## PS 2273 *In Silico* Workflow for Assessing Skin Irritation, Penetration, and Sensitization Potentials Using Chemotype-Based Models and Alerts

J. Rathman[2, 3], J. Schwöbel[1], T. Magdziarz[1], A. S. Mostrag-Szlichtyng[2], A. Tarkhov[1], L. Terfloth[1] and C. Yang[2, 3]. [1]*Molecular Networks GmbH, Erlangen, Germany,* [2]*Altamira LLC, Columbus, OH and* [3]*Chemical and Biomolecular Engineering, The Ohio State University, Columbus, OH.*

We present an *in silico* workflow for evaluating chemical toxicity instigated upon dermal contact. The first step identifies compounds that will not be absorbed and removes these from further consideration. Compounds that are absorbed and cause skin irritation are identified next, while absorbed non-irritating compounds are passed on to the next module for evaluation of skin sensitization potential. Probable metabolites are added to the workflow along with the parent molecules. Skin sensitization potential is predicted by modeling mouse local lymph node assay (LLNA) data, with values ranging from non-sensitizing to weak, moderate, strong or extreme. Covalent modification of proteins by sensitizers by well-known reaction mechanisms represents the molecular initiating event for the induction. ToxPrint chemotypes, structural fragments encoded with physicochemical properties and electronic system information, are used to categorize chemicals into MIE classes. Skin metabolic rules, coded in chemotypes, were also used to predict bioavailability and reactivity. Results from multinomial ordinal classification QSAR models for each MIE class are combined using a rigorous weight-of-evidence approach that explicitly quantifies the uncertainty associated with each prediction. Our approach has been externally validated using skin irritation and sensitization results from literature studies. The workflow effectively separates irritants from non-irritants. Approximately 70% of sensitizers are predicted in the correct category and better than 90% are predicted within one category or their reported experimental value. Further, all sensitizers are associated with chemotype alerts, illustrating the power of this approach in overcoming limitations of classical structural alerts. The workflow comprehensively addresses chemical toxicity via dermal contacts.

## PS 2273a Computational Molecular Modeling for the Assessment of Nanoparticle Toxicity: Interactions with Biomolecules

N. Yanamala[1], V. E. Kagan[2] and A. A. Shvedova[1, 3]. [1]*HELD/PPRB, CDC/NIOSH, Morgantown, WV,* [2]*Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA and* [3]*Department Physiology and Pharmacology, West Virginia University, Morgantown, WV.*

Over the past two decades, nanotechnology has emerged as a key player in various disciplines of science and technology. A detailed understanding of the molecular details of interactions between nanoparticles (NP) and biomolecules is crucial for obtaining adequate information on mechanisms of action of nanomaterials and their possible toxicological outcomes. There has been a recent surge in the application of in silico based methods and approaches to address interactions of NPs with biomolecules providing insights into their mechanisms. To do this, we used structure-based computational modeling as a tool to predict the molecular interactions between carbonaceous NPs and cellular proteins and lipids. We demonstrated that specific interactions of NPs with proteins/lipids resulted in a coating on its surface, ultimately masking their inherent properties, thus leading to modified distribution in cells, recognition and uptake by cells. We also provide evidence that interactions of basic/positively charged amino acids of the enzymes (e.g. peroxidases) with the carboxyl moieties on carbon nanotubes and graphene – positioning them in close proximity to the catalytic site of the enzyme – are essential for the effective catalysis and safe degradation of these materials in vivo. Structure based computational modeling is a useful and effective approach that could facilitate the design and development of safe engineered nanomaterials.

## PS 2273b Benchmarking Assessment of Open Source and Newly Released *Salmonella* Mutagenicity (Q)SAR Models for Potential Use under ICH M7

