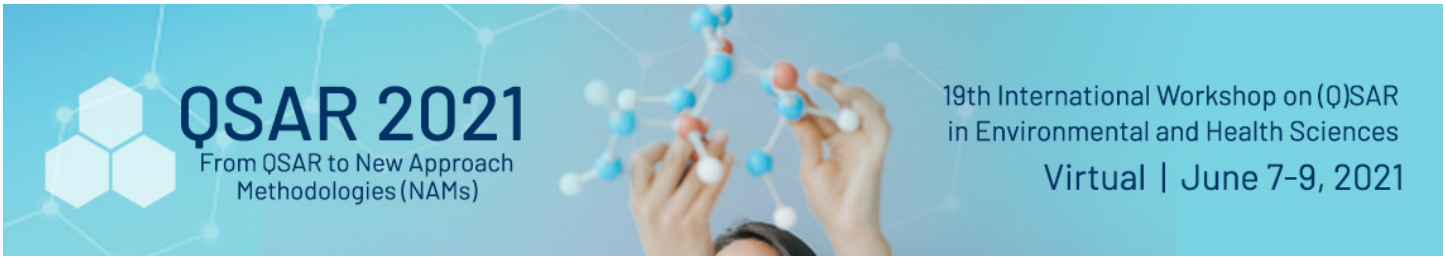


19th International Workshop on (Quantitative) Structure-Activity Relationships in Environmental and Health Sciences

June 7th – June 9th, 2021

Workshop Program

Table of Contents

June 7th, 2021

Development, Evaluation and Application of QSARs to Fill Data Gaps

286
Using physiologically-based kinetic models to inform read-across

Judith Madden[1], Courtney Thompson[1], Steven Webb[2], David Ebbrell[1], Peter Penson[1], Yu-Mei Tan[3], Alicia Paini[4]

[1]Liverpool John Moores University, Liverpool, United Kingdom. [2]Syngenta, Bracknell, United Kingdom. [3]US Environmental Protection Agency, Research Triangle Park, USA. [4]European Commission Joint Research Centre, Ispra, Italy

Abstract

Physiologically-based kinetic (PBK) models can be used to describe organ level concentration-time profiles of xenobiotics. This is key to accurate prediction of the potential effects of xenobiotics as these are determined by both inherent activity and internal exposure. Read-across, an increasingly important tool in many sectors, is reliant on data being available for other “similar” chemicals; similar in terms of activity and internal exposure profile. PBK models are data-hungry and time-consuming to develop *de novo*. However, it has been shown that using data from an existing model can be used to inform the development of a model for a similar chemical (Lu et al 2016). In order to ascertain for which chemicals PBK models are currently available, we have undertaken a systematic review of literature, to generate a readily-searchable source of existing PBK models. Selecting the most appropriate model to use as a template and combining this with appropriately adjusted input parameters is key to generating a reliable model for the target chemical. Here we discuss the results of the systematic review and demonstrate how an existing PBK model for one chemical was used to develop an acceptable PBK model for an analogue.

Lu et al (2016) PLoS Comput Biol 12(2): e1004495.

Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency

The funding of the European Partnership for Alternative Approaches to Animal Testing (EPAA) is gratefully acknowledged.

333
Analog Approach for PBPK Modeling of Synthetic Food Dyes

James Rathman[1,2], Vinnie Ribeiro[1], Judith Madden[3], Aleksandra Mostrag[1], Bryan Hobocienski[1], Mark Cronin[3], Chihae Yang[1,4,2]

[1]MN-AM, Columbus, USA. [2]Ohio State University, Columbus, USA. [3]Liverpool John Moores University, Liverpool, United Kingdom. [4]MN-AM, Nuremberg, Germany

Abstract

To improve our understanding of the fate of synthetic food dyes in vivo, physiologically based pharmacokinetic (PBPK) modeling was used to explore exposure scenarios for several FDA-approved synthetic dyes. Given a target structure for which the available data are insufficient for building a PBPK model, we describe a read-across inspired approach in which data and PBPK models for one or more data-rich analogs were used to develop a PBPK model for the target. A large database covering a diverse chemical space (e.g., pharmaceuticals, agrochemicals, cosmetics, food ingredients) was leveraged to find analog structures and identify relevant studies. Oral absorption (HIA), plasma protein binding (PPB) and blood-brain barrier (BBB) permeability were necessary inputs for the PBPK models in this study. QSAR models were developed for these properties to enable their estimation when experimental values were not available. As an example, relatively few data were available for Sunset Yellow or its metabolites, so analog candidates were identified from the PK

knowledgebase. Amaranth and Tartrazine were identified as the closest analogs. PBPK simulations for Tartrazine, a data-rich food dye, and its metabolites were performed to explore the effects of varying dose, routes of administration (oral-gavage, oral-dietary), and species (mouse, rat). This Tartrazine model was then used to construct a PBPK model for Sunset Yellow. Accurately estimating the additional uncertainty introduced by using analog data, rather than data for the target itself, depends on quantitatively capturing the target-analog similarity in terms of the relevant chemical and biological mechanisms.

