December 2015

CSS Pathways: Anticipating Impacts of Chemicals

CHEMICAL SAFETY FOR SUSTAINABILITY RESEARCH NEWS

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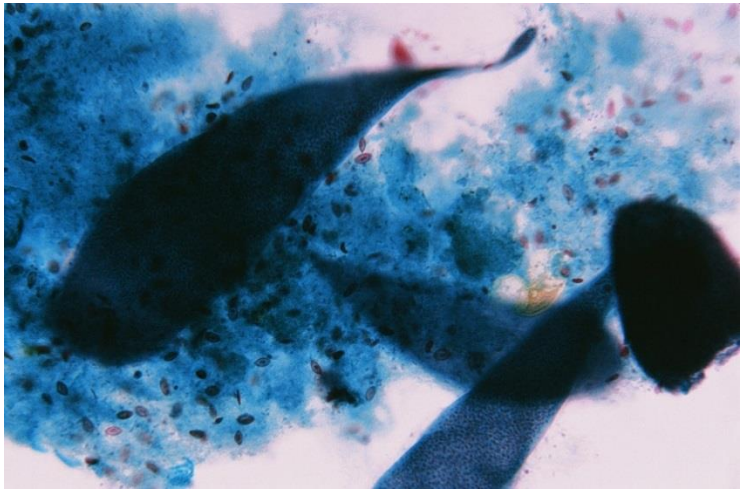
CSS Highlights

Advances in Toxicology

Sequencing the Fathead Minnow Genome



The fathead minnow (*Pimephales promelas*) is an important model organism for aquatic toxicology research and regulatory testing. It is the most widely used small fish model for research supporting regulatory ecotoxicology in North America. However, the lack of genome sequence information, when compared to other small fish, (e.g. zebrafish) has limited researchers' ability to use the fathead minnow.

A paper titled *Sequencing and de novo draft assemblies of a Fathead Minnow (Pimephales Promelas) reference genome* written by a team of CSS researchers and collaborators from DuPont will appear in *Environmental Toxicology & Chemistry*, and reports on the first sequencing and two draft assemblies of a fathead minnow reference genome.

The study builds the foundation needed for using the fathead minnow model to predict ecotoxicity and to inform ecological risk assessments. The paper dissects complex traits, genetic marker discovery, identification of gene regulatory domains, and determines biological networks. The use of this genome will aid transcriptomic, proteomic, and other molecular analyses. The authors hope that this work will be the basis for further refinements of a reference genome for the fathead minnow which will lead to fully using this species for 21st-century ecotoxicity modeling.

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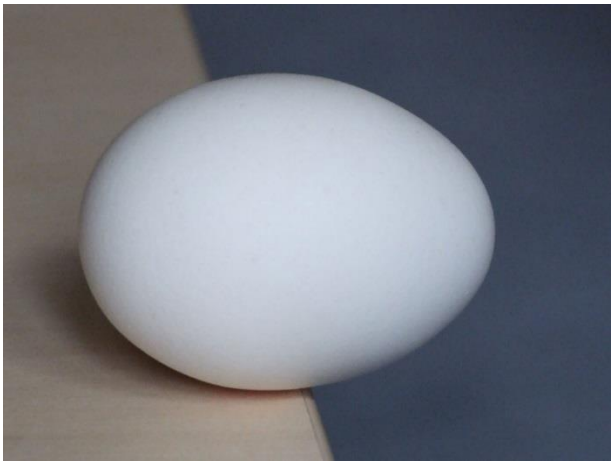
Identification of Toxicological 'Tipping Points' Using High-Content Imaging

High-throughput screening (HTS) methods to assess biological responses to chemicals allow scientists to organize data into toxicity pathways. One of the challenges of using this type of data to evaluate chemicals is determining 'tipping points', the points when pathway perturbations cause a lasting change potentially leading to adverse effects. CSS scientists, including first author Imran Shah, published a paper in *Environmental Health Perspectives* titled *Using ToxCast data to reconstruct dynamic cell state trajectories and estimate toxicological points of departure.*



This study evaluated the effects of 967 chemicals at 10 treatment concentrations during a 72 hour exposure period in HepG2 cells. High-content imaging (HCI) captured multiple features of the cells using fluorescent labels to measure concentration-dependent dynamic changes including oxidative stress, cytoskeletal changes, and cell number endpoints among others. The HCI responses were analyzed by their propensity to recover to normal conditions allowing for the determination of critical non-recoverable concentrations. The findings of this work show the utility of HCI for reconstructing cell state trajectories and provide insights into adaptation and resilience of *in vitro* cellular systems. The hope is that cellular tipping points may be used to define a point of departure for risk-based prioritization of environmental chemicals.

