Using New Approach Methodologies to Address Variability and Susceptibility Across Populations

A State of the Science Symposium Webinar

— Presentation Abstracts —

— Day 1 —
Wednesday October 26, 2022

Overcoming Challenges in Use of NAMs to Inform Population Variability and Susceptibility in Regulatory Decision-Making

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New approach methodologies (NAMs) may be an important tool for increasing the throughput of future regulatory decision-making. The development and application of NAMs are designed to support the assessment of potential risks from environmental chemicals and support the US Environmental Protection Agency mission to protect public health and the environment. The Agency has invested for decades in developing a strong, integrated research program focused on the development and application of NAMs to support multiple statutory requirements and policy initiatives that prioritize reduction of animal testing (*e.g.*, the 2018 Toxic Substances Control Act (TSCA) Alternatives Strategic Plan). In 2021, EPA released an update to the New Approach Methods Work Plan, which describes the Agency roadmap to develop, utilize, and incorporate NAMs applications into regulatory frameworks while ensuring that the Agency meets its regulatory, compliance, and enforcement activities, remaining fully protective of human health and the environment. EPA has similarly engaged in far-ranging efforts to address the disproportionately adverse human health and environmental impacts in overburdened communities by integrating environmental justice considerations throughout the agency NAMs, as emerging technologies, have traditionally not been designed to address population susceptibility and/or variability. The Administration focus on environmental justice and community engagement emphasizes the need to evaluate how assessments integrate data from NAMs with evaluations of population variability and possibly non-chemical stressors (*or determinants of health)* to enable holistic approaches to risk management. These approaches may also include the development of NAMs focused on human health, ecology or exposure. In this talk, Dr. Gwinn will highlight the state of the science within the development and implementation of NAMs to inform regulatory decisions and discuss challenges and opportunities in the development of NAM tools, resources, and data to address environmental justice goals.

Disclaimer: The views expressed in this abstract are those of the author and may not reflect the views of the U.S. Environmental Protection Agency.

Chemical Exposures in the Community: Voice of the People

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The health of the environment impacts both individual and community health, with chemical exposures from products, environmental media, and occupation being major contributors to overall health outcomes. Both intrinsic (e.g., life stage, reproductive status, gender, age, genetic traits) and extrinsic (e.g., socioeconomics, racism/discrimination, workplace, food insecurity, geography) factors impact how chemical exposures and other stressors affect health. It is critical that these factors be considered early and at multiple stages during the chemical risk assessment and evaluation processes to ensure that chemical regulation fully considers the health and environmental impacts of chemicals used in products and processes. At the local public health level, data show that health disparities are clearly linked to socioeconomic vulnerability and susceptibility factors that influence exposures to, or impacts of, chemicals on health. Working alongside communities that are most impacted by chemical exposures, it is clear that the chemical assessment process misses many impacts to sensitive and vulnerable populations, contributing to inequitable outcomes. This presentation provides an overview of the impacts of chemical exposures from the local health department perspective, with a focus on developmental outcomes and community perspectives. Recommended actions to better protect vulnerable and sensitive populations during chemical assessment and evaluation are provided, with areas of possible utility for New Approach Methodologies in addressing highlighted gaps.

Kidney Disease Epidemic in Tropical Farming Communities and Challenges in Environmental Exposure and Toxicity Assessments

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Chronic kidney disease of unknown etiology (CKDu) is an emerging global health concern primarily affecting tropical rural farming communities including in Mesoamerica and South Asia. CKDu is a chronic tubulointerstitial nephritis and is linked to agrochemical exposure as well as heat stress. With the lack of conventional risk factors of chronic kidney diseases (e.g., diabetes and hypertension), disease diagnosis is delayed and therefore exposure assessment remains critical. Our research is focused on CKDu impacted communities in Sri Lanka and examines likely exposures to heat stress and agrochemicals, particularly through drinking water contamination. Parallel studies are focused on identifying early diagnostic biomarkers of exposure, disease onset, and mechanisms of kidney impairment through urinary proteomic and DNA analyses and higher throughput toxicity assays using the zebrafish model. Broadly, our results indicate a potential early-life onset of this disease following exposure to a mixture of pesticides and heavy metals. We postulate that this may increase kidney susceptibility to occupational exposure to agrochemicals and heat stress later in life leading to CKDu. The likely multifactorial and time sensitive environmental contributions to CKDu onset and progression highlight the profound challenges in current environmental health risk assessments, especially in vulnerable communities. Nonetheless, integrated *in vitro, in vivo, in silico* and population health analyses to examine drivers of CKDu may provide a framework for addressing complex environmental health outcomes.

