June 2016

CSS Pathways: Anticipating Impacts of Chemicals

CHEMICAL SAFETY FOR SUSTAINABILITY RESEARCH NEWS

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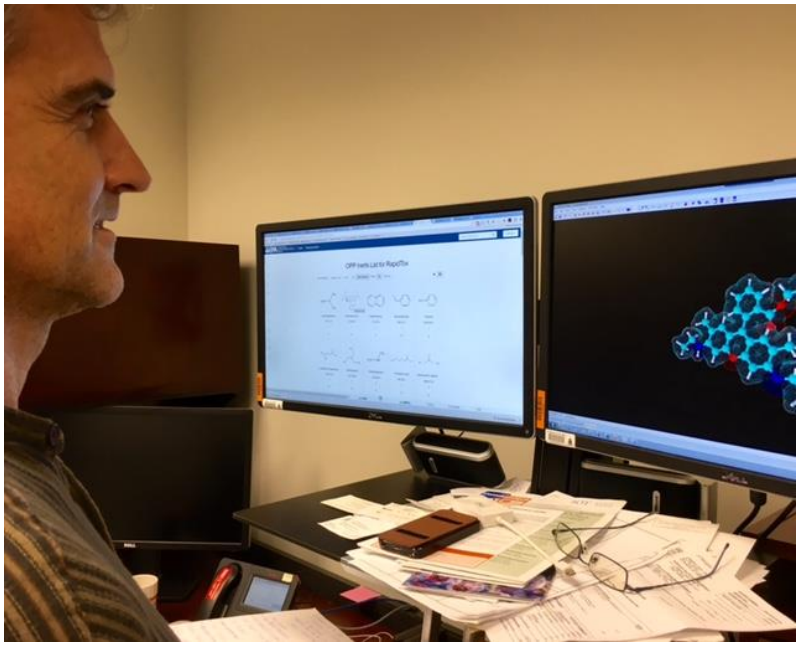
Data and Models

iCSS Chemistry Dashboard: One Stop Shopping for Chemistry Data



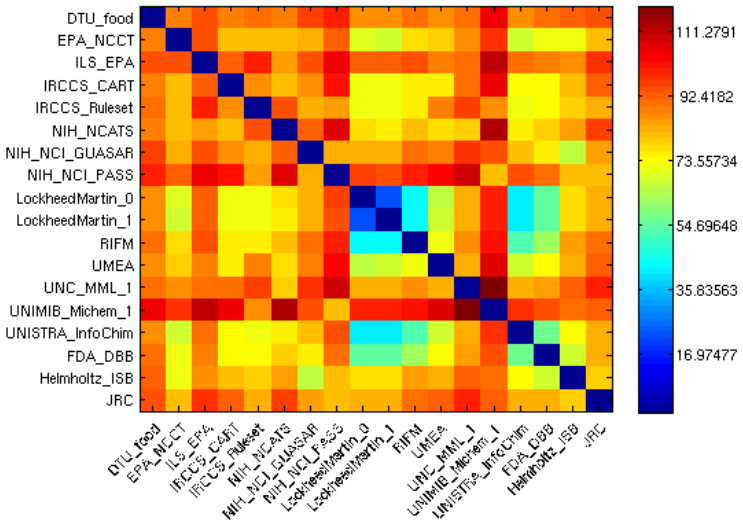
Caption: Project Lead, Antony Williams, demonstrating the new iCSS Chemistry Dashboard.

In a continued commitment to improve the public's access to data, the National Center for Computational Toxicology (NCCT) released a new interactive Chemical Safety for Sustainability Chemistry Dashboard (iCSS Chemistry Dashboard), with chemistry information for over 700,000 chemicals. The dashboard's beta version builds on efforts by U.S. EPA to develop innovative methods to evaluate the potential health risks of chemicals. The publically available dashboard is a gateway to an array of related public domain databases, provides improved access to data and models associated with chemicals of interest, and is a hub that links together many U.S. EPA research databases. The user-friendly interface provides access to chemical structure information, tens of thousands of physicochemical properties – used to develop machine-learning models, and millions of additional data points. With links to over 20 relevant websites and applications, the iCSS Chemistry Dashboard brings U.S. EPA one step closer to a one-stop-shop for your data needs regarding environmental chemistry data. This beta version is just the beginning; efforts toward feature expansion, additional datasets, and further curation of data are ongoing and frequent updates are expected. Get your chemical identifiers and give the dashboard a test drive!

Read more about the iCSS Dashboard on the EPA blog!