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On Flame Retardants

Studies Examine the Neurological Effects of Alternative Flame Retardants

Brominated flame retardants (BFR) are being phased out of commercial use due to their toxicity and persistence in the environment. In their place, alternative chemicals such as organophosphorus flame retardants (OPFR) and halogenated classes are being used. However, limited information regarding the human health effects of these chemicals makes their use worrisome, particularly as it relates to nervous system development. OPFR have a similar chemical structure to organophosphorus insecticides, which show increasing evidence of developmental toxicity and neurotoxicity. In two recent studies, appearing in *Neurotoxicology and Teratology,* researchers compared the biological activity between newer OPFR and phased out BFR. Results of both studies suggest more research is warranted with regards to hazards associated with newer flame retardants.

In one study titled *Use of alternative assays to identify and prioritize organophosphorus from retardants for potential developmental and neurotoxicity,* CSS researchers along with others from the University of Louisville and Kelly Government Solutions, evaluated OPFR using a number of high throughput, high-content *in vitro* cell-based assays and alternate animal models for potential developmental, neurodevelopmental, and neural activity. The novel methodology in this research compared the relative activities of the chemicals based on point-of-departure (POD - the lowest concentration where the response was higher than background variability) for each assay. The results indicate that for several of the OPFR the POD values obtained are equal to those measured from the BFR, suggesting the alternative chemicals may not be a safer alternative and hazard characterization needs to be better evaluated.

In the second study, *Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish*, researchers from the EPA, the University of North Carolina, and National Institute of Health Sciences (NIEHS), evaluated the effects of eleven phased out and new flame retardant compounds using *in vivo* models in zebrafish larvae. Investigators did not concentrate on lethality and teratogenic endpoints, but rather on more subtle effects such as whether these chemicals can change locomotor activity post-fertilization. All of the tested flame retardants perturbed the behavior of the six day old zebrafish larvae. Behavioral effects were identified at developmental exposure concentrations 4 to 10 times lower than lethal or malformation concentrations. Additionally, in many cases a 'no-effect level' was not achieved. Because of the similarities between zebrafish and mammalian developmental pathways, the results of this model are robust for inferring potential human neurological effects from both phased out and alternative flame retardants.

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Upcoming & Recent Events

Society of Toxicology FutureTox III: Bridges for Translation | November 19-20, 2015

Members of Society of Toxicology gathered to address the accomplishments and on-going challenges of the 21st Century vision and strategy for toxicology. This third in a series of FutureTox meetings was co-chaired by Dr. Tom Knudsen of the National Center for Computational Toxicology (NCCT) and Dr. Daland Juberg of Dow Agrosciences and focused on translation of the emerging science for use in policy. In a keynote address, Mr. Jim Jones, Assistant Administrator for the Office of Chemical Safety and Pollution Prevention (OCSPP) described the opportunities to use 21st Century science to accelerate the pace of decision making. Other talks and presentations focused on "big data" generated from high-throughput screen technologies and novel methodologies such as *in vitro*, *in silico*, and virtual tissues models for exposure and hazard assessment. Drs. Thomas Knudson, Dan Villeneuve, John Wambaugh, David Dix, and Tina Bahadori from the CSS community spoke at the meeting. Numerous EPA scientists also presented their cutting-edge research at the poster session. More information about this meeting can be found at the Society of Toxicology website.

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CSS Researcher presentation at the National Toxicology Program | November 4, 2015

Dr. John Wambaugh (National Center for Computational Toxicology -NCCT) presented *Building Fit-for-purpose Pharmacokinetic Models* as part of National Toxicology Programs (NTPs) webinar series, *In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making*. This series of four webinars is leading up to a February 2016 workshop. The purpose of the webinar series and workshop is to address the capabilities and the limitations of *in vitro* to *in vivo* extrapolation (IVIVE) within the context of risk decision making. More information on the webinar series can be found here.

Society of Environmental Toxicology and Chemistry (SETAC) 26th Annual Meeting | November 1 – 5, 2015

EPA scientists showcased their research through symposia, workshops, platform presentations and poster sessions at the 2015 SETAC 26th Annual Meeting in Salt Lake City, Utah on November 1-5. EPA hosted a kick-off meeting event in conjunction with SETAC for the systems-based ecological modeling Science to Achieve Results (STAR) grants. EPA also sponsored an exhibit booth which featured demonstrations of online EPA research tools and provided SETAC participants information about research, career opportunities and available grant funding. More information about the SETAC Annual meeting and complete conference materials are available on the SETAC webpage.