— Day 2 —
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Investigating GxE Neurotoxicant Vulnerabilities Across Life Stage and Populations Using iPSCs

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Chronic exposures to manganese (Mn), methylmercury (MeHg) and other neurotoxicants can cause latent long-lasting neurological effects long after exposure has ceased. The developing nervous system is especially vulnerable to these effects. To understand the mechanisms behind latent and persistent neurotoxicity we have utilized a human induced pluripotent stem cell (hiPSC) model of differentiating cortical GLUergic and other neuronal lineages to model such neurotoxic effects. hiPSCs undergoing neuronal differentiation and maturation are exposed to environmentally- and human-relevant Mn and MeHg levels during varying stages of differentiation, either early when neuronal stem cells and intermediate progenitor cells are first generated, or later after neurons and astrocyte functional networks are established. We will present here evidence of differences between acute and chronic exposures, as well as evidence for persistent effects both functional and at the level of genetic and signaling pathways. We show evidence that development exposures to MeHg lead to latent/persistent effects well after exposure has ceased and levels have returned below detection. Indeed, single-cell RNA sequencing revealed a robust pattern of differentially expressed genes playing key roles in functional and biological pathways including signaling pathways linked to healthy aging and metabolic regulation. Similar pathways were found to be altered by chronic Mn exposures of functional human neuronal networks. Our results of chronic Mn toxicity using western blot and gene expression analysis suggest a shift in the nature of healthy aging and metabolic signaling as exposures go from acute to chronic phases of exposure. These neurotoxicant effects of both MeHg and Mn have functional consequences observed by micro-electrode arrays (MEAs) more than 100 days after the exposure ceased in some cases. We hypothesize that chronic exposures may alter susceptibility to later-life stressors and that genetic risk factors of brain disease (e.g. Alzheimer's Disease and related dementias, Huntington's Disease, and Parkinson's Disease) as well as genetic variations in the population intersect with these prior and subsequent exposures in the etiology of chronic neurological disease.

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Comparative Genomics for Precision Toxicology

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Phenotypes are the result of complex interactions between the genotype and the environment. Even subtle differences in genotype and/or environment can have profound effects, as robustly illustrated by sex determination mechanisms that result in dimorphic bodies, physiology, and disease susceptibilities. While we tend to think of genetic variability as a within species problem, evolution provides us with a wide range of sequence variation in genes that have been conserved for millions to billions of years. We are exploiting subtle variation in genotype to explore with-species differences in the response to chemicals and drugs between the Drosophila sexes and within inbred lines, and more profound sequence variation between species using C. elegans, Daphnia, Zebrafish, Frogs, Drosophila, and Human tissue culture cells, under the umbrella of the Precision Toxicology Project (precisiontox.org).

Integrating Bayesian Approaches with PBPK Modeling in a Human Health Risk Assessment: A Case Study with Perfluorooctane Sulfonate (PFOS)

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Inter- and intra-species variability in chemical pharmacokinetics and toxicological endpoints results in a significant difference in the estimation of reference dose (RfD), thus leading to an enormous challenge in human health risk assessments. Therefore, it is important to address an integrated framework with new approach methods (NAMs) to characterize variability and susceptibility. Recently, we developed an integrated framework by combing Bayesian statics with physiologically based pharmacokinetic (PBPK) models to characterize uncertainty and variability between species, individuals, and life stages. This Bayesian population PBPK model has been used in the estimation of RfD from interspecies extrapolations, simulation of the internal dose metrics for potentially sensitive subpopulations, and prediction of in vitro to in vivo extrapolation (IVIVE) of kinetic and toxicity data. In this presentation, I will introduce how we develop mechanistic PBPK model structure in different species, chemicals, and life stages within the Bayesian hierarchical framework and application for a case study with Perfluorooctane Sulfonate (PFOS) risk assessments.