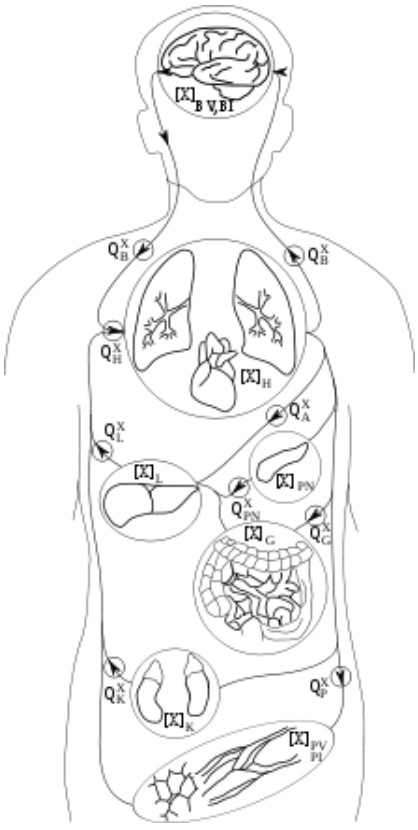
Consensus Modeling: Powering Prediction Through Collaboration

Predictive computational models can efficiently help us prioritize thousands of chemicals for additional testing and evaluation. CSS scientists Kamel Mansouri and Richard Judson, from the U.S. EPA's National Center for Computational Toxicology (NCCT), led a large-scale modeling project called the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). CERAPP demonstrated the efficacy of using computational models with high-throughput screening (HTS) data to predict potential estrogen receptor (ER) activity of over 32,000 chemicals. This international collaborative effort (17 research groups from the United States and Europe) used both quantitative structure-activity relationship models and docking approaches to evaluate binding, agonist and antagonist activity of chemicals. A total of 48 models were developed. Each model was evaluated and weighed for its predictive accuracy using ToxCast and Tox21 ER HTS results along with data collected from peer-review literature. To overcome the inherent limitations of single model predictions, all predictions were combined to create a consensus model. This model predicted ~4,000 (12.3 %) of the chemicals evaluated to be high priority ER active compounds and ~6,740 (20.8%) as chemicals with potential ER activity that should be considered for further testing. This manuscript demonstrates the feasibility of screening large numbers of chemicals *in silico*. Take a look at the results by visiting the U.S. EPA Endocrine Disruptor Screening Program (EDSP) Dashboard. Looking at other endocrine disrupting pathways, similar research is underway to predict the potential androgen receptor (AR) activity of chemicals through a project called Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA). These consensus modeling approaches present new options for the path forward for predicting the impact of chemicals on biological endpoints.



Correlation matrix of the CERAPP continuous ER models predictions

Where Does the Chemical Go? New PBPK Knowledgebase to Help Models Find the Answer



Physiologically-based pharmacokinetic (PBPK) models describe what the body does to a chemical. In particular, how are the chemicals adsorbed, distributed, metabolized and excreted by the body? PBPK models provide important information about how much of a chemical ends up in a given organ or tissue. Traditionally, the rate at which we can assess chemicals using these models is extremely limited by available data. On average, PBPK models can be developed for 14 unique chemicals each year. Though an impressive achievement, the models will not likely assess all the arsenal of over 100,000 chemicals in commerce anytime soon. To help bridge these knowledge gaps, CSS researchers mined thousands of peer-reviewed articles to create a PBPK knowledgebase to facilitate the generation of provisional PBPK models as chemical inventories continue to expand. Although an approach of using pre-existing models is widely accepted, it is often a time-intensive task for investigators. The PBPK knowledgebase described in the recent publication, Developing a Physiologically-Based Model Knowledgebase in Support of Provisional Model Construction provides an efficient approach for using chemical structure information to identify published models as starting points to construct new PBPK models. The knowledgebase can be coupled with *in vitro* or *in vivo* chemical-specific data, or with *in silico* predictions, to pave the way for more rapid PBPK model development in support of modern risk assessment.