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California Endangered Species Act (ESA) Training and Engagement Workshop | October 19 – 23, 2015

The CSS program's ecological research includes an aquatic endangered species case study in the Sacramento River Basin, CA. The case study focuses on improving the science for evaluating the risk of chemical exposure to threatened and endangered species. CSS worked closely with the California Department of Pesticide Regulation and Agriculture Commissioner to plan a workshop to better understand the ESA processes and to discuss plans for the case study. The workshop provided training regarding the federal and state processes required to comply with the ESA. A better understanding of these processes will help design fit-for-purpose research products for the case study. Additionally, the workshop taught participants about the species of interest and chemical usage within the case study area. Participants improved their understanding of federal and state processes for complying with ESA, the biology and ecology of endangered species within the study area, geography influencing chemical fate and transport within the study area, and the application, use, and economic considerations of pesticides.

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International Society of Exposure Science Annual Meeting | October 18 – 22, 2015

The 25th annual International Society of Exposure Science (ISES) meeting was held in southwest Nevada on October 18-22. Many EPA scientists showcased CSS exposure: science including advances in life cycle and human exposure modeling, high throughput exposure modeling, biomonitoring, and non-targeted analyses. ISES brings together exposure scientists from across disciplines ranging from analytic chemistry to epidemiology, toxicology, public and ecological health, and risk assessment. More information about the ISES Annual meeting and complete conference materials are available on the ISES Webpage.

NAS Meetings for Unraveling Low Dose: Case Studies of Systematic Review of Evidence | October 13 – 14, 2015

As a follow-up study to the National Academies of Science (NAS) review of the draft Non-Monotonic Dose Response State-of-the-Science Paper, the NAS National Research Council (NRC) convened an expert committee to develop a systematic approach for determining whether EPA's current hazard assessment approach is sufficient to consider evidence of low-dose adverse effects that act through an endocrine-mediated toxicity pathway. To date, NRC has held two expert committee meetings. Both meetings provided the opportunity for public comment. More information about this project, as well as the schedule of subsequent meetings, can be found on the NAS Project Information page.

CSS BOSC Subcommittee Meeting | October 6 – 8, 2015

The CSS-HHRA Board of Scientific Counselors (BOSC) Subcommittee Meeting was held in Research Triangle Park (RTP), North Carolina on October 6-8 to provide advice, information, and recommendations to program leadership on technical and management issues of the CSS Research Program. The workshop was organized by Designated Federal Officer (DFO), Megan Fleming, and led by Chairman, Dr. Ponisseril Somasundaran, from Columbia University and Vice Chair, Dr. Gina Solomon, from California EPA. The committee of nine reviewers listened to in-depth presentations from Dr. Tina Bahadori, Dr. John Vandenberg, and CSS scientists. They also toured EPA's laboratory facilities and participated in demonstrations of many CSS online tools. More information and BoSC materials can be found here. The report from this meeting will be presented and discussed at the meeting of the Executive Committee of the BoSC December 7-9 in Washington DC.

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Invited Expert Meeting on Revising U.S. EPA's Guidelines for Deriving Aquatic Life Criteria | September 14-16, 2015

On September 14-16, 2015 EPA's Office of Water (OW) and Office of Science and Technology held an invited Expert Meeting in Arlington, VA to kick off the discussion around revising Guidelines for Deriving Aquatic Life Criteria. A number of CSS scientists including Dr. Mace Barron and Dr. Carlie LaLone were invited to participate and present. This meeting also provided a platform to bring emerging CSS science into consideration for the revision of these guidelines. Discussions from the meeting prompted CSS and Safe and Sustainable Water Resources (SSWR) to join OW for a strategic conversation (or Chautaqua) in early December to explore collaboration opportunities to support this OW priority.

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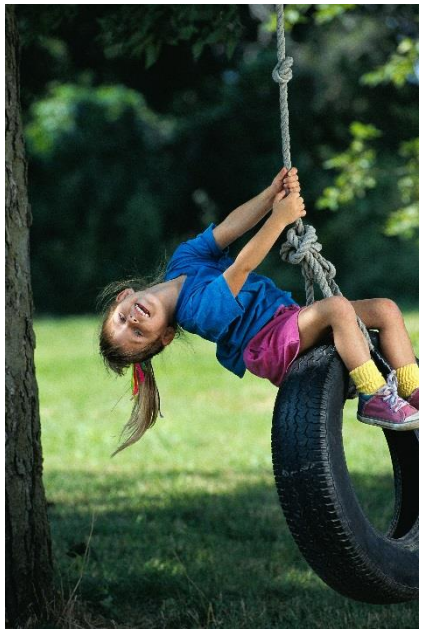
Children's Health Corner

2015 EPA/NIEHS Children's Centers Annual Meeting | October 29 – 30, 2015



EPA joined National Institute of Environmental Health and Safety (NIEHS) to co-sponsor the Annual EPA/NIEHS Children's Centers Meeting. The meeting brought together researchers, clinicians, and representatives from professional organizations to discuss the intersection of research, clinical applications, and policy to better protect children's health. The meeting focused on developing improved collaboration between the scientific community to share research findings and technical information with parents and the public. Dr. Thomas Burke, the Deputy Assistant Administrator of the EPA Office of Research and Development and Dr. Ruth Etzel, the Director of the EPA Office of Children's Health Protection, presented work highlighting the Agency's commitment to children's health. Also Dr. Andre Geller, Deputy National Program Director of Sustainable and Health Communities Research Program chaired a session. More information about this meeting can be found here.