210
Simulating the kinetic of metabolism for explaining differences between *in vitro* vs *in vivo* mutagenicity

Petko Petkov[1], Masamitsu Honma[2], Takashi Yamada[2], Takeshi Morita[2], Ayako Furuhama[2], Hristiana Ivanova[1], Stefan Kotov[1], Elena Kaloyanova[1], Ovanes Mekenyan[1]

[1]Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria. [2]Center for Biological Safety Research, National Institute of Health Sciences, Kawasaki, Japan

Abstract

The traditional (Q)SAR models predict mutagenicity as a result of identification of alerts for the interaction of chemicals with macromolecules. However, the *in vivo* mutagenicity tests have longer duration as compared with the *in vitro* tests which is one of the factors to make them incomparable. In the current existing (Q)SARs different duration of mutagenicity tests are not taken into account. Conceptually new SAR approach is introduced accounting for the duration of the test and relating the potency to the amount of formed DNA/protein adducts, which, in turn, depends on the kinetic of metabolism and adducts formation. The differences between *in vitro* and *in vivo* metabolic systems are investigated for chemicals having *in vitro* negative and *in vivo* positive data in mutagenicity tests with similar capacity (interacting by same macromolecules), such as the pairs *in vitro* Ames vs. *in vivo* TGR and *in vitro* CA vs. *in vivo* MN tests. Kinetic models have been derived for these mutagenicity effects. Two major factors are found to affect the conflicting mutagenicity data: 1) the generation of *in vivo*-specific metabolites driven by different enzyme expression and 2) duration of the *in vitro* and *in vivo* mutagenicity tests. Addressing these two factors requires explicit introduction of metabolic transformations simulating the formation of DNA/protein adducts. Empirically-defined thresholds for the adducts are introduced to each mutagenicity alert to distinguish mutagens from non-mutagens. Developing of the new kinetic models allows to explain the differences between in vitro and *in vivo* mutagenicity.

317
Predicting *in vitro* intrinsic hepatic clearance in mammals

Ester Papa[1], Linda Bertato[1], Ilaria Casartelli[1], Nicola Chirico[1], Alessandro Sangion[2,3], Karen Foster[2], Alexandra Looky[2], Jon Arnot[2,3,4]

[1]University of Insubria, Varese, Italy. [2]ARC, Toronto, Canada. [3]University of Toronto Scarborough - Department of Physical and Environmental Sciences, Toronto, Canada. [4]University of Toronto - Department of Pharmacology and Toxicology, Toronto, Canada

Abstract

Quantifying toxicokinetic (TK) processes such as biotransformation rates is fundamental to bioaccumulation, exposure, and risk assessment. I*n vitro* biotransformation rates can be estimated using microsomal, S9 homogenate, and hepatocyte-based assays to quantify the *in vitro* intrinsic clearance (CL_{int}). In addition *in vitro-in vivo* extrapolation (IVIVE) models and Quantitative Structure-Activity Relationships (QSARs) can be used to maximize the information available from *in vitro* and *in vivo* measurements. The integration of these different data streams (*in vitro, in vivo, in silico*) for biotransformation rate estimation in a coherent framework is essential for addressing uncertainty and data gaps in TK knowledge.

This work presents an approach to generate OECD validated QSAR models based on reactivity patterns, i.e., sites of metabolism in CYP450 profiled by the SMARTCyp module embedded in Toxtree software (JRC EU-Commission), for more than for >10000 organic chemicals.

QSARs were developed on the basis of an *ad hoc* curated database which included critically evaluated experimental CL_{int} derived from microsomal, S9 homogenate, and hepatocyte-based assays performed in human and two rodent species (i.e. *Rattus* norvegicus and *Mus musculus*).

More than 90 pathway specific models were generated with satisfactory predictive performances (R^2> 0.70; Q^2_{loo}> 0.65; Q^2_{ext}>0.6).

These QSARs are available to predict CL_{int} for new chemicals and to address data gaps in various contexts of chemical assessment.

