as nonlinearities in dose-response or toxicokinetics, early markers of effects, mode of action, and anticipated human exposure levels. This presentation will use two case studies to illustrate how the EPA integrates data from short-term *in vivo* studies and new approach methods, as well as toxicokinetic information, to assess appropriate dose settings in animal studies. Each case will highlight specific scenarios, such as top dose selection when data from previous studies indicate absorption saturation or strategies to avoid selecting doses that could lead to excessive toxicity. Our approach focuses on tailoring dose setting to yield informative and relevant insights into human health risks, rather than merely detecting toxicity that may not be pertinent to human exposures. This abstract has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication.

1259 Incorporating Stress as a Variable Into Toxicological Testing: Advancing Our Understanding of Cumulative Impacts

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With greater understanding of the complex interactions between different biological systems and the social, occupational, and chemical environment, there is increasing interest in understanding the potential differences in the adverse effects of chemicals. Consideration of differences in susceptibility to adverse effects from various exposures extends beyond that of genetic differences actively being investigated in various animal or *in vitro* models. One such environmental factor that comes into play is the influence of non-chemical stress on chemical-biological interactions. While considerations for stress to impact toxicity testing are well-recognized (e.g., animal handling), studies are largely not designed to examine the explicit role of additional stress to potentially impact susceptibility to adverse effects. As such, there is a need to understand how stress whether occupational, personal, or societal may impact the ultimate susceptibility of individuals in advanced risk assessments. This session will focus on several experimental approaches designed to explicitly incorporate stress as an experimental variable. Such approaches offer understanding into the interaction between the biology of stress and the impact on chemical toxicity (e.g., stress potentiating or mitigating toxic effects). First, results from a targeted scoping review will characterize the breadth of available experimental models that consider stress, as well as illustrate why stress is an important consideration in toxicological testing. The second talk will expand on the US Environmental Protection Agency's actions toward investigating stress and the prioritization of chemicals being considered in their assays. The remaining talks will each present unique experimental models designed to consider the impact that stress has on chemical response. In all, this session will highlight the importance of considering stress within some experimental models and present several approaches that attempt to address this research need.

1260 Targeted State of the Science Scoping Review for Incorporating Stress Within Experimental Models of Chemical Toxicity

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As the interest in complex cumulative assessments from regulatory authorities increases, considering multi-faceted exposures, including non-chemical stressors, is a necessary but challenging aspect. The impacts of non-chemical stressors, i.e. stress, on basal biology have begun to be characterized but any impacts on the body's ability to respond to additional insults is less clear. Given the interest in ensuring that such assessments are appropriately accounting for the true risk posed to individuals following chemical exposures, the incorporation of non-chemical stressors and an understanding of these impacts is an area of much needed research. Previous investigations provide limited insight about the interaction between stress (elicited by a number of different societal or cultural factors) and chemical toxicity as they lack quantitative impacts on susceptibility and mechanistic understanding. Experimental models offer the potential to address the quantitative susceptibilities and mechanistic underpinnings of such an interaction. The objective herein is to provide the results from a targeted scoping review of published experimental models that have explicitly incorporated stress as a variable in toxicity studies. Due to the extensive nature of the stress literature, targeted publications were selected and used for citation mining and reference searching. References were screened against inclusion criteria based on model type and how stress was incorporated into the experimental set up. Results from the targeted screening were mapped and examined for trends, limitations, and research opportunities. A variety of studies that attempt to connect stress with chemical susceptibility were found to cover a range of biological species and forms, e.g. rats, zebrafish, and *in vitro*. Notably, the variety of experimental approaches highlights the need to consider the fit-for-purpose development of the model as some stress models, e.g. stress-induced ulcers, may offer insight into a specific endpoint. Furthermore, such models can also provide key events or adverse outcomes that could be considered when evaluating the potential interaction between chemical and non-chemical stressors. Lastly, this presentation will serve as a primer for the remaining session presentations on non-chemical stressor considerations and stress models within chemical toxicity testing.

