in British Columbia that includes 27,464 workers, employed by14 sawmills for 1 year or more, between 1950 and 1995. He also reviewed findings of other epidemiologic studies of PCP.

PCP webinar ↗ information is available on the NTP website.

Partners launch DREAM Toxicogenetics Challenge

Reprinted from *eFACTOR*, July 2013

Co-founder, president, and director of Sage Bionetworks Stephen Friend, M.D., Ph.D., explored the challenge concept during a talk at NIEHS (see story) earlier this year. (Photo courtesy of Steve McCaw)

An innovative crowdsourced computational challenge, the DREAM Toxicogenetics Challenge, launched June 11 with an announcement by Sage Bionetworks. The goal of the three-month challenge is to find better ways to predict the toxicity of chemicals, to increase understanding of how a person's individual genetics can influence cytotoxic response of exposure to widely used chemicals.

The challenge is being led and organized by scientists from Sage Bionetworks, DREAM (Dialogue for Reverse Engineering Assessments and Methods), the University of North Carolina at Chapel Hill (UNC), NIEHS, and the NIH National Center for Advancing Translational Sciences (NCATS). These groups have generated population-scale toxicity data in a human *in vitro* model system.

The partners utilized human cell lines from the 1000 Genomes Project, which consists of correlated genomic data and cell lines collected from individuals representing nine distinct populations with defined genetic heterogeneity. The NIEHS-NCATS-UNC team has conducted the largest ever population-based *in vitro* cytotoxicity study, by evaluating the extent of cytotoxicity induced by 179 common pharmaceutical or important environmental chemicals in 1086 human lymphoblastoid cell lines. The challenge is asking a wide range of researchers to use the genomic and cytotoxicity data to build models that can predict variation in individual response to a chemical, based on genomic data.

Challenges such as this engage diverse communities of scientists to competitively solve a specific problem in a given time period, by placing scientific data, tools, and the resulting predictive models into an open commons or workspace — in effect, crowdsourcing data analysis.

Tice is the NTP lead on the Tox21 consortium, a partnership of NIEHS, the U.S. Environmental Protection Agency, U.S. Food and Drug Administration, and NIH Chemical Genomics Center. (Photo courtesy of Steve McCaw)

Those interested in participating in this challenge, and two others, can sign up at a dedicated Web page. The challenge will close on Sept. 15 and the top-scoring team(s) will be announced at the sixth annual RECOMB/ISCB conference on Regulatory and Systems Genomics, with DREAM Challenges, Nov. 8-12 in Toronto.

A big data approach to understanding chemical toxicity

"Predicting how different people or groups of people will respond to certain chemicals is difficult to determine, but important for protecting the public's health," said Raymond Tice, Ph.D., who heads the NTP Biomolecular Screening Branch at NIEHS and is leading an NTP initiative to develop a paradigm of predictive toxicology using high-throughput screening. "This challenge represents a novel partnership and a novel approach to addressing, more effectively and efficiently, big data problems in environmental health science," added Allen Dearry, Ph.D., director of the NIEHS Office of Scientific Information Management, which coordinated interaction with Sage/DREAM.

"We are delighted to partner with Sage/DREAM, to release this unique dataset obtained through a broad partnership with NIEHS and NCATS," said Ivan Rusyn, M.D., Ph.D., professor of environmental sciences and engineering at the UNC Gillings School of Global Public Health. "The collaboration with Sage/DREAM is an important extension of our ongoing partnership with NIEHS and UNC," added Anton Simeonov, Ph.D., NCATS acting scientific director of discovery innovation.

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This is the type of challenge that all of the partners are most interested in running — those with the potential to provide powerful scientific insights and meaningful public impact. Toxicity testing that monitors health risks posed to humans through chemical exposure is a crucial component of public health. Yet, for every chemical that has been tested for toxicity, there are thousands that remain untested.

To address this backlog, toxicologists are interested in leveraging the dramatic technological advances in molecular biology and computer science that now make it possible to use high throughput *in vitro* biochemical and cell-based assays with banks of genomic data for toxicological testing. The challenge aims to advance the pace of using and analyzing such complex data, in order to accelerate the generation of useful information for the scientific and public health communities.

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Challenges open June 11 to Sept. 15

The NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge is one of three challenges that Sage Bionetworks and DREAM opened to the public. The two other challenges involve breast cancer networks and whole cell model parameters.