L. Stavitskaya, B. L. Minnier and N. L. Kruhlak. *Food and Drug Administration, Silver Spring, MD.* Sponsor: R. Rouse.

The current draft of the International Conference on Harmonisation (ICH) M7 guideline describes the use of (quantitative) structure-activity relationship ((Q) SAR) models during drug safety evaluation. The guideline, however, does not specify the use of any particular model, but instead recommends that the models meet the general definition of statistical or rule-based methodologies, and allow the identification of structural alerts. In this study, we evaluated the performance of Toxtree, a freely-available, open source SAR model and two newly-released, commercial (Q)SAR programs, Sarah Nexus and Leadscope Expert Alert System, as potential candidates for qualifying pharmaceutical impurities. To effectively assess the performance of Toxtree, an in-house Salmonella mutagenicity database of 3979 compounds (43% positive) and a highly-curated version of the Hansen dataset of 3734 compounds (58% positive) were used. Performance statistics for the two datasets ranged from 79% to 85% sensitivity and 83% to 73% negative predictivity, respectively. The performance of the statistical-based system, Sarah Nexus, was assessed using the in-house Salmonella dataset after removal of compounds that overlapped with the training set. The resulting dataset comprised 809 chemicals (42% positive), and yielded sensitivity and negative predictivity of 68% and 79%, respectively. The rule-based Leadscope Expert Alert System was evaluated using the curated Hansen dataset of 3734 chemicals (58% positive) and yielded performance of 85% sensitivity and 78% negative predictivity. These performance statistics compare favorably with those of the three most widely-used commercial model systems tested with the same data sets, indicating their suitability for the qualification of pharmaceutical impurities under ICH M7.

## PS 2273c Pragmatic Issues in Applying Multiple *In Silico* Systems for Drug Safety Assessment

R. Benz[1], K. P. Cross[2] and G. J. Myatt[2]. [1]*OmnyCorp, Rockville, MD and* [2]*Leadscope, Inc., Columbus, OH.*

The current draft of the International Conference on Harmonisation (ICH) M7 guidelines on the "Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk" outlines the use of two complementary in silico methodologies to qualify impurities as not mutagenic, alongside an expert review. One system should be an expert alert-based system with the other a statistical-based methodology. The practical use of multiple systems presents a number of challenges and this poster enumerates and quantifies the performance implications of three important issues. Firstly, it discusses how mechanistically plausible alerts with limited supporting data (termed "indeterminant alerts") should be used and interpreted as part of an overall M7 assessment. Secondly, it discusses the importance of applicability domains when using alert-based systems. Finally, it reviews methodologies for combining the results from different in silico systems, along with available experimental data. A highly-curated version of the Hansen dataset of 3734 compounds with Salmonella data was used to evaluate the performance of the combined systems. By using a series of consensus rules combining both predictions and experimental data, the resulting sensitivity increased in a range from 9.1% - 12.1% and negative predictivity increased by 10.6% - 15.6% over using individual systems alone.

## PS 2273d Metabolism Simulation and Toxicity Prediction in the Evaluation of Food Ingredient/Contaminant Safety

L. Terfloth[1], K. Arvidson[2], K. Muldoon-Jacobs[2], P. Volarath[2], A. Tarkhov[1], T. Magdziarz[1], J. Rathman[3, 4], D. Hristozov[4] and C. Yang[1, 4]. [1]*Molecular Networks GmbH, Erlangen, Germany,* [2]*Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, U.S. Food and Drug Administration, College Park, MD,* [3]*Chemical and Biomolecular Engineering, The Ohio State University, Columbus, OH and* [4]*Altamira LLC, Columbus, OH.*

During the safety assessment of food additives and their impurities, metabolic knowledge becomes critical when *in vivo* data are unavailable for the specific compound. Inclusion of metabolism information into the *in silico* workflow is therefore a pre-requisite for the US FDA's Chemical Evaluation and Risk Estimation System (CERES). The chemical space of food additives was profiled using public ToxPrint and metabolic (human liver and S9-fraction) chemotypes. Chemotypes are structural fragments encoded with physicochemical properties, and are considered as alerts when associated with a specific endpoint. The metabolic potential was predicted by applying a diverse set of over 100 phase I as well as more than 20 phase II conjugation reactions of human liver metabolic chemotypes. As an example, the effect of S9 metabolic chemotypes on Ames mutagenicity was analysed against the food additives. Although nearly 20% of the compounds were perceived as genotoxic carcinogens by chemotype alerts, only 4% of such compounds were actually predicted to be mutagenic under CERES mechanistic QSAR paradigm. Nearly 50% of the food additives predicted to be mutagenic were matched with chemotype alerts for genotoxic carcinogens. When repeating the analysis after removing the compounds that may be detoxified by S9, the reliability of the genotoxic alerts is increased almost 3 times. This study demonstrates the value of the use of metabolic rules in conjunction with known chemotype alerts to reduce the false positive rate of structural rules. Implementation of the metabolic rulebase in CERES is also presented. The research was funded by EU FP7 and Cosmetics Europe. (Grant n° 266835).

# The Toxicologist

Supplement to *Toxicological Sciences*

## 53rd Annual Meeting and ToxExpo™

March 23–27, 2014 • Phoenix, Arizona


An Official Journal of the Society of Toxicology

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science of Toxicology

www.toxicology.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 138, Issue 1
March 2014

www.toxsci.oxfordjournals.org