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Advances in Neuro-Development Studies

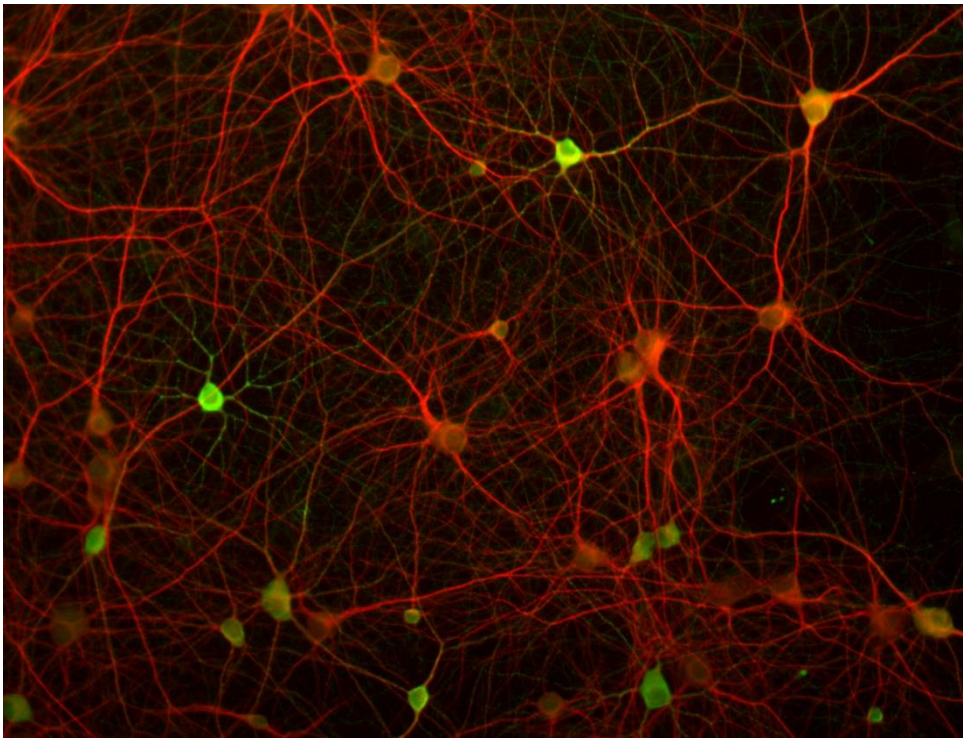
A High-throughput Thyroid Assay to Augment ToxCast Assay Portfolio

The thyroid gland is one of the most powerful drivers of metabolism in the body. When individuals are exposed to certain chemicals in the environment, the levels of hormones produced by the thyroid can be altered significantly, resulting in potentially serious health issues. Researchers in NCCT and NHEERL have developed and tested an approach to screen chemicals for effects on hormone production. This is the first high-throughput screening assay in ToxCast for the thyroid pathway beyond direct effects on the thyroid receptor, and researchers are using insights from this study to develop more. In a recent study published in the Toxicological Sciences, Tiered High Through-put Screening Approach to Identify Thyroperoxidase (TPO) Inhibitors Within the ToxCast Phase I and II Chemical Libraries, U.S. EPA researchers used their approach to detect and confirm the effects of various chemicals within the ToxCast Phase I and II Chemical Libraries on a critical enzyme in the synthesis of thyroid hormone. The paper described use of an Amplex UltraRed-thyperoxidase (AUR-TPO) assay designed to identify chemicals that inhibit thyperoxidase (TPO), an enzyme found in the thyroid gland. Research indicates that decreased TPO activity in the body reduces thyroid hormone (TH) synthesis.

Chemicals identified in the first assay were subsequently tested using additional assays to confirm their impact on TPO activity. These assays included cytotoxicity assays to estimate the cellular tolerance limit of exposure to these chemicals, TPO inhibition using a different assay format, and non-specific effects against an unrelated enzyme. This study is the most substantial screening effort to date and provides scientists with an effective screening approach that focuses resources, maximizes assay throughput, and reduces animal use.

Do Humans Model Humans Better than Rats do?

CSS researchers have shown that human induced pluripotent stem cell (iPSC) derived neurons can be used to study developmental neurotoxicity in high-throughput, high-content imaging assays. This is a considerable improvement from the current rat cortical neuron models used, as iPSC neurons behave very similarly to their counterparts in the human body – both morphologically and physiologically. Researchers exposed these iPSC neurons and primary rat neurons to an array of eight chemicals previously shown to impact neurite growth in rat and human cells. Human derived iPSCs provide a unique opportunity for scientists to continue their work since they overcome many of the issues presented by cells taken from other organisms. Most notably, iPSCs can capture individual genetic information from patients with specific mutations or diseases.



Caption: Microscopic view of a rat neuron.

