pathways. Through these activities the CoR will provide tools for improving the overall quality of experimental data being generated in EU and US research communities.

W 788 High-Throughput Screening of Nanomaterial Bioactivity/Toxicity: The Computational Side Is Just As Important As the Testing Assays and Characterization.

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High-throughput screening (HTS) of bioactivity/toxicity is currently the only cost-efficient and rapid tool to screen the numerous nanomaterials (NMs) in use and under development. In the EPA ToxCast program, diverse classes of NMs and their micro-particle and ionic salt counterparts are tested in HTS assays to help prioritize NMs for further targeted testing. While the measured HTS endpoints are the same as those tested for traditional soluble chemicals, specific challenges arise for NMs for both experimental procedures and computational analysis. Challenges include no standard nomenclature, comparison of potency between different classes of NMs each tested at a different concentration range, linking NM physicochemical (pchem) characterization data into the analysis, and assay interference by NMs. With no standard nomenclature, we identified NMs by combining information on group (nano, micro, ion), chemical composition of the core and coating, primary particle size, and source. CAS numbers were purposely not used for NMs to avoid data being aggregated with bulk counterparts. We accounted NM exposure potential and tested NM at various concentrations, while all soluble chemicals were tested at the same concentrations in ToxCast and their sigmoidal AC50s were compared. NM bioactivity data is being analyzed using various dose metrics (e.g., either NM mass or surface area per medium volume or cell surface area) and potency estimates (LEC, sigmoidal AC50, etc.) for NM toxicity ranking. To link NM pchem properties into the bioactivity data, we choose to build a distinct database of NM pchem characterization results, instead of modifying the existing ToxCast database of bioactivity results. While HTS assays we used have successfully screened hundreds of soluble chemicals, inspecting the NM bioactivity results carefully resulted in discontinuing the use of one of the testing platforms because NMs interfere with the assay. Future research needs include developing computational models using NM pchem properties and/or in vitro data to predict in vivo effects.

W 789 Computational Dosimetry for Nanomaterial Risk Assessment from Transcriptomic and HTP Data.

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The convergence of evolutionary changes to the field of toxicology and the rapid emergence of an immense new class of toxicologically untested nanoscale materials has led to development of new genomic and high-throughput in vitro screening tools for toxicological assessment of nanomaterials. These advancements and refinements in the measurement and analysis of response have not however, been followed by equally important advancements nanoparticle kinetics and in the measurement of cellular or tissue exposure to test materials. The absence of adequate dosimetry data for nanomaterial toxicity studies is one of the largest sources of uncertainty in current testing paradigms. We present an integrated computational dosimetry framework for placing the results of in vitro genomics and high throughput (HTP) toxicity data in the context of in vivo animal and human exposures and improving the basis for hazard rankings. The framework is applied in three case studies to demonstrate the impact of an evolution from "exposure" to target cell dose based nanotoxicity assessments: 1) the disruption of macrophage pathogen clearance by macrophages in vitro; 2) in vitro cytotoxicity screening and hazard ranking of 25 metal oxides; and 3) in vitro screening and hazard ranking of nanomaterials from the U.S. EPA's ToxCast program.

W 790 Integrative Nanotoxicology: Linking Rapid Assays and Informatics to Predict Nanomaterial-Biological Interactions.

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While numerous nanotechnology and nanomaterial-based applications promise benefit to human health or the environment, the potential health and environmental risks associated with the unique properties of nanoscale materials are unknown and may lead to unintended health and safety consequences. The current gap in nanoparticle toxicological data dictates the need to develop rapid, relevant and efficient testing strategies to assess these emerging materials of concern prior to large-scale exposures. Among these are informatics approaches to speed the rate at which we can gain information on the fundamental relationships between specific nanomaterial features and their behavior in the environment as well as their interactions with living systems. Data compiled using a dynamic whole animal (in vivo) assay to reveal whether a nanomaterial produces adverse responses have been made available through the Nanomaterial-Biological Interactions (NBI) knowledgebase (nbi.oregonstate.edu). Endpoints such as mortality, development, malformations and behavior were assessed in the embryonic zebrafish model. Data compression of the 23 individual endpoints provided the numerical representation of overall mortality and morbidity elicited by a particular nanomaterial at a given concentration. Computational analysis performed on 82 nanomaterial datasets has revealed the importance of surface chemistry as a driver for nanomaterial toxicity across material classes. Furthermore, data mining techniques to model the biological effects of nanomaterials were applied to this case study. Results illustrate that individual endpoints have different predictability given the same set of algorithms and cumulatively the combined values can provide significant insight into the potential toxicity associated with nanomaterials for use in hazard ranking.

W 791 Usefulness of *In Vivo* Genomics for *In Vitro* Screening in Nanotoxicity.

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Literature-based network analysis of in vivo microarray data, which yields biologically relevant molecular networks from the dataset, is becoming an increasingly useful tool to identify nanoparticle-induced signaling. This approach can be used to discover molecules that contribute to endpoint health effects and otherwise unknown mechanisms of action. While animal inhalation exposures may be the most relevant for predicting human health effects of nanomaterials, it is not always feasible because of the vast number of particles being manufactured. Therefore, in vitro high-throughput screening (HTS) is being used to predict their potential toxicity. While HTS may be necessary, in vivo genomic studies still provide useful information for screening broad classes of nanomaterials. Similar to physiological experiments in which three results are expected—increase, decrease, and no change—the question of whether network-based genomics from in vivo studies is useful for in vitro screening can be answered yes, no, and maybe. The output from these studies provides significant molecular detail of an exposure. Advanced analysis can indicate specific transcription factors involved in the response, upstream, and downstream signaling, and also which cell type may be the most affected by a particular nanomaterial. However, there are challenges to converting genomic data from in vivo exposures to in vitro screening. These include responsiveness of the cell type in vitro vs observed in vivo changes, distinguishing temporal effects, and an isolated single cell response in vitro that lacks regulatory effects occurring in vivo. The in vivo genomic findings also have limitations including whether altered molecular networks from studies in rodents are applicable to the human, and therefore applicable to studies utilizing human cell lines. In addition, experimental design (e.g., dosing relevant to human exposure levels) should be evaluated when interpreting genomic analysis from in vivo studies. In summary, genomic analysis from in vivo studies, although not without limitations, can offer insight for HTS.

W 792 Scientific and Regulatory Advances in Genetic Toxicology Safety Assessment.

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Recent reviews of genotoxicity assay performance, the use of these data in the safety evaluation process, and the development of new assays have led to important advancements in regulatory and scientific recommendations in the area of genetic toxicology. For instance, the International Conference on Harmonization (ICH) has recently finalized guidelines on genetic toxicology testing for drugs. The OECD is updating 15 year-old guidelines for genetic toxicology assays. International validation of new assays like the Comet assay have been completed. Workshops held by international expert groups on new approaches for genetic toxicology assessments highlight the importance of incorporating new approaches in drug safety evaluations. In recent years, significant progress has been made in incorporating quantitative approaches to genotoxicity dose response in order to identify a point of departure for application in risk assessment process. These important initiatives impact the science and practice of genetic toxicology safety assessments globally and across all sectors including drugs, chemicals, and consumer products. This workshop brings together international experts representing key geographies involved in leading these efforts. In an effort to discuss scientific and regulatory advances in genetic toxicology safety assessment, the following key aspects will be addressed in this workshop: (1) US FDA implementation of ICHS2 (R1) guidelines, (2) Latest updates and new approaches in international guidelines for genetic toxicology assays,

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