188
Machine learning models for predicting human *in vivo* PK parameters using chemical structure and dose

Filip Miljković[1], Anton Martinsson[1], Olga Obrezanova[2], Beth Williamson[3], Martin Johnson[4], Ioana Oprisiu[1], Andreas Bender[2], Nigel Greene[5]

[1]Data Science & Artificial Intelligence, Imaging & Data Analytics, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden. [2]Data Science & Artificial Intelligence, Imaging & Data Analytics, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Cambridge, United Kingdom. [3]Drug Metabolism and Pharmacokinetics, Research and Early Development, Oncology R&D, AstraZeneca, Cambridge, United Kingdom. [4]Clinical Pharmacology & Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D AstraZeneca, Cambridge, United Kingdom. [5]Data Science & Artificial Intelligence, Imaging & Data Analytics, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Waltham, USA

Abstract

Animal and human pharmacokinetic (PK) data are routinely used in drug discovery to understand absorption, disposition, metabolism, and elimination (ADME) of candidate drugs. Over the past decade, a multitude of *in vitro* and *in vivo* assays, as well as *in silico* models, have been developed for this purpose. An accurate prediction of human *in vivo* PK parameters early on would help prioritize clinical candidates with desirable PK profiles.

In this work, we present a number of machine learning (ML) models able to predict human *in vivo* PK parameters using chemical structural information and dose as inputs. For this purpose, Elsevier's PharmaPendium PK module was used to extract and curate heterogenous human PK data originating from different sources. A total of 1,000 diverse chemical structures spanning 4,500 compound-dose combinations were encoded as 2D structural descriptors and used in combination with *in silico* ADME and rat PK predictions from our previous work to build ML models. We successfully predicted several PK parameters including peroral C_{max} and intravenous V_d with good correlation between experimental and predicted values and root-mean-squared errors approaching experimental values.

Hence, our models are the first fit-for-purpose human PK models, which are able to assist candidate prioritization to progress compounds with improved PK properties towards the clinic. They can be either applied on individual project compounds, as well as in combination with generative models in the context of Design-Make-Test-Analyse molecular design cycles.

Cheminformatic Approaches to 'Big Data' and Biological Activity Profiling

268
Estimating points of departure (PODs) for human toxicity effects from experimental animal data

Nicolò Aurisano[1], Lei Huang[2], Weihsueh A. Chiu[3], Suji Jang[3], Richard Judson[4], Olivier Jolliet[2], Peter Fantke[1]

[1]Quantitative Sustainability Assessment, Department of Technology, Management and Economics, Technical University of Denmark, Kgs. Lyngby, Denmark. [2]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, USA. [3]Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, USA. [4]National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, USA

Abstract

Chemical management and assessment frameworks, as life cycle impact assessment, aim at evaluating toxicological impacts on human health from chemical exposures. Such assessments typically rely on chemical-specific points of departure (PODs) from regulatory toxicity data sources, but such data are not available for the majority of chemicals to which people are exposed. Thus, experimental animal data may complement regulatory data to derive PODs that most closely mimic one that would be selected in regulatory assessments. This study aims to propose a method for consistently deriving PODs for substances for which regulatory data are missing. As starting point, we extracted and curated experimental animal toxicity data from the US EPA CompTox Dashboard. We considered only oral repeat-dose studies and three non-cancer effect level types: lowest-observed-adverse-effect level (LOAEL), no-observed-adverse-effect level (NOAEL) and benchmark dose lower bound (BMDL). Curation steps included harmonization of units in mg/kg/d and extrapolation of LOAELs and BMDLs to NOAELs. We then estimated PODs for 1625 chemicals based on the 5th percentile of all data available for the same substance across animal species, assuming a lognormal distribution. These PODs correlate well with the 447 available regulatory PODs (adjusted test R^2=0.69; RSE=0.65 log10 units). This method significantly broadens the coverage of chemicals by estimating PODs consistent with regulatory values for a larger dataset. Next steps include using this curated dataset to train a machine-learning-based prediction model to estimate PODs for the even larger population of substances without experimental animal data. This abstract does not necessarily reflect US EPA policy.

264
Harder, Faster, Better, Stronger: Towards a High-Throughput 3D Virtual Screening Triage Framework of the entire CompTox chemical inventory

Chris Williams

Chemical Computing Group ULC, Montreal, Canada

Abstract

Purpose: The EPA's computational toxicology dashboard chemical inventory currently contains nearly 880,000 chemicals. In vitro screening of this entire inventory would be a costly and lengthy endeavor, yet critical to further advance our understanding of molecular toxicology. The last attempted multiple-target virtual screen (DockScreen) was too computationally intensive (2 months on 21 processors for 1000 chemicals on 144 targets) making libraries on the size 1000 times larger challenging. Additionally, new vendor libraries of synthesizable chemistries (i.e. RealSPace or Enamine) or combinatorially screened ultra-large DNA-encoded libraries (i.e. HitGen/Enko/XChem/WuXi) are in the billions of chemistries, making traditional virtual screening (docking) intractable and requiring tiered virtual screening workflows (pharmacophores).

