August 2015

CSS Pathways: Anticipating Impacts of Chemicals

CHEMICAL SAFETY FOR SUSTAINABILITY RESEARCH NEWS

Contents

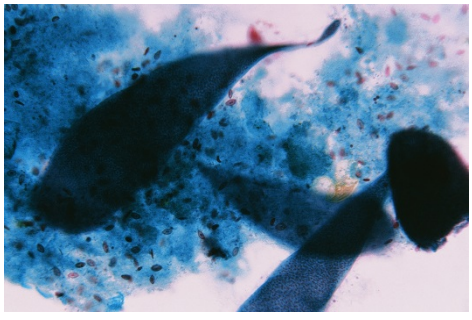
CSS Highlights

Promoting Ecological Wellbeing

STAR Grants Awarded for Research on Ecological Impacts of Manufactured Chemicals

EPA awarded more than $4 million to six academic institutions for research that will advance scientific understanding of potential for impacts to ecosystem wellbeing associated with the use of manufactured chemicals. The projects will develop and apply innovative systems-based approaches to better understand and predict the biological and ecological consequences of exposures to chemicals in environmental systems. Projects will translate emerging and advanced methods, data, and computational tools to address the complexity of these systems and to distill drivers of adverse outcomes to ecological organisms and populations. EPA is planning a grantee kick-off meeting during the annual meeting of the Society for Environmental Toxicology and Chemistry, November 1-5, in Salt Lake City, Utah. Learn more about the grantees and their research plans here.

Comprehensive Dataset Available for Predictive Aquatic Toxicology



EPA scientists Mace Barron, Crystal Lilavois, and Todd Martin published a manuscript describing an acute aquatic toxicity database to support predictive model development. In the research, published in the journal *Aquatic Toxicology* this past April, Aquatic toxicity mode of action (MOA) assignments were determined for 1213 chemicals and acute toxicity values were determined for 674 chemicals. The resulting database has application to quantitative structure activity modeling. Future work will include developing an internet accessible and searchable platform. The full manuscript can be viewed online.

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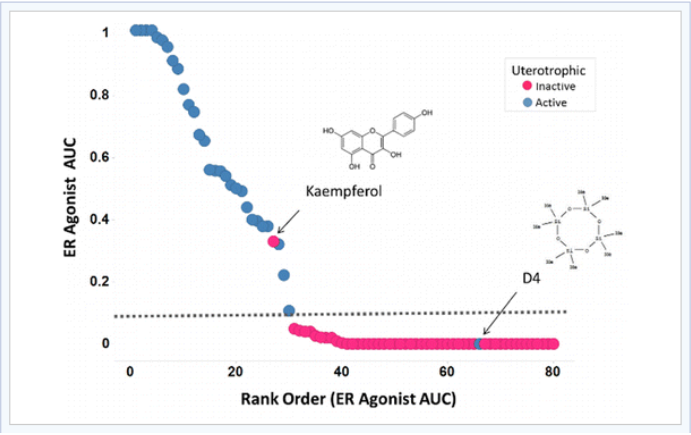
Transforming Chemical Evaluation

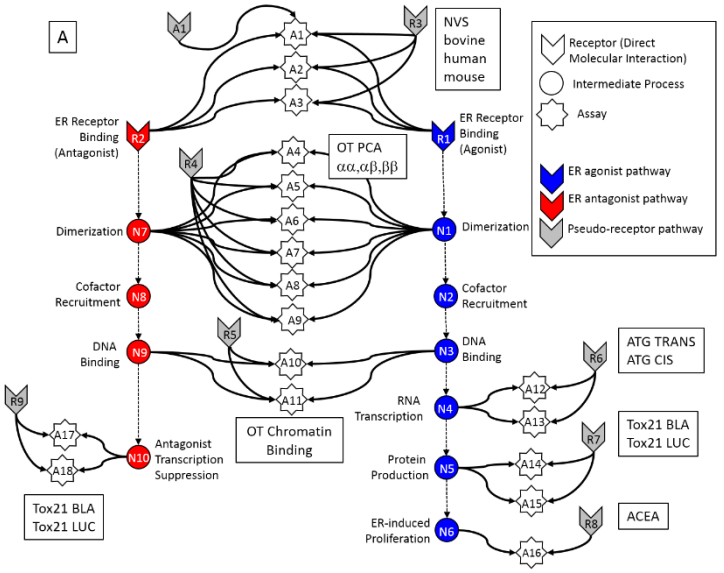
EPA Introduces New Technology to Screen Chemicals for Endocrine Disruption