- **The Heritage Provider Network-DREAM Breast Cancer Network Inference Challenge** —Participants in this challenge will be provided with an extensive proteomics time-course dataset on four breast cancer cell lines and tasked with analyzing these data to solve three sub-challenges — building network models that represent the active cell signaling pathways in breast cancer; predicting the dynamic response of various phospho-proteins to drug perturbations; and proposing novel strategies to visualize these high dimensional data.
- **The Whole-Cell Parameter Estimation DREAM Challenge** — Participants will be provided with a whole cell model of the sexually transmitted pathogen Mycoplasma genitalium and tasked with estimating the model parameters, from simulated data, for specific biological processes. The simulated data to be provided represents possible measurements in actual experiments, as participants interact with a credit system to purchase this data on demand, with the aim to refine the parameters under estimation.

NTP researchers win International Society for Neurochemistry recognition

By Heather Franco, reprinted from *eFACTOR*, June 2013

While a trip to Cancun may mean a vacation to many, for scientists in the NTP Laboratory Neurotoxicology Group at NIEHS, headed by Jean Harry, Ph.D., it marked an opportunity to present their scientific work and participate in an extraordinary experience with leaders in their field. Biologist Chris McPherson, Ph.D., and visiting fellow Ruben Orihuela, Ph.D., earned places in the highly competitive International Society for Neurochemistry (ISN) Advanced School April 16-20.

Along with some 1,000 scientists, they also attended the biennial meeting of ISN April 20-24, held jointly with the American Society for Neurochemistry (ASN).

Shown in their lab at NIEHS are members of the Harry Group, left to right, McPherson, Harry, and Orihuela. (Photo courtesy of Steve McCaw)

As part of their experience at the ISN Advanced School, the members of the Neurotoxicity group presented posters detailing their recent scientific works (see text box). McPherson's work was honored with a top ISN Advanced School award for poster presentations.

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Rare experience yields valuable opportunities

"Participating in the ISN Advanced School was my most unique science training experience," said McPherson. This prestigious opportunity provides support and training for 70 graduate students and new Ph.D. scientists in the field of neurochemistry.

"I was ecstatic for both of them to be selected for the school," said Harry. "It is rare to have two students selected from the same laboratory." This honor speaks not only to the quality of both junior scientists, but also to the mentoring of lead investigator Harry.

The researchers participated in seminars detailing the current state of the field of glial-neuronal interactions. In addition, they were able to present and discuss their own work in an informal setting. "Because of the small size and international attendance, the school gave me the opportunity to interact with both junior and senior investigators from all over the world in a more intimate setting," explained Orihuela. The study presented by Orihuela prompted a solicitation for manuscript submission by an editor of a special issue of the British Journal of Pharmacology. This confirmed to Orihuela the value of such interactions for visibility of one's work.

Both McPherson and Orihuela were able to make connections that will enhance their future careers. McPherson has aspirations to continue his studies integrating environmental exposures with human health issues. Orihuela strives to bring his cross-disciplinary approach to a research team at a premier university or research center.

Enhancing both their science and career paths

"Participating in these types of activities provides trainees with experiences that will enhance their scientific endeavors and their future career paths," said Harry. Both McPherson and Orihuela appreciated the opportunity to attend these events.

"Thanks to the support of both Jean and NIEHS, I was able to attend this school and magnificent conference, where I was able to interact with, and present my work to, the leaders in my field," states Orihuela. "It is great working for a mentor who values and encourages us to take advantage of these types of training opportunities," confirms McPherson. Both agree it is this focus on overall training that has led to the success of the group. ●

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Reproductive Developmental Biology Group.)

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Understanding the role of inflammation following neuronal injury

As Harry explained, "Injury to the neurons of the hippocampus can have detrimental effects on brain function and result in conditions such as Alzheimer's disease and epilepsy." To resolve these injuries, specialized macrophages, called microglia, produce inflammatory factors to aid in the repair process. "Microglia exist in two states — pro-inflammatory M1 and anti-inflammatory M2 — which produce a unique set of inflammatory factors," she said.