1261 Equity in Toxicity: Unmasking the Hidden Impact of Stress on Chemical Toxicity in Environmental Justice Communities

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Low income and minority communities are often at increased risk of exposure to environmental chemicals and development of adverse health outcomes, which is an Environmental Justice (EJ) concern. Beyond facing elevated exposures, these communities have been shown to experience heightened vulnerability to chemical toxicity due to elevated stress levels. A challenge for modeling this relationship, however, is that the interaction between chemical exposure and stress levels is chemical specific. Possibilities include being synergistic, additive, or antagonistic, and with different magnitudes of effect. Therefore, we have developed a chemical screening approach that explores how varying levels of the stress hormone, cortisol, shifts dose-response relationships following environmental toxicant exposure using a combination of *in vitro* and *in vivo* approaches. This presentation will provide an overview of the process we used to select EJ-relevant chemicals for our medium- and high-throughput screens, and will discuss the mechanistic insights our data provide about how stress impacts susceptibility and acts as a modifying factor in toxicity profiles. This method can help categorize chemicals that will likely have a broader or narrower range of responses across the population, including within less-stressed vs more-stressed communities. Thus, this research will help provide needed insight into cumulative impacts from chemical and non-chemical stressors and will advance understanding of susceptibility and risk determination in EJ communities. The views are the author's and do not necessarily represent the views of the US EPA.

1262 Validating a Model of Gulf War Illness: Chronic Exposure to Glucocorticoids Primes the Neuroinflammatory Response to Diisopropyl Fluorophosphate Resulting in Long-Lasting Sensitivity Sensitivity to Subsequent Challenges

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Gulf War Illness (GWI) is a multi-symptom disorder diagnosed by symptoms including persistent headaches, chronic fatigue, memory loss, confusion, skin and gastrointestinal problems. These features are characteristic of persistent sickness behavior, which is known to result from underlying neuroinflammation. Chronic exposure to corticosterone (CORT), at levels associated with high physiological stress, can prime the CNS to mount an exacerbated neuroinflammatory response, indicated by an increase in proinflammatory cytokines/chemokines, following systemic exposure to challenge. By mimicking the stresses of war with exogenous CORT (200 mg/L 0.6% EtOH in drinking water) for 7 days prior to exposure to sarin surrogate acetylcholinesterase inhibitor (AChEI), diisopropyl fluorophosphate (DFP; 4 mg/kg, i.p.), heightened neuroinflammatory responses were observed without astrogliosis or neurodegeneration. While these observations recapitulated early symptoms of GWI, the essential pathobiology of this illness is persistence of heightened responses to external stimuli for the 20+ years after the instigating exposures. Here, we employed episodic exposure to CORT in drinking water to emulate episodic stress incurred by ill veterans following their exposures to AChEI agents in theater. As the GWI phenotype is punctuated by symptom flare-ups, systemic exposure to lipopolysaccharide (LPS – a bacterial mimic; 0.5 mg/kg, s.c.), was used to challenge the GWI phenotype. While CORT pretreatment primes the neuroinflammatory response to produce augmented LPS-induced inflammation, a single dose of DFP significantly exacerbated this effect. Using a comprehensive survey of molecular markers, blood cytokine expression profiles of ill veterans compared to our GWI mouse model revealed a significant overlap of the phenotype between man and mouse. This correlation supports the hypothesis that exposure to sarin, or a similar AChEI, in theater served as a major precipitating factor for the development of GWI. Overall, we demonstrated that a paradigm of CORT in the drinking water with a single DFP exposure followed by episodic CORT instigates a primed neuroinflammatory phenotype similar to that of Gulf War Illness. Together, these data suggest that GWI is a chronic, stressor primed, neuroinflammatory condition.

1263 Non-chemical Stressors Affect Behavioral Function and Alter the Cardiopulmonary Response to Acute Extreme Heat and Wildfire Smoke Exposures

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Extreme heat events from climate change are classified as the leading cause of weather-related death in the United States and are associated with cardiovascular morbidity and mortality. The American Heart Association has also released a scientific statement describing the importance of housing on cardiovascular health and well-being and emphasized the impact of the broader physical and social environment. Thus, increased temperatures due to climate change and lack of environmental enrichment (e.g. inaccessibility to greenspace, increased stress) represent two of the most pressing issues facing large sectors of the population in the United States. Epidemiological evidence has shown that socio-economic status and psychosocial stress might act as modifying factors of the cardiopulmonary response to climate

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