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## **S** 2446 Developing, Applying, and Evaluating Models for Rapid Screening of Chemical Exposures

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Chemical risk estimation requires quantitative information on exposures and toxicological effects. Quantitative exposure information can include chemical intake rates and (bio)monitoring data; however, such information does not exist for the vast majority of marketed chemicals. In addition to limited exposure data there is limited information on chemical use patterns and production and emission quantities. These data gaps require the application of mass balance, statistical and quantitative structure-activity relationship (QSAR) models to predict exposure and exposure potential for humans and ecological receptors. Models and modeling frameworks that can be parameterized and used for high-throughput screening (HTS) with the currently available (limited) chemical information are being developed and evaluated to obtain essential estimates of exposure for data poor chemicals. This presentation provides an introduction to underlying principles of some models used for exposure- and risk-based HTS for chemical prioritization for human health, including tools used in the ExpoDat project (USEtox, RAIDAR, CalTox) and other initiatives (SHEDS-HT). Case study examples of HTS include (i) model applications for screening thousands of chemicals for far-field human exposure, (ii) comparisons of far-field and near-field human exposure model results, and (iii) model evaluations with biomonitoring and monitoring data. These illustrations show how the current tools can be used in a regulatory setting and what improvements in the models and chemical information used to parameterize the models are needed to address uncertainty in HTS exposure estimation.

## **S** 2447 The Impact of Rapid Bioactivity-Exposure-Based Prioritization on Chemical Safety

S. M. Knott. Office of Science Coordination and Policy, Exposure Assessment Coordination and Policy Division, US EPA, Washington, DC. Sponsor: B. Wetmore.

In 1996, several federal mandates including amendments to The Federal Food Drug and Cosmetic Act and the Safe Drinking Water Act identified the need to screen thousands of chemicals for their ability to perturb the endocrine system. Development of the Endocrine Disruptor Screening Program (EDSP) ensued to identify strategies to screen this universe of untested chemicals and has identified the utility of high throughput screening (HTS) and *in silico* tools to inform the process. The Environmental Protection Agency's (EPA) EDSP (i.e., ToxCast) has strived to incorporate transparency in data generation, processing and analysis, requesting comments from a Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) review in January 2013. Recent advances in bioactivity identification have been coupled with advances in HT toxicokinetic (HTTK) methods and HT exposure (HTE) estimation (e.g., ExpoCast) tools (reviewed by a FIFRA SAP in July 2014). EPA is now proposing an Integrated Endocrine Bioactivity and Exposure-Based approach for prioritization and screening in which (1) *in vitro* HTS data identify potential targets; (2) HTTK methods estimate external doses that achieve internal concentrations sufficient for bioactivity; and (3) putative bioactive doses are then directly compared to HTE predictions to estimate likelihood of exposures that cause bioactivity. Chemicals where the putative human bioactive dose is comparable to HTE predictions become targets for further study. This approach will include several datasets and considerations to probe critical points along the Adverse Outcome Pathway (AOP) for endocrine modalities. Such an approach is anticipated to address not only the needs of the EDSP but also holds potential to inform other source to outcome pathway issues of note to the Agency. This talk will outline this strategy and discuss its impact from a policy perspective, addressing its value to stakeholders in public and scientific communities. This abstract does not necessarily reflect U.S. EPA policy.

## **S** 2448 Biomonitoring As an Exposure Assessment Tool in the Context of High-Throughput Screening (HTS): Concepts, Challenges, and Approaches

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Biomonitoring provides an integrated assessment of chemical exposure, reflecting internal dose encountered from all exposure routes, but is resource intensive and focused on a relatively small universe of "well-studied" chemicals. Creative approaches to design of biomonitoring studies, interpretation of *in vitro* toxicologically relevant exposure levels in the context of biomonitored matrices, and development of broader tools for prediction of toxicokinetic properties of data-poor chemicals are needed to enhance the utility of biomonitoring in population chemical exposure and risk assessment in an HTS framework. *In vitro* tested concentrations have been compared to blood concentrations in previous assessments, suggesting that blood-based concentrations of HTS compounds can be compared to *in vitro* active concentrations as a prioritization tool. Strategies for use of biomonitoring can move away from comprehensive population-based sampling to use of pooled serum sampling for screening and prioritization. Targeting analysis of pooled serum samples to achieve detection limits below active biological concentrations can provide screening-level information for prioritization of chemicals for further exposure and dose-response evaluation. Study designs using pooled serum samples with replicate pools per demographic group can provide information on both central tendency and population variation of biologically relevant internal exposure levels for comparison to *in vitro* active concentrations. Empirical examination of existing biomarker datasets can inform likely population variation from the central tendency as a function of toxicokinetics for biomarker concentrations. For example, for persistent compounds, the ratio of 95th percentile population concentration to the population mean is seldom greater than 4; for non-persistent compounds this ratio can approach 30 or more. This talk will address challenges and outline approaches to further integration of biomonitoring in HTS-based exposure and risk assessment.

## **S** 2449 Using Environmental and Biological Measurements to Develop Generalizable Relationships for Exposure Models

R. Rudel, R. Dodson and J. Brody. Silent Spring Institute, Newton, MA.

Comparing high-throughput exposure predictions with National Health and Nutrition Examination Survey (NHANES) data shows that consumer use is an influential variable, even when defined crudely. It follows that more sophisticated modeling of consumer exposure will reduce uncertainties in risk estimates, and so "near-field" exposure models are being developed. This talk will illustrate the use of environmental and biological measurement data to develop generalizable relationships that should be reflected in these models. First, we will demonstrate validation of indoor partitioning models for semivolatile organic chemicals based on simultaneous measures of 60 analytes, including a variety of chemical classes, in indoor air and house dust from 170 homes in two geographic regions. For phthalates, pesticides, PCBs, and flame retardants, simultaneously collected biomonitoring data allows us to identify key exposure determinants. Second, we will use NHANES and environmental measurements to describe population exposure variation and explore how to balance reducing model uncertainty with accurately predicting the highest-exposed subpopulations, since exposure distributions are often markedly skewed and can include extreme values. Finally, many consumer product chemical exposures are correlated, either because the chemicals co-occur in products or because of consumer behaviors. We will present key examples of mixtures at multiple levels, including from measurements of consumer products, indoor media, and biomonitoring, and discuss implications for exposure modeling and risk assessment.

## **W** 2450 Microphysiological Models of the Developing Nervous System: Biologically Driven Assembly Inspired by Embryology and Translated to Human Developmental Toxicology

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Recent advances using human stem cells and other cells that can be ushered through differentiation and developmental maturation offer an unprecedented opportunity to develop predictive systems for toxicological assessment. The use of human cells is an advantage because there is no need to extrapolate across species, but even so, there may be the requirement that different cell types interact in a three-dimensional (3D) relationship in order to provide prediction of the intact human. For