

NTP board green lights research concepts and predictive toxicology efforts

By Robin Mackar

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).

(<http://ntp.niehs.nih.gov/go/9741>)

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.

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



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)



Chapin, left, 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)



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Casey discussed work being done on identifying adverse outcome pathways. His group provides scientific and operational support for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), an interagency committee of 15 U.S. federal regulatory and research agencies that generate and use toxicity testing data. (Photo courtesy of Steve McCaw)



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Taylor presented before BSC for the first time. (Photo courtesy of Steve McCaw)



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Timothy Buckley, Ph.D., Director of the Human Exposure and Atmospheric Sciences Division at EPA, and NTP OHAT Director Kristina Thayer, Ph.D., responded to questions from BSC about a unique proposed pilot, between NTP and EPA, to assess how questionnaires reflect personal care product use and exposure. (Photo courtesy of Steve McCaw)



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Sutherland ably presented two research concepts to BSC. (Photo courtesy of Steve McCaw)



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Birnbaum, front, enjoyed a light-hearted moment with BSC members. Bucher, left, listened closely to all the presentations and discussions. (Photo courtesy of Steve McCaw)



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Peterson listened carefully to all the discussions that took place over the day and a half. (Photo courtesy of Steve McCaw)

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](#),

(<http://ntp.niehs.nih.gov/?objectid=06002ADB-F1F6-975E-73B25B4E3F2A41CB>)

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](#)

(<http://www.oecd.org/about/>)

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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