sitivity, 94% specificity, and 97% coverage were achieved. The impact of the predicted confidence level to the predictive performance is discussed. Special attention is devoted to the proper documentation of the assessment results for regulatory submissions.

1758 Comparative Case Studies to Establish a Standardized Process for Read-Across within a Daily Safety Assessment Workflow

T. Kawamoto[1], A. Granitzny[2], J. Rathman[3,4], A. Mostrag[4], and C. Yang[4]. *[1]Kao Corporation, Ichikai-machi, Japan; [2]Kao Germany GmbH, Darmstadt, Germany; [3]Ohio State University, Columbus, OH; and [4]MN-AM, Columbus, OH.*

Read-across is one of the alternative methods considered for regulatory purposes to fill data gaps encountered in product safety assessments. The toxicity potential of a chemical is inferred from known toxicity of compound(s) having a similar structure and property profile. Nevertheless, read-across is an evolving method with several open issues, one of which is related to the lack of consensus regarding the extent and type of evidence necessary to support a read-across. To achieve reliable read-across results, a quantitative and transparent methodology is required for similarity assessment as well as hypothesis-driven evaluation. We applied commercial and public software tools to establish standardized workflow. Chemical safety of two cosmetic ingredients (Isopropyl palmitate and Neopentyl Glycol Dicaprate) were assessed by analogue-based read-across method for target evaluations including Point of Departures from repeated dose and reproductive/developmental studies, sensitization, and genetic toxicity. The chemical similarity was compared for structural fingerprints from multiple sources (RDKit, MCCS Keys, ToxPrints, and CDK) using ChemTunes.ToxGPS® and AMBIT. Properties-based similarities were calculated from ToxGPS. Toxicity data were compiled from ChemTunes and AMBIT databases. TIMES-SS and ChemTunes.LiverBioPath were used to address metabolites and reaction similarity. Final combinations of diverse evidence based on different similarities were performed using the quantitative weight-of-evidence approach available within ToxGPS® Read-Across tool. Metabolic similarity gave rational hypothesis along with read-across scenario which is required for selecting appropriate analogues. Isopropyl myristate for Isopropyl palmitate as well as Neopentyl glycol dicaprylate, Pentaerythrityl tetrastearate and Trimethylolpropane trinonanoate for Neopentyl Glycol Dicaprate were selected as analogue with regard to metabolic similarity. This case study demonstrated identification of reasonable analogues by the complementary use of commercial and public read-across tools. Systematic and reproducible outcomes can be attained along with estimation of the associated uncertainty. This standardized workflow can be applied for day-to-day safety assessment.

1759 Biocelerate Sendharmonization Initiative: A Proposal to Better Harvest the Value from Send Data

M. A. Carfagna[1], T. G. Bjerregard[2], T. Fukushima[3], W. Houser[4], K. Mera[3], and T. J. Page[1]. *[1]Eli Lilly and Company, Indianapolis, IN; [2]Novo Nordisk, Copenhagen, Denmark; [3]Shionogi & Co., Ltd., Osaka, Japan; and [4]Bristol-Myers Squibb, New Brunswick, NJ.*

BioCelerate, a subsidiary of TransCelerate BioPharma, Inc., is a preclinical industry consortium driving initiatives to increase efficiency and productivity in early stage R&D. The Standard for Exchange of Nonclinical Data, or SEND, identifies an approach to gathering and representing nonclinical data in a consistent format and its use is currently required for data submission to US FDA. We have identified a significant degree of variability in SEND data sets created from disparate sources that can interfere with cross-study analysis, thereby diminishing some of the potential value contained within the SEND standard. BioCelerate aims to collaborate with various stakeholders across industry to evaluate options and potential recommendations for SEND data set structure that will facilitate comparison and analysis of SEND data across studies. To prepare a framework for engagement, the consortium has first identified the key drivers of variability in SEND data sets and developed example algorithms as a test case for understanding how users of the data sets might calculate common study parameters in the future. The consortium is currently engaging stakeholders to clarify the problem statement and to begin to understand options for future harmonization of SEND through CDISC. The implementation of the SEND harmonization recommendations that result from this initiative will allow comparison of warehoused SEND data and unlock value that is currently unrealized. These comparisons include the ability to compare the progression of findings over time with a single molecule and a comparison of target organs across multiple molecules directed against the same target. This poster/presentation outlines the breakdown of the methodology for mapping of SEND data variability and the cross-stakeholder engagement framework proposed to identify solutions for SEND data harmonization, ultimately contributing to the goals of increased efficiency and productivity in early stage R&D.