EPA released a Federal Register Notice on June 19 proposing a plan for the Endocrine Disruptor Screening Program (EDSP) to use ToxCast high-throughput screening assays and models built on the output of the assays. The goal of EDSP is to help insure that people and wildlife are not exposed to chemicals that inadvertently perturb the endocrine system, which could lead to harmful effects including developmental and reproductive problems, increased risk of certain kinds of cancers, or significant decreases in populations of ecological species such as fish, frogs or birds. Use of high-throughput assays and computational methods has the potential to accelerate the pace of screening, decrease costs, and reduce animal testing. EPA's plan to use this new approach is described in the journal *Environmental Science & Technology* in a manuscript coauthored by EPA scientists Patience Browne, Russell Thomas and Richard Judson, and collaborators at the National Institute of Environmental Health Sciences (NIEHS). This paper is the first description of using ToxCast high-throughput screening data as an alternative for regulatory guideline studies. The FR Notice, the EPA press release, and the ES&T paper are available online.

High-Throughput Model Predicts Estrogen Receptor Activity

Evidence is mounting that some chemicals may disrupt the endocrine system by interacting with the estrogen receptor (ER). A large team of scientists from EPA, NIEHS, and academia led by EPA scientist Richard Judson recently published a manuscript demonstrating a computational network model that integrates results of 18 *in vitro,* high-throughput screening assays. The network model uses activity patterns across the *in vitro* assays to predict whether a chemical is an ER agonist or antagonist.



Importantly, this model and the results have been vetted through two public Scientific Advisory Panel reviews, which endorsed using the model to replace two of the lower-throughput in vitro assays in the current EPA Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA worked with NIEHS to show that the ER model also does a good job predicting one of the EDSP animal-based studies (the uterotrophic assay). As a result, EPA stated its intention to allow companies to use the results of this model to replace data from the two low-throughput *in vitro* tests and the uterotrophic assay.

There are approximately 10,000 chemicals that are required to be tested in these three assays. Using the methods that are currently standard, less than 60 have been evaluated in the last several years. With this model, EPA now has data from >1000 on the EDSP chemical list, with another 1000 likely to be evaluated in the next year. The model provides the ability to prioritize a large set of important environmental chemicals with human exposure potential for additional *in vivo* endocrine testing. In addition, this model is generalizable to any molecular pathway for which there are multiple upstream and downstream assays available. The model is described in a paper published the journal *Toxicological Sciences*.

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New in Brain Research

Advancing Methods to Evaluate Neurotoxicity

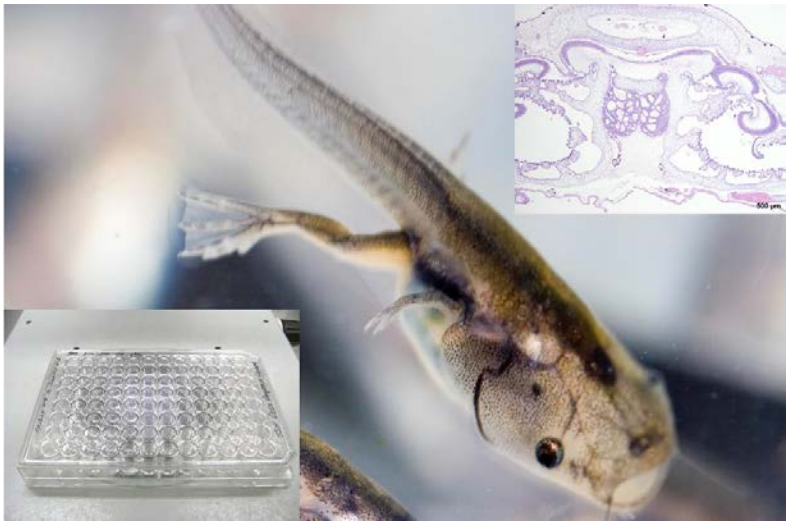
EPA research led by Drs. William Mundy and Timothy Shafer focuses on developing new approaches for using higher throughput *in vitro* methods to characterize neurotoxicity from exposure to chemicals.