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Children's Health Protection Advisory Committee (CHPAC) | November 12 – 13, 2015

CHPAC is a body of external researchers, academicians, health care providers, environmentalists, state and tribal government employees, and members of the public who advise EPA on regulations, research, and communications related to children's health. The two day committee meeting on November 12 and 13 provided members an update on the EPA's Office of Children's Health Protection Activities and updates on Agency regulations that directly impacts children's health, such as No_x National Ambient Air Quality Standards (NAAQS). Dr. Thomas Burke, the Deputy Assistant Administrator of the EPA Office of Research and Development, presented the EPA's vision of children's health research directions. More information on CHPAC is available here.

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NPD Corner

Health Canada Solicits Feedback on Cumulative Risk Approaches

Dr. Elaine Cohen Hubal, CSS Deputy Director, serves as a core member of Health Canada/Environment Canada Chemicals Management Plan (CMP) Science Committee. The purpose of the CMP Science Committee is to contribute expertise to Health Canada and Environment Canada on scientific considerations for evaluating chemicals under the CMP. The committee convened in Ottawa, Canada on November 18-20 to provide input on criteria and approaches for conducting cumulative risk assessments under the next phase of the CMP. More details about the committee's recommendations and the charge questions can be located here.

NPD Visits NHEERL's Western Ecology Division (WED) | October 19, 2015

Accompanied by Region 10's Dr. Bruce Duncan and National Health and Environmental Effects Research Laboratory (NHEERL)-CSS Matrix Interface, Dr. Joe Tietge, Dr. Tina Bahadori visited WED to learn more about their research capabilities and infrastructure and to explore additional opportunities for innovative and integrated research related to fate, transport, and ecological impacts of engineered nanomaterials and ecological modeling. In addition, the group discussed how the regions can be engaged to help shape, translate, and deliver the products of CSS research.

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Notables

Public release of the CSS Strategic Research Action Plan

The Chemical Safety for Sustainability Strategic Research Action Plan (StRAP) 2016-2019 was publically released October 9, 2015. The StRAP outlines the future direction of the program specifically around the four research topics - Chemical Evaluation, Life Cycle Analytics, Complex Systems Science, and Solutions-Based Translation and Knowledge Delivery. The plan maps out the research and collaborative strategy for both near-term and long-term needs of transforming chemical evaluation. The CSS StRAP 2016-2019, along with the other strategic research action plans, can be found here.

Pathfinder Innovation Projects (PIP) Awards

The 5th round of Stage 1 Pathfinder Innovation Projects (PIP) awards were awarded to a number of researchers conducting work related to chemical safety. These projects were recognized by ORD as out-of-the-box and forward thinking ideas having the potential to transform environmental protection and protection of human health. Congratulations!

PIP5 Stage 1 Awardees:

Building a Network to Measure the Totality of Chemical Exposures
Team: Jon Sobus (PI), Mark Strynar, Elin Ulrich, Matthew Scott Clifton, Kristin Isaacs; Antony Williams, Ann Richard, John Wambaugh

Did mom make you fat? Fetal Origins of Life Stage Disease
Team: Michelle Angrish (PI), Brian Chorley, Stephanie Padilla

Make a Beeline to a Sustainable Future
Team: David Lehmann (PI), Eugene Flournoy-Gibbs; Thomas Steeger

Metabolomics to Differentiate Amphibian Responses to Multiple Stressors
Team: Marcia Snyder (PI), S. Thomas Purucker, Matthew Henderson

Treatment of Emerging Contaminants Using UV Light, Percarbonate and Peracetic Acid
Team: Mallikarjuna Nadagouda, Vasudevan Namboodiri

Using Pluripotent Stem Cells to Transform High-throughput Screening of Inhaled Toxicants
Team: David Diaz-Sanchez (PI), Shaun McCullough, Robert Devlin

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CSS in the News

Recent News Articles

- U.S EPA and Unilever announce major new research collaboration to advance non-animal approaches for chemical risk assessment
  - -Discussed by Dr. Russell Thomas on YouTube: here.
  - -Additional news coverage can be found: here.
- Testing chemical risk in MN lakes, scientists shrink to the cell level
- Links between health problems and endocrine-disrupting chemicals now stronger, statement argues
- EPA Expects to Authorize More Rapid Toxicity Tests
- EPA Scientists Working to Continue EDSP 'Pivot' to CompTox Assays

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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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