In this study, Comparison of Human Induced Pluripotent Stem Cell-Derived Neurons and Rat Primary Cortical Neurons as *In vitro* Models of Neurite Outgrowth, the iPSC neurons reacted differently to certain chemicals than their rat counterparts. This not only demonstrates iPSCs viability as a reliable source of differentiated human cells, but also contributes to the growing body of work indicating that human-derived neural cells respond differently to chemical exposure compared with other animal neural cells. The results provide further support to the idea that human iPSCs are more useful than rodent cells as predictive models to humans.

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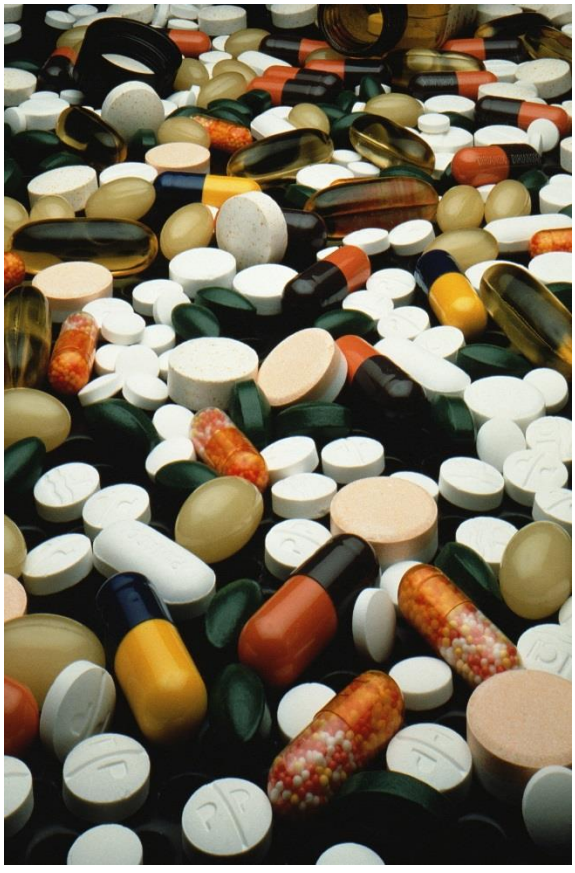
Environmental Impacts of Pharmaceuticals



Thousands of pharmaceutical ingredients enter the aquatic environment through human and/or animal waste every year. Their effects on wildlife have become an international research priority. The amount of empirical pharmaceutical toxicity information available for aquatic species is relatively sparse, with the majority consisting of acute toxicity measurements and little to no data regarding sublethal responses, such as growth or reproduction impacts. Another layer of complexity is the range of pharmaceutical therapeutic classes with vastly different structures and potency that need to be assessed for possible effects in non-target species. The first step in tackling this growing challenge is to focus resources on prioritizing those active pharmaceutical ingredients (API) with the greatest hazard potential. An important data source for chemical prioritization is from drug development and/or safety testing.

Mammalian pharmacological and safety information is available for almost all APIs through various medical texts, public databases, and primary literature. In a recent article, Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large-scale mammalian pharmacological dataset, US EPA researchers and their collaborators applied concepts of species read-across on mammalian pharmacokinetic data to systematically prioritize API impacts by estimating their potential to cause adverse biological consequences to aquatic organisms, using fish as an example. Mammalian absorption, distribution, metabolism, and excretion (ADME) data were collected and curated to create the Mammalian Pharmacokinetic Prioritization for Aquatic Species Targeting (MaPPFAST) database representing 1070 APIs. From these data, a probabilistic model and scoring system were developed and evaluated. Individual APIs and therapeutic classes were then ranked based on clearly defined read-across assumptions to estimate potential hazard in fish. It is anticipated that the MaPPFAST database and the associated API prioritization approach will help guide research and/or inform ecological risk assessment. This research was recently published in a special issue of *Environmental Toxicology and Chemistry* on Pharmaceuticals in the Environment. This special issue presents an interesting cross-section of current research interest in this area.

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Notables

The Long Awaited SeqAPASS Release

The Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool, long used within EPA, is finally public. Through the work of CSS researcher, Dr. Carlie LaLone, this tool will allow researchers and regulators to extrapolate toxicity information across species. SeqAPASS extrapolates from data rich organisms to thousands of other non-target species to evaluate their potential chemical susceptibility through the presence or absence of proteins that interact with chemicals. Chemicals such as pharmaceuticals and pesticides have relatively well-defined protein targets; a majority of these proteins are curated in the National Center for Biotechnology Information (NCBI) protein database, maintained by the National Library of Medicine at the National Institutes of Health. SeqAPASS evaluates protein structures to identify whether a protein target is present for a chemical interaction in non-target species. The resulting interaction may potentially disrupt a series of important biological processes and cause unintended, adverse effects. A manuscript demonstrating applications of this tool has been submitted for publication.