A paper published in the journal *NeuroToxicology* describes research conducted using microelectrode array (MEA) recordings. Scientists grow cultures of rat central nervous system tissues on the MEA to create and measure neural-network activity as well as cell health on the same MEA. These "spikes" of activity represent action potential of the brain. Scientists expose these networks to a variety of pharmaceutical compounds and chemical toxicants to evaluate how they affect the electrical activity generated by the neural cultures. The results of this research demonstrate a simple and rapid method for the simultaneous determination of test compound effects on spontaneous electrical activity and cell health from the same network, and will facilitate rapid screening of compounds for potential neurotoxicity. The complete article can be found on the journal website.

A second paper published in the journal *Toxicology* describes how *in vitro* assays may be used in a battery of tests for detecting chemicals that could result in developmental neurotoxicity. Apoptosis—normal, biologically controlled cell death—contributes to nervous system development by regulating the quantity of the neuroprogenitor cells. The balance between cellular proliferation and apoptosis during neuroprogenitor cell propagation helps to determine the size and shape of the nervous system. Therefore, chemicals that affect apoptosis during neuronal development can have harmful effects on the developing brain. This research examined the utility of a high-throughput assay to detect chemical-induced apoptosis in mouse or human neuroprogenitor cells, as well as differentiated human neurons derived from induced pluripotent stem cells. You can learn more about the research methods and results online.

Advancing Methods to Evaluate Thyroid Toxicity

Drs. Michael Hornung and Sigmund Degitz are among a team leading EPA research to develop higher throughput methods for measuring chemical impacts on thyroid function. Their most recent paper was highlighted in the August Issue of *Toxicological Sciences.* In this paper, the authors describe their investigation of the potential adverse health effects of endocrine disrupting chemicals on thyroid hormone homeostasis and development of a sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to quantify thyroid hormone production at the picomole level. Their results indicate that inhibition of thyroid peroxidase (TPO) activity *in vitro* is a good indicator of a chemical's potential for thyroid hormone disruption *in vivo* and may be useful for prioritizing chemicals for further investigation. The full paper is available online.



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Recent and Upcoming Events

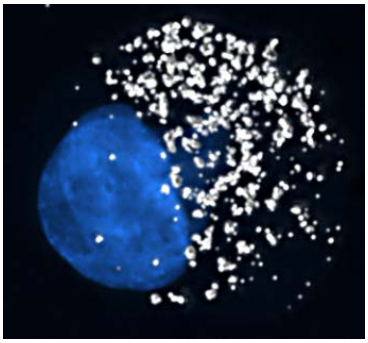
EPA Hosted Metabolomics Meeting | August 18-19, 2015

EPA hosted a Non-targeted Analysis Workshop in **Research Triangle Park, NC on August 18-19, 2015.** The purpose of this meeting was to gather experts in non-targeted screening to discuss innovative methods and best practices for collecting, analyzing, and interpreting xenobiotic chemical exposure data. More detailed information about this meeting, agenda, and presentations can be found online.

EPA and NIEHS Join to Strengthen Risk Assessment for Improved Public Health

July 15-16, 2015 in Research Triangle Park, NC: EPA and NIEHS convened a joint risk assessment workshop*, Strengthening the Scientific Basis for Chemical Safety Assessment.* The purpose of this workshop was to identify high priority topic areas that present the greatest opportunity for reducing uncertainty in and improving human health risk assessments for chemicals. Opening remarks were provided by Jim Jones from EPA's Office of Chemical Safety and Pollution Prevention, Linda Birnbaum from NIEHS, and Tom Burke from EPA's Office of Research and Development. Several case studies were presented to illustrate and provide background for key topic areas including accounting for exposures during critical developmental windows, capturing variability in population susceptibility, translating experimental animal findings to humans, and addressing cumulative exposures. Leading academic researchers in relevant fields provided suggestions for ways to fill scientific gaps in these topic areas and to translate scientific research for application to chemical risk assessments. Participants agreed to continue the engagement between public health researchers and users of the research to optimize and capitalize on the emerging data and science to conduct chemical assessments and make decisions that are public health protective.

Nanotechnology Conference Raises Profile of Exposure Science



EPA scientists were well represented at the recent conference "Quantifying Exposure to Engineered Nanomaterials from Manufactured Products" (QEEN) in Arlington VA, **July 7-8 2015**. The goal of the meeting, co-sponsored by the National Nanotechnology Initiative (NNI) and the Consumer Product Safety Commission (CPSC), was to evaluate the state of the science, tools and methods currently used to characterize and quantify exposure to engineered nanomaterials found in consumer products. EPA researchers, Drs. William Boyes and Richard Zepp co-chaired two of the workshop sessions, and Drs. Kim Rogers Chris Knightes presented their research. Dr. Tina Bahadori participated in the roundtable, "Exposure Science in the 21st Century", and Dr. Elaine Cohen Hubal served on the workshop organizing committee. The meeting agenda can be found at http://nano.gov/node/1327.