Method: We developed 3D-DSSTOx, a conformational library of nearly 900,000 molecules and over 25 million 3D conformations for rapid pharmacophore screening, geometry-optimized and charged at its major charge state (neutral pH) in MOE 2020. Along with new automated structure-based pharmacophore generation tools, we demonstrate the practicality of 3D screening ER alpha, AR, and TR across the entire 3D-DSSTox in hour timescales.

Results/Conclusion: We demonstrate a virtual screening workflow that enables the scoping of the toxicant-target paradigm more efficiently across larger chemical libraries and vaster target space. The demonstrated approach comprised of multiple generated target pharmacophore models, and the largest 3D conformational library of the CompTox dashboard inventory to date.

352
Transcriptomic Connectivity for Read-Across Inference of Chemical Bioactivity

Imran Shah, Bryant Chambers

US EPA, Research Triangle Park, USA

Abstract

Transcriptomic connectivity analysis is a powerful approach for finding relationships between chemicals, pathways, and diseases. It assumes that transcriptomic profiles capture biological samples' state using the universal language of genes, and similarity between profiles imply common biological mechanisms, or “connections.” The technological maturity, scalability, and broad mechanistic coverage of transcriptomics coupled with connectivity analysis could enable read-across inference of bioactivity for new chemicals. This talk will provide an overview of transcriptomic connectivity analysis approaches and their application to screening libraries of untested chemicals for bioactivity. First, we provide an overview of the leading transcriptomic technologies and public domain data repositories useful for creating reference databases and annotating bioactivity. Second, we propose a unified nomenclature to organize the diversity of transcriptomic similarity scoring methods based on gene expression profiles and gene signatures. Third, we demonstrate the utility of connectivity analysis for read-across inference of bioactivity through two types of case-studies on chemicals that activate specific targets and non-specific chemicals that activate stress response pathways. Lastly, we discuss strategies for applying this approach to concentration-response transcriptomic data to estimate benchmark concentrations. Our findings suggest that transcriptomic connectivity analysis is a powerful new approach methodology (NAM) that extends chemical structure-based read-across to fill data gaps for untested chemicals.

This abstract does not reflect US EPA policy.

307
DTU interpretation procedure for US Tox21 data for QSAR modeling of absolute minimum potency

Eva B. Wedebye, Ana. C.V. Martins, Nikolai G. Nikolov

Technical University of Denmark, National Food Institute, Kgs. Lyngby, Denmark

Abstract

The US Toxicology in the 21st Century program (Tox21) is releasing experimental *in vitro* results for many endpoints of relevance for human health. This data is a huge source of information for QSAR development, which is also one of the claimed aims of the program. For QSAR modelers to make the best use of the data and define clearly the QSAR endpoints as they wish to model them (OECD Validation principle number 1), it is very important to understand the data and find ways to extract data points according to the defined QSAR endpoint. Therefore, we have developed a comprehensive in-house data curation procedure to interpret Tox21 datasets for QSAR development.

Our procedure contains the following elements:

1) selecting actives according to 'absolute' potency cut-offs, requiring non-cytotoxicity at effect concentration

2) extracting only the most robust inactives (i.e. tested up to high concentration without cytotoxicity)

3) filtering out substances tested in low purity

4) filtering out results giving assay interference according to DTU-interpretation of artifacts

5) accounting for possible loss of test substance for negatives results due to volatility and lipophilicity

6) expanding the existing DTU in-house structure curation to give consistent representation of tautomeric classes of substances

Using this procedure, training sets for different minimum potency cut-offs for a number of Tox21 assays have been derived. Examples of developed QSAR models based on DTU-interpretations of Tox21 data compared to ditto based on US Tox21 Summary Calls e.g. in the ongoing EU H2020 FREIA project will be presented.