Orihuela — characterizing the microglia population

Orihuela sought to better understand these two microglial states using an *in vitro* microglial cell line. Upon differentiation of the cells to the M1 state, he found an increase in the expression of oxidative stress genes, nitric oxide levels, and reactive oxygen species. The cells also showed a decrease in basal respiration and an increase in the acidification rate. Together these results demonstrate a change in the bioenergetic profile of the mitochondria, consistent with increased oxidative stress. These responses were not observed upon differentiation to the M2 state. Thus, these distinctions in mitochondrial bioenergetics of the M1 and M2 microglia may help explain the different phenotypes of these two states.

McPherson — an environmental exposure model of neuronal injury

In his award-winning experiments, McPherson investigated the role of the M1 and M2 inflammatory factors in the repair process following brain injury. He used a model in which the hippocampal toxicant trimethyltin (TMT) was administered to mice. "Exposure to this toxicant in mice causes hippocampal injury similar to Alzheimer's disease," McPherson explained. "Using this model system, we are able to examine the contribution and shift of the various M1/M2 states of the brain macrophages." He found that with the onset of neuronal death and phagocytosis, microglia display an M1 stage of activation, and that a shift to the M2 repair phase was critical for promoting the brain to generate new neurons to replace those lost in the hippocampus. Therefore, each of the stages provided a critical step for the full process, and suggested a shift to the M2 phenotype to facilitate the differentiation of stem/progenitor cells to neurons. He is continuing this work to identify the nature of the trigger for this shift.

Insights into the causes of neurodegenerative diseases

Combining the mechanistic data from Orihuela's work, with the functional data from McPherson's research, these studies provide a new understanding of the microglia state following brain injury. "We use TMT as a chemical tool to understand the processes associated with neuroinflammation and adult neurogenesis," McPherson said. "While TMT is not currently in use in the United States, other countries, such as those on the Asian continent, still use TMT commercially as a polyvinyl chloride heat stabilizer and in biocides."

Risk assessment workshop features cutting-edge toxicogenomic research

By Sara Mishamandani, reprinted from *eFACTOR*, July 2013

Scientists and regulators from around the world met to review progress in human carcinogenesis safety evaluation strategies and cancer risk assessment May 16-17 at the Moving Forward in Human Cancer Risk Assessment in the Genomics Era 2.0 workshop held at the OECD (Organisation for Economic Co-operation and Development) Congress Centre in Paris. The meeting was co-sponsored by NIEHS.

Scott Auerbach, Ph.D., a molecular toxicologist with the National Toxicology Program and NIEHS-funded Superfund Research Program (SRP) grantee Ivan Rusyn, M.D., Ph.D., a professor of environmental sciences and engineering at the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill, were among the speakers at the meeting. Richard Paules, Ph.D., the Molecular Genomics Core director at NIEHS, was one of the organizers of the workshop and served as session chair, roundtable discussion leader, and presenter of the meeting summary. They joined representatives of the academic and industry safety assessment communities, government regulators, and risk assessors from the U.S., European Union, and Japan.

Auerbach (second from left) discussed integrating genomics in carcinogenicity testing during his presentation. (Photo courtesy of Rene Reijnders, Maastricht University)

"Getting regulators, toxicologists, and informaticians to talk to each other, and translate paradigms and views across knowledge domains, helps advance the goals of 21st century toxicology," said Auerbach. "One of the things you really notice at meetings like this one is that there are people with problems without solutions — regulators and toxicologists — and people with solutions without problems — informaticians — finding each other and later working together to find a solution that works across multiple domains. In many ways, the meeting was a reflection of the cross-disciplinary nature of the toxicological sciences in today's world."

Rusyn used his NIEHS-funded research to explain how to combine biological and chemical information to better understand human toxicity. (Photo courtesy of Rene Reijnders, Maastricht University)

Expanding the boundaries of toxicogenomics

Rusyn presented a vision for effectively integrating data to facilitate hazard characterization. He discussed how to combine gene expression data with chemical information to improve predication of drug and chemical toxicity.

The number of toxicogenomic studies that incorporate dose-response and population-based designs is on the rise, and the applicability of such data to hazard assessment is increasing. Rusyn described a user-friendly computational approach for dose-response analysis of gene expression data at the pathway level. He also suggested that the challenge of understanding inter-individual differences in toxicity may be met through a combined analysis of toxicity phenotypes and gene expression data from genetically diverse, recombinant inbred mice.