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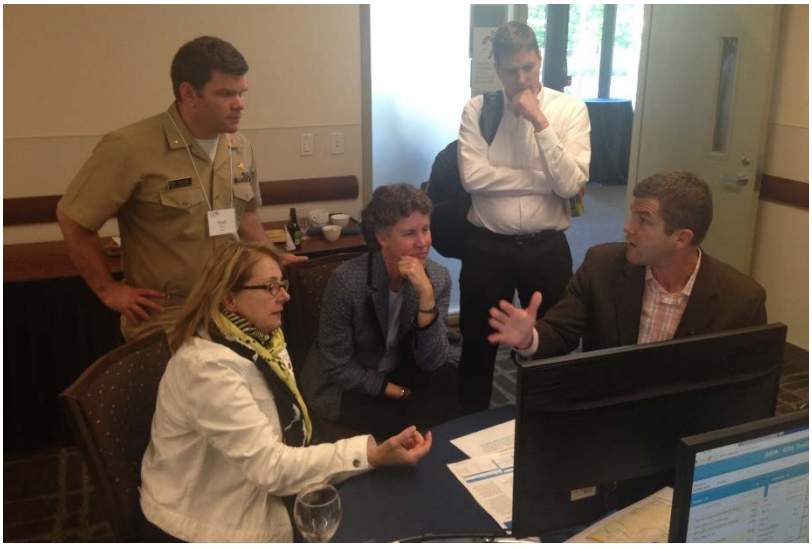
EPA and NIEHS Leadership Meet at Environmental Defense Fund (EDF) Workshop

Drs. Tom Burke (EPA) and Linda Birnbaum (NIEHS) headlined a June 18-19 workshop in Davis, CA organized by the Environmental Defense Fund (EDF). Hosted in partnership with EPA and the National Toxicology Program (NTP), the workshop focused on "Elucidating Environmental Dimensions of Neurological Disorders and Diseases: Understanding New Tools from Federal Chemical Testing Programs". EPA was well represented at the workshop; Drs. Tina Bahadori and Russell Thomas played key roles in leading discussions; and Drs. Matt Martin and Keith Houck also presented. The purpose of the workshop was to discuss the potential applications of high-throughput ToxCast and Tox21 data to enhance epidemiology research. The federal ToxCast and Tox21 programs were reviewed in detail and one-on-one Genius Bar sessions provided attendees an opportunity to explore new data sets and tools with EPA and NIEHS staff scientists. By bringing together leading researchers from a range of scientific disciplines, meeting organizers facilitated outreach and integration among the fields.



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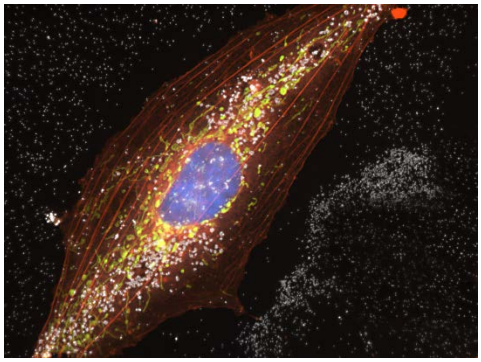
Gordon Research Conference Focuses on Safer Nanotechnology

Increasing numbers of commercial, industrial and environmental products and processes are using nano-enabled systems. The 3rd Gordon Research Conference on Environmental Nanotechnology focused on safe use of these systems. EPA researchers were among the participants at the June 21-26 meeting in Mount Snow, VT. The meeting agenda can be found on the GRC website.



Grantees Corner

Systems-Based Research for Evaluating Ecological Impacts of Manufactured Chemicals

EPA will host a **grantee kickoff meeting** to introduce and congratulate the STAR grantees and their research at the SETAC annual meeting in **November 2015**. More information about the SETAC 36th annual meeting can be found online.

NPD Corner

European Food Safety Authority Consults on Assessment Methodology

EPA's CSS National Program Director (NPD), Dr. Tina Bahadori participated in the European Food Safety Authority (EFSA) Workshop: *Increasing Robustness, Transparency, and Openness of Scientific Assessments*, held in Brussels, Belgium on June 29-30**.** **Leading experts and practitioners of regulatory science were invited from across Europe and beyond to** provide feedback to improve the scientific basis of EFSA health risk assessments. The complete news story on this meeting is available online.