321
Incorporating Active Site Mapping in Computational Models Predictive of Target-Specific Biological Activity

Preston Griffin[1], Andrew Crutchfield[2], Geetesh Devini[1], Jakub Kostal[1]

[1]The George Washington University, Washington, USA. [2]Cornell University, Ithaca, USA

Abstract

Safety often plays a secondary role in the design of industrial chemicals, and tests are conducted, if at all, after chemicals are developed. This process poses high risk toward human and environmental health, and is expensive for the chemical industry, when adverse effects are discovered either late in the development process or after the chemical has been commercialized. Due to high costs associated with animal testing and new regulatory actions aimed at reducing the use of animal models, new approaches must be developed that ensure low risk of industrial chemicals at reasonable cost to chemical manufacturers. Here we describe an in-silico approach for designing safer chemicals that considers both mechanisms of action and function in redesigning existing commercial chemicals for greater safety and improved performance. Our approach is complementary to modern QSAR-type approaches, and relies on transforming proven methods from computational drug discovery, such as virtual screening and molecular simulations. We show these methods can be used to effectively redesign existing flame retardants and pesticides to develop safer alternatives. Furthermore, we describe a new computational method developed by our group, which enables efficient and accurate mapping of enzymatic active sites across different targets and species to quickly identify molecules with differential activity against preselected biological targets. Our method affords quick analysis of the tradeoffs for chemical classes, where mechanism of action and function overlap, and strives to identify structural features in chemicals that promote desirable biological activity while minimizing unwanted toxicological effects.

Keynote – Professor Mark Cronin

366
Did QSAR Save Toxicology? And What's Its Next Trick?

Mark Cronin

LJMU, Liverpool, United Kingdom

Abstract

Did QSAR save toxicology? Probably not, but without QSAR as a readily-available resource to fill data and knowledge gaps, we wouldn't be moving chemical safety assessment so efficiently to being a data-driven science. Nearly 40 years of International Workshops on QSAR have captured this paradigm shift, stimulating change and enabling considerable progress. This presentation will draw on progress from QSAR in the 1980s when we created empirical models by hand, to the realisation of the age of big data, chemoinformatics, deep learning, rapid communication and immense computational speed. The foundations of QSAR in the 1980s can still be seen today: modelling of endpoints, calculating properties and descriptors, investigating mechanisms of action, utilising multivariate statistics, regulatory applications, software development, storing chemical information in searchable databases… Our integrated exposure driven, systems toxicology approaches to chemical safety in the future probably will not use the phrase "quantitative structure-activity relationship", but it is exciting to think much of the informatics and science has been laid down by the QSAR community. As we move forward, let's remember the essentials of good modelling, data storage, knowledge capture and the need for expert oversight and vision that have provided our current successes.

Poster Sessions Track 1

358
Collaborative Evaluation of In Silico Predictions for High Throughput Toxicokinetics

Rocky Goldsmith[1], Nisha Sipes[1], Jon Arnot[2], Trevor Brown[2], Daniel Dawson[1], Michael Devito[1], John DiBella[3], Stephen Ferguson[4], Chris Grulke[1], Richard Judson[1], Michael Lawless[3], Kamel Mansouri[4], Ester Papa[5], Prachi Pradeep[1], Alessandro Sangion[2], Risa Sayre[1], Rogelio Tornero-Velez[1], John Wambaugh[1]

[1]US Environmental Protection Agency, Research Triangle Park, USA. [2]ARC Arnot Research and Consulting Inc., Toronto, Canada. [3]Simulations Plus, Sunnyvale, USA. [4]Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, USA. [5]Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy

Abstract

Chemical hazard, exposure, and the shape of the dose-response curve are typically evaluated to predict potential human health risk. The dose-response curve and estimates of internal exposure (dose) depend upon chemical-specific toxicokinetics – the absorption, distribution, metabolism, and excretion (ADME) of chemicals. Unfortunately, this information is not available for most of the chemicals in commerce and the environment. However, a combination of *in vitro* experimentation, *in silico* methods, and generic toxicokinetic modeling has allowed for "high throughput toxicokinetics (HTTK)" to predict these properties for drug leads. The past decade has witnessed an explosion of *in vitro* toxicokinetic data for the non-pharmaceutical chemical space and new tools are being developed to make predictions based upon these new data. The advent of a new database for in vivo chemical concentration vs. time data (Sayre et al., 2020) allows empirical evaluation of the new tools. In this collaborative trial we systematically compare a variety of tools in order to establish overall predictivity as well as estimate chemical-specific domains (that is, some tools may be more appropriate for certain chemical classes). The tools consist of several *in silico* QSAR predictions and their usage in a variety of public and commercially-available HTTK models. The end goal is to improve predictive models and develop consensus

predictions that include quantified, chemical-specific assessment of uncertainty. Carefully evaluated in silico HTTK methods represent a powerful new approach methodology to inform of potential risk posed by thousands of data-poor chemicals. This abstract may not reflect U.S. EPA policy.

280
Assessing the accessibility and reproducibility of published physiologically-based kinetic models