"This meeting afforded a unique opportunity for a candid conversation with practitioners and regulators about the value of genomics in decision-making with respect to human health assessments of drugs and environmental chemicals," said Rusyn. "A real opportunity exists for moving the field of human health risk assessment into the future, by expanding the use of omics beyond heatmaps and network diagrams."

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Moving cancer risk assessment forward

The driving force of the workshop was the need to improve human cancer risk assessment with better assessment approaches, assays, exposure estimates, and decision trees, so that toxicologists can ultimately use fewer animals in testing and provide more reliable information concerning human risk.

The current safety paradigm for assessing carcinogenic properties of drugs, cosmetics, industrial chemicals, and environmental exposures relies mainly on *in vitro* genotoxicity testing, followed by two-year rodent bioassays. This testing battery is extremely sensitive, but has low specificity. Rodent bioassays are also associated with high costs, high animal burden, and limited predictive value for human risks. Workshop participants discussed developing alternative testing strategies for carcinogenicity, with emphasis on potential contributions from omics technologies.

"As pointed out by one of the participants, there was a recognition and acknowledgement that advances in technology, that will revolutionize human cancer risk assessment, are coming, some of which are here now, and are unstoppable," said Paules.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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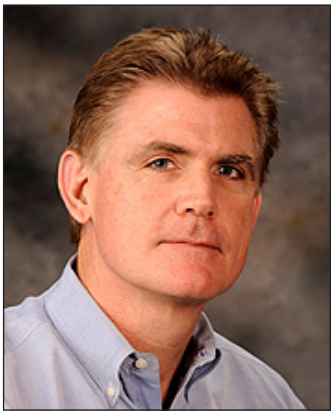
Casey presents at workshop on stem cells in cardiotoxicity studies

By NICEATM, reprinted from *eFACTOR*, May 2013



Casey, acting director of NICEATM, spoke at a recent workshop on how cultured heart cells could be used to understand how chemicals may affect heart muscle function. (Photo courtesy of Steve McCaw)

Pollutants and toxicants in the environment have the potential to damage cells in the heart. Known as cardiotoxicity, it is also a major reason for drug development failure. Because of its importance, scientists from all over the world gathered in Boston March 18-19 to share the best and latest research methods in the field.

One of those scientists was Warren Casey, Ph.D., acting director of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Casey joined an international group of presenters, representing research institutions, pharmaceutical companies, and government agencies, at the Stem Cell-Derived Cardiomyocytes as Models of Cardiac Pathobiology and Toxicology Workshop.

The Health and Environmental Sciences Institute (HESI), a nonprofit institution that brings scientists together to address global health and environmental issues, sponsored the workshop as a way to assess the current status and potential applications of the use of stem cell-derived cardiomyocytes, or cultured heart cells, for studying cardiotoxicity.

Casey's presentation described how testing approaches, that use cultured cells, might be used in regulatory or safety decision-making contexts.

"Stem cells and other technologies can help us better understand the mechanisms underlying toxicity and disease," he said. "For example, they can help us understand how the genetic diversity of target populations affects toxicity. But, as we move toward using emerging technologies, such as stem cell-derived cardiomyocytes for safety testing, it's important that we develop appropriate validation criteria, so that the data these test methods provide are useful to regulators."

The workshop's goal was to evaluate how such technologies may be used to evaluate risks to human cardiac health from pharmaceuticals and environmental chemicals. Topics discussed included the biology of cultured cardiomyocytes, specific approaches to using them to assess toxicity, how those approaches might be used to benefit public health, and future research and development needed to achieve those public health benefits.

A report from the workshop will be published in a scientific journal, and the recommendations will help pharmaceutical companies and other stakeholders develop improved approaches for this important safety testing area.