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Health Canada Solicits Feedback on Risk Assessment Framework

Dr. Elaine Cohen Hubal, EPA CSS Deputy Director, serves as a core member of Health Canada/Environment Canada Chemicals Management Plan (CMP) Science Committee. The Chemicals Management Plan (CMP) Science Committee contributes expertise to Health Canada and Environment Canada on scientific considerations for evaluating chemicals under the CMP. The committee convened in Ottawa, Canada on June 2-3 to provide input on a planned level-of-complexity risk assessment framework for addressing the remaining priorities under the next phase of the CMP. The committee made recommendations that included suggestions for how to best operationalize this framework. More details about the recommendations and the charge questions can be found here.

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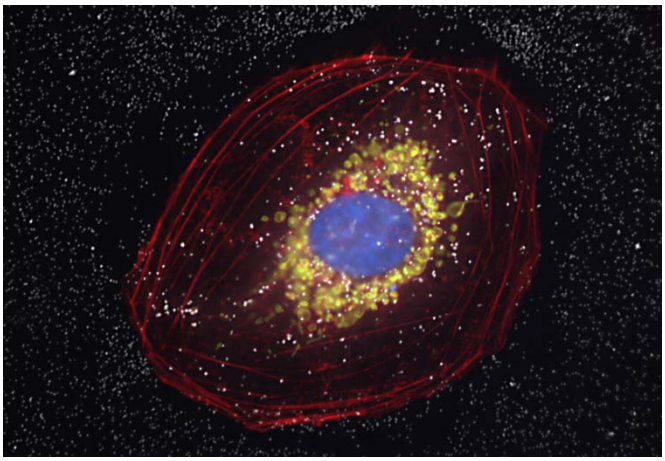
U.S. and EU Bridge Nano Environmental Health and Safety Research



The *2015 U.S. –EU: Bridging NanoEHS Research Efforts joint* workshop was held on March 12-13 in Venice, Italy. The workshop was organized by the U.S. National Nanotechnology Initiative (NNI) and the European Commission. The purpose of this fourth workshop was to further deepen and promote EU-U.S. collaboration on nanomaterials-related environment, health, and safety (nanoEHS) research. Dr. Tina Bahadori presented on the U.S. EPA's perspective regarding present R&D efforts for the assessment of human exposure to nanomaterials as well as toxicity evaluation. The report from this meeting is expected to be posted shortly.

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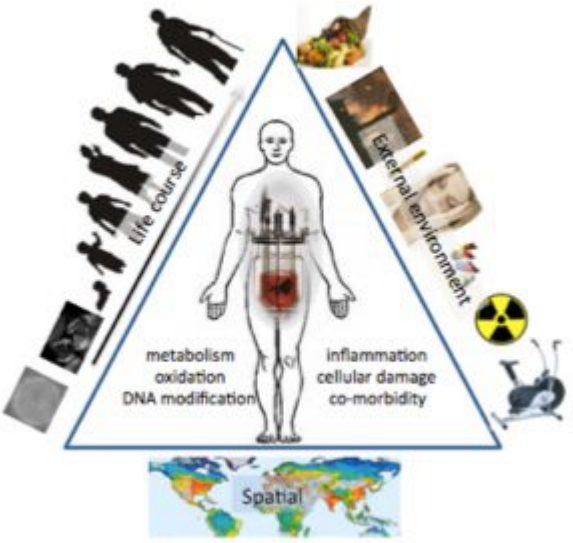
NAS Discuss Opportunities to Apply Metabolomics to Characterize the Exposome

The National Academy of Science sponsored the workshop, "Metabolomics as a Tool for Characterizing the Exposome," in Washington DC, on May 28-29. The workshop gathered leading researchers to explore application of metabolomics to advance understanding of environmental impacts on human health. Dr. Elaine Cohen Hubal presented in the final session focused on implications of the metabolomics methods and the exposome for decision making. More details on this meeting can be found here.



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CSS in the News

Recent News Articles

- EPA Endocrine Managers Prepare New Policy to Outline Shift to New Tests
- A New Way to Evaluate Chemical Safety – TOX21: A Risk Bites video
- Society of Toxicology Highlight EPA Scientists' Presentations at March SOT Annual Meeting

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Meet CSS Scientists

- Tina Bahadori
- Tom Knudsen
- Bill Mundy
- Sandy Raimondo
- Tim Shafer
- Dan Villeneuve
- John Wambaugh

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