1760 Development of an Adverse Outcome Pathway (AOP) Network for Carcinogenicity Using Expert-Derived (Q)SAR Knowledge

S. Stalford, A. Cayley, R. Foster, S. Kane, and R. Williams. *Lhasa Limited, Leeds, United Kingdom.* Sponsor: C. Barber

The prediction of carcinogenicity and related toxicity endpoints has always been a principal area of research for *in silico* (Q)SAR systems and as a result, software relating to these endpoints is well developed. Indeed, in recent years predictions provided by these systems have become embedded in regulatory guidance, where they may be used to replace or augment other testing methods. Consequently, it is important that the predictions are as accurate as possible and are provided in such a way that they can be easily integrated with other sources of evidence. Derek Nexus (DX) is an expert rule-based SAR system with a well-developed knowledge base for carcinogenicity and related endpoints. Within this knowledge base, there is information on molecular-initiating events (MIEs), as well as other potential key events (KEs) and modes of action (MoA) associated with the compound classes covered by the alerts. In this work, we investigated 310 alerts related to carcinogenicity in DX and used the knowledge contained to link these to 85 different MIEs and KEs. These linkages provided a skeleton AOP network containing 26 AOPs. This network was then subjected to a detailed review using public literature to supplement the AOPs with evidence for biological plausibility, and information such as species relevance. This review dramatically increased the scope of the network, with the number of pathways associated with the 26 MIEs increasing from around one pathway per MIE to more than 70 in total. The review also allowed for the association of each pathway with events at the protein level. This network can be used as a rudimentary profiling tool for carcinogenicity MoA prediction. A combination of literature review and profiling of carcinogenicity data sets using our model also identified additional MIEs and KEs for future investigation and integration into the network. It is hoped that this approach to knowledge presentation will allow for easier interpretation of the evidence available relating to a given prediction. Presenting more detailed information on potential pathways allows for better integration of existing and emerging *in vitro* and *in vivo* tests at the protein level with predictions produced by DX. This methodology also allows for expansion of the scope of predictions which can be made for this endpoint, allowing for integration of MIEs, ADME data and other data not necessarily related to toxicity outcomes.

1761 Machine Learning Approaches to Categorize Carbonaceous Nanomaterials Based on Patterns of Inflammatory Markers and Pathological Outcomes in Lungs

I. Desai[1,2], W. Miller[1], V. Kodali[1], G. Syamlal[1], J. Roberts[1], A. Erdely[1], and N. Yanamala[1]. *[1]NIOSH, Morgantown, WV; and [2]Ohio State University, Cleveland, OH.*

As technology advances to incorporate nanoparticles (NP) in various industries, the exposures associated with these particles also increase. Exposure to carbonaceous NPs has been found to be associated with substantial pulmonary toxicity, including inflammation, fibrosis, and/or granuloma formation. Despite several attempts made previously, grouping or categorizing NPs based on their intrinsic properties and certain inflammatory endpoints remains a challenge. The inconsistency and a large number of variables across studies considered by different groups for evaluating toxicity responses of NPs, the lack of precise understanding of the role of different NP characteristics on various biological responses, as well as missing NP data under *in vivo* biological conditions and pathological outcomes often the result of chronic inflammatory responses further complicates hazard ranking of NPs. This study attempts to categorize the toxicity profiles of various carbon allotropes, in particular, carbon black, different multi-walled carbon nanotubes, graphene-based materials and their derivatives. Statistical and machine learning based approaches were used to identify groups of CNMs with similar pulmonary toxicity responses from a panel of proteins measured in bronchoalveolar lavage (BAL) fluid samples and with similar pathological outcomes in the lungs. Thus, grouped particles based on their pulmonary toxicity profiles, were used to select a small set of proteins that could potentially identify and discriminate between the biological responses associated within each group. Specifically, MDC/CCL22 and MIP-3β/CCL19 were identified as common protein markers associated with both toxicologically distinct groups of CNMs. In addition, the persistent expression of other selected protein markers in BAL fluid from each group suggested their ability to predict toxicity in the lungs, i.e., fibrosis

and/or microgranuloma formation. The advantages of approaches described in this study can have positive implications for further research in toxicity profiling. *Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.*