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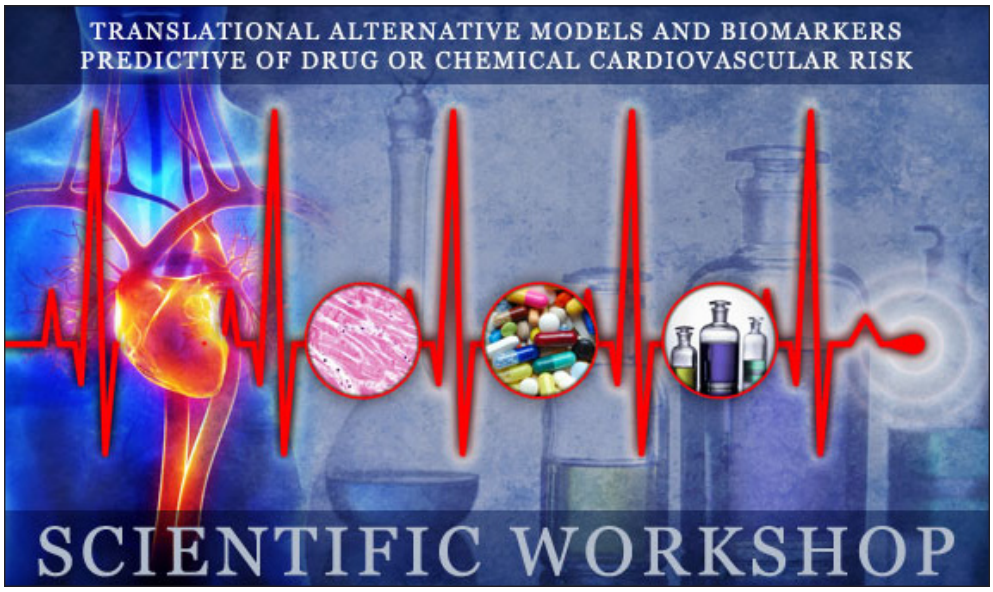
NICEATM/EPA workshop on evaluating cardiovascular safety

By Cathy Sprankle, reprinted from *eFACTOR*, July 2013



Pollutants and toxicants in the environment have the potential to damage cells in the heart and circulatory system. This type of toxicity, known as cardiovascular toxicity, is also a major reason for drug development failure. The environmental and medical aspects of cardiovascular toxicity make this research area interesting to a broad audience, including clinical researchers, environmental health researchers, government regulators, and drug developers.

Because of the broad current interest in cardiovascular toxicity, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is joining with the U.S. Environmental Protection Agency to present a workshop addressing development of new methods to assess and predict whether substances might affect cardiovascular safety in humans. The workshop, "Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk," will be held Oct. 10-11 at NIEHS.

"Cardiovascular disease is the leading cause of death in the United States," noted Warren Casey, Ph.D., acting director of NICEATM and a co-chair of the workshop. "One objective of this workshop is to assess the role of chemical exposures in cardiovascular disease. We're also going to be examining current approaches for identifying substances likely to cause cardiovascular toxicity, and discuss how that could be done more effectively."

Determining whether a substance is likely to cause cardiovascular toxicity presents a number of challenges. Current approaches involve testing in animals and rely on observing effects, such as organ damage and blood chemistry changes, which provide evidence of toxicity, but little information about the mechanism of toxicity. The animal tests used by drug developers are much better at identifying the immediate acute effects than the damage that might occur after taking a drug for a long period of time. Because there are no standardized regulatory guidelines for cardiovascular toxicity testing, approaches for testing vary widely among industries, with testing practices among industrial chemical manufacturers being very different from those used by drug manufacturers.

The workshop will bring together scientists from these industries, academia, and regulatory agencies to consider new approaches to cardiovascular toxicity testing that will provide better safety and risk assessments while reducing or eliminating animal use. Participants will consider how to prioritize research initiatives in this area, and how to bring together data on test substances from various test methods and sources, to develop better cardiovascular toxicity hazard assessments.

More information about the workshop, including an agenda and registration information, is available on the NIEHS website at http://www.niehs.nih.gov/about/visiting/events/highlight/cardiovascular-toxicity-workshop/.

(Cathy Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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Committee Responds to NIEHS Director's Statement on the Future of NICEATM and ICCVAM

By Catherine Sprankle

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which is administered and supported by NICEATM, has responded to a recent editorial by NIEHS and NTP Director Linda Birnbaum, PhD, that addressed the current status and future direction of ICCVAM.

In the editorial, published in the Feb. 1 issue of Environmental Health Perspectives, Birnbaum presented a new vision for NICEATM and how NICEATM will interact with ICCVAM in the future. The goals of the new vision are to allow ICCVAM's activities to be driven by the regulatory agencies that participate on ICCVAM and to enable NICEATM to support ICCVAM more effectively in addressing how data from high-throughput assays can be integrated into the regulatory framework.