Updates to Web-ICE

The Web-based Interspecies Correlation Estimate (Web-ICE) application was recently updated with new data, specifically for threatened and endangered species. This application allows users to estimate toxicity of a chemical to a species, genus, family or multiple species from a single known toxicity value. Web-ICE has modules to predict acute toxicity to aquatic (fish and invertebrates) and terrestrial (birds and mammals) wildlife for use in ecological risk assessment. It can also generate Species Sensitivity Distributions (SSD) from the generated data. The recent updates include:

- First time chemical curation and increased chemical and structural diversity,
- Increased species diversity, including new data for threatened and endangered species of mussels and fairy shrimp, and
- Revision of the endangered species module based on minimum toxicity models providing more conservative estimation for listed taxa.

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Upcoming & Recent Events

Aggregate Exposure Pathway Workshop | May 9-11, 2016

CSS recently co-hosted a workshop with the U.S EPA National Exposure Research Laboratories (NERL) and the National Health and Environmental Effect Research Laboratories (NHEERL) titled *Aggregate Exposure Pathways (AEP): A Conceptual Framework to Advance Exposure Science Research and Complete the Source-to-Outcome Continuum for Risk Assessment*. The workshop gathered expert scientists and leaders from EPA in the field who worked together to evaluate the need for and applicability of the AEP, which was recently defined by researchers from EPA, the Pacific Northwest National Laboratory, and Oregon State University in a publication from Environmental Science and Technology. The AEP was proposed to organize data emerging from the expanding field of exposure science and complement the Adverse Outcome Pathway framework for biological information to support integration of exposure and toxicity testing data.

National Academy of Sciences Indoor Microbiome Meeting | April 11-12, 2016

The National Academy of Sciences committee convened for the first time to investigate the Microbiomes of the Built Environment: From Research to Application in Washington D.C. on April 11th, 2016. The committee assessed the current state of knowledge regarding microbial communities (bacteria, viruses, fungi, etc.) in the built environment. Topics focused on improving the design, construction, and operation of the built environment, as well as understanding the microbiome's influence on human health, sustainability, and security. This meeting gathered experts from the microbiome-built environment field with presentations on the microbiome and the US military, along with the microbiome in built water systems. Registration is open for the next meeting of this committee on June 21-22 in Washington, DC. More about the study and recordings of this meeting can be found here.

Society of Toxicology Comes to the Big Easy | March 13-17, 2016

U.S. EPA scientists showcased their research through symposia, workshops, platform presentations, poster sessions, and a central booth at the 2016 SOT 55th Annual Meeting in New Orleans on March 13-17, 2015. Several CSS scientists were acknowledged with awards (see table below for just a few of the recipients).

U.S. EPA hosted several special events in conjunction with SOT, including a joint-meeting of U.S. EPA researchers and Science to Achieve Results (STAR) grantees, "3D or Not 3D: That Is the [Predictive Toxicology] Question…" to discuss organotypic and three-dimensional cell culture systems. Research on tissue systems, including the brain, liver, kidney, testis, breasts, heart, and neurovascular systems, complements ongoing EPA research to refine complex models of how organs and systems respond to environmental chemicals.

Information about the SOT Annual Meeting, satellite meetings, and conference materials are available on the SOT conference webpage.

Gerald Ankley, Stephen Edwards, Dan Villeneuve	1st place award by the Society of Toxicology's Risk Assessment Specialty Section in the category of Outstanding Paper Published in 2014 Advancing the Science of Risk Assessment
Imran Shah, Grace Patlewicz	"A Top Ten Abstract" from the Risk Assessment Specialty Section
Jasmine Brown	Toshio Narahashi Conference Award from the Neurotoxicology Specialty
	Student Travel Award from the Regulatory Safety and Evaluation Specialty Section
Jenna Currier	1st Place Postdoctoral Award *In vitro* and Alternative Methods Specialty Section
Julia Rager	"A Top Ten Abstract" from the Risk Assessment Specialty Section
Justin Conley	Postdoctoral Travel Award by the N.C. Chapter of SOT
Michelle Angrish	2nd Place *In vitro* and Alternative Methods Specialty Section

CSS in the News

Recent News Articles

- Coloring eggs from the inside
- A Simple Way to Track Your Everyday Exposure to Chemicals
- UNC-TV Exposure Science
- New Approaches to Predict the Effects of Chemicals