1762 Identifying the Link between Chemical Exposures and Incidence of Triple-Negative Breast Cancer in African American Women

K. M. Polemi, J. Heidt, V. Nguyen, A. Kahana, O. Jolliet, and J. A. Colacino. *University of Michigan School of Public Health, Ann Arbor, MI.*

The incidence of triple negative breast cancer (TNBC), an aggressive subtype of breast cancer for which there is no targeted therapy, is approximately three times higher in non-Hispanic black (NHB) women compared to non-Hispanic white (NHW) women. The mechanisms driving this difference are unknown, and likely lie in an interaction between genetic and environmental factors. Here, we aimed to identify chemical exposures which may play a role in TNBC disparities. Using chemical biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) and biological activity data from the US EPA's ToxCast program, we identify chemicals at higher concentrations in NHB women and assess their toxicological relevance to breast cancer. A total of 44 chemicals showed significantly higher biomarker concentrations in NHB women. Investigation of these chemicals in ToxCast resulted in a total of 22,061 assays for analysis, 5,343 of which contained adequate modl_ga (logAC50) and modl_tp (scaled top value of dose response curve) data. BPA, known to be associated with breast cancer, and PFOS were most tested, and had 19.98% and 20.46%, respectively, of assays tested reported as active. Of interest are PFDA, PFUnDA, PFNA, and Chlordane due to their higher concentration in NHB women and moderate testing and activity in ToxCast. Furthering our chemical prioritization, Gene Set Enrichment Analysis (GSEA) provided pathway association between active genes analyzed in ToxCast and putative TNBC mechanisms. Using publicly accessible high throughput data, we have prioritized chemicals of interest to further investigate for their relevance in TNBC disparities.

1763 Integrate Mechanistic Knowledge with High-Throughput Data to Assess Risk for Drug-Induced Liver Injury Using Adverse Outcome Pathway Networks

K. Khadka, M. Chen, Z. Liu, W. Tong, and D. Wang. *US FDA/NCTR, Jefferson, AR.*

Due to the well-known limitations for current animal testing based approaches to predict drug induced liver injury (DILI), there is heightened interest in incorporating high throughput assays into the evaluation framework for DILI risk. However, the diverse and high dimensional nature of these data poses serious challenges for common data mining and machine learning techniques even with recent advances. Integrating high throughput assay information with mechanistic knowledge in the form of expert opinion and literature findings might provide a promising approach to fully utilize the power of both mechanistic understanding and new testing technologies. In this presentation, we discuss our pilot study using adverse outcome pathway (AOP) networks to provide a base model for incorporating high throughput data from L1000, CMap, and Tox21 for gene expression changes and nuclear receptor binding. AOP networks were formed by integrating published AOPs for liver steatosis, cholestasis, fibrosis, and liver tumor. Information for relevant nuclear receptors and genes was then extracted from these networks. We obtained measurements on nuclear receptor binding and differential gene expression for a collection of drugs in the Liver Toxicity Knowledge Base. A rule ensemble learning model was then built to infer liver toxicity from these molecular predictors resulting in competitive performance with other approaches. Our result suggests that current knowledge encoded in AOPs can be successfully utilized for dimension reduction for high throughput data and leading to capable predictive models. With continued improvement in AOP development and new testing technologies, combining mechanistic insight with high throughput data holds great promise in advancing DILI risk assessment.

1764 QSAR Models for Mean LD50s Are More Predictive Than for Minimum LD50s

A. J. Prussia[1], and R. C. Siwakoti[1,2]. *[1]CDC/ATSDR, Atlanta, GA; and [2]Emory University, Atlanta, GA.*

In April 2018, ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods) held a workshop on "Predictive Models for Acute Oral Systemic Toxicity." The Committee invited participants to develop *in silico* models to predict median lethal doses (LD50s) for a large dataset of chemicals they had curated. A subset of chemicals were included with multiple LD50s per chemical. For this subset, the Committee selected the more protective LD50 point estimate. Based on LD50 variability (Siwakoti et al., 2018), a minimum LD50 will necessarily carry greater experimental uncertainty. We hypothesized that using the mean LD50 instead of the minimum would result in QSAR models with better predictive ability. To test this idea, identical model-building conditions were used to develop models for both the mean LD50 and the minimum LD50 as response variables. The overall predictive ability of these global models is moderate, but the mean LD50 was a consistently better response variable than the minimum LD50. For incorporation of alternative models in risk assessment, this exercise demonstrates the value of characterizing the variability in the endpoint to be modeled. *Disclaimer: the findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry and should not be construed to represent any agency determination or policy.*

1765 Reconciling *In Vitro* and *In Silico* Approaches for Drug-Induced Liver Injury Prediction

O. J. Béquignon, S. Wink, S. W. Hiemstra, J. E. Klip, W. den Hollander, G. J. van Westen, and B. van de Water. *LACDR, Leiden, Netherlands.*

Drug-induced liver injury (DILI) is one of the main reasons of drug attrition during clinical trials and of withdrawal from the market. This makes the early identification of hepatotoxicity of compounds a critical challenge. *In silico* hepatotoxicity prediction models make a cost-effective approach able to prioritize compounds for preclinical and clinical studies. Recent efforts have been made to create more accurate quantitative structure-property relationships (QSPR) models relating hepatotoxicity to chemical structure features. However, to this date only few have integrated *in vitro* data to their models. This study aims at integrating *in vitro* activation signal of stress response pathways involved in DILI to standard molecular description of compounds to better identify substructures inducing hepatotoxicity. A library of 118 compounds was screened on a panel of 8 previously established HepG2 BAC-GFP reporter cell lines that capture endoplasmic reticulum (ER) stress, DNA damage, heat shock response and inflammatory responses. Fluorescence microscopy images were taken at 24, 48 and 72 hours after addition of the compounds (concentration ranging from 1 to 100 *Cmax*). Additionally, propidium iodide (PI) and annexin V (AnxV) staining was performed to detect necrotic and apoptotic cells. Quantitative image analysis was performed with CellProfiler. GFP integrated signals, *Cmax*, AnxV and PI values were used as descriptors of the compounds along with extended connectivity fingerprints of radius 3 (ECFP_6) physicochemical descriptors of the compound structures. Statistical models (Bayesian, Random Forests, Gradient Boosted Decision Trees) were applied to relate both *in vitro* derived data and molecular structure description to the US FDA approved DILI annotation (Most, Less, No and Ambiguous DILI concern). Our results demonstrate that the integration of both *in silico* chemical descriptors and *in vitro* quantitative mode-of-action data increased the predictive performance of the predictive models. This work highlights the importance of integrating both *in silico* and *in vitro* approaches in the construction of predictive models for DILI. *This work was supported by the IMI eTRANSAFE project (grant agreement 777365) and the H2020 EU-ToxRisk project (grant agreement 681002).*

1766 Database of Pharmacokinetic Time-Series Data and Parameters for Environmental Chemicals

R. R. Sayre[1], J. F. Wambaugh[2], and C. M. Grulke[2]. *[1]ORISE, Research Triangle Park, NC; and [2]US EPA, Research Triangle Park, NC.*

Time courses of compound concentrations in plasma are used in chemical safety analysis to evaluate the relationship between external administered doses and internal tissue exposures. This type of data is experimentally generated for chemicals like pharmaceuticals or cosmetics, but is not usually available for the thousands of other chemicals to which people may potentially be exposed. An understanding of the pharmacokinetics for these chemicals can be developed using *in vitro* assays and *in silico* models, but the certainty of the quantitative application of these estimates to chemical safety evaluations

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