In a letter released after its April meeting, ICCVAM stated that the committee is "pleased to see the new philosophy for ICCVAM" and that it looks forward to "working with NICEATM to forge the new direction" described in the editorial. The committee expects that the proposed changes will improve efficiency of the ICCVAM test method review process and its relevance to the agencies.

Links to Dr. Birnbaum's editorial and the ICCVAM response are available on the ICCVAM website.

ICCVAM stakeholders will have an opportunity to learn more about and comment on the direction and scope of future activities at the upcoming meeting of ICCVAM's advisory committee. The Scientific Advisory Committee on Alternative Toxicological Methods will meet at NIEHS on September 24, 2013. Information about the meeting is available on the NTP website at http://ntp.niehs.nih.gov/go/32822. The meeting will be webcast, and a link to the webcast will be available on this page on the meeting days.

(Cathy Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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Industry scientist discusses statistical approach to safety testing

By Cathy Sprankle and Tom Burns

Jaworska is recognized as a leading authority on developing the next generation of adaptive, integrated testing strategies for skin sensitization. (Photo courtesy of Joanna Jaworska)

Linked video:

Watch Jaworska's keynote address, "Integrated testing strategies — opportunities to better use existing data and guide future testing," at the Center for Alternatives to Animal Testing workshop in 2010 on "21st Century Validation Strategies for 21st Century Tools" (01:15:00)

(Launches in new window)

Manufacturers test cosmetics, household cleaners, and other chemical products before marketing, to identify any hazards they might present. One of those hazards is skin sensitization, or the potential for a product to cause an allergic skin reaction. The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is studying new methods to test substances for skin sensitization hazards, and in May hosted a visit from a leading industry scientist to collaborate on development of a promising new testing approach.

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Joanna Jaworska, Ph.D., a principal scientist with Procter and Gamble in Brussels, Belgium, visited NIEHS May 20–21. While at NIEHS, Jaworska presented a seminar titled "Bayesian Integrated Testing Strategy to Assess Skin Sensitization Potency: From Theory to Practice," and met with NICEATM and other NTP scientists to work on creating an integrated testing strategy to identify potential skin sensitizers using non-animal test methods.

Preventing allergic contact dermatitis

Regulatory agencies around the world require testing to identify substances that may cause allergic skin reactions. Repeated exposure to these substances can cause allergic contact dermatitis (ACD), a skin condition characterized by redness, swelling, blistering, and itching. Poison ivy is a well-known cause of ACD, but chemicals that are used in consumer products, such as formaldehyde and nickel, can also cause the condition. ACD is hard to treat, so it is important to identify and properly label substances that may cause it. With proper labeling, people handling these substances have the information they need to prevent exposure.

Traditional testing methods to identify substances that cause ACD use animals, but concerns about testing efficiency and animal welfare are driving efforts to replace traditional testing methods with non-animal methods. In practice, it usually takes several non-animal tests to provide the same level of information as a single animal test.

Moving toward alternative testing

The integrated testing strategy developed by Jaworska and colleagues at Procter and Gamble provides an approach for analyzing information from non-animal tests and other information about a test substance, such as chemical structure and solubility. The analysis considers all the available relevant information about a substance and produces a numerical probability that the substance is a sensitizer. This probability could potentially be used to make decisions about whether substances require hazard labeling, without requiring animal testing.

The software used by Procter and Gamble for these analyses is patented, so Jaworska and the NTP scientists are collaborating to develop similar tools using free, publicly available software, to make the integrated testing strategy approach more widely available. "If our collaboration is successful, people and organizations worldwide will be able to use this approach for identifying potential sensitizers," commented NTP senior toxicologist Warren Casey, Ph.D., acting director of NICEATM. "It's an example of how international cooperation can support the effort towards eliminating animal testing in this area." ●

(Cathy Sprankle and Tom Burns are employees of ILS Inc., support contractor for NICEATM. Sprankle is senior communications specialist and Burns is a senior project coordinator/technical writer.)

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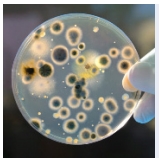

NTP Fact Sheet on Mold
Available at: http://www.niehs.nih.gov/health/materials/mold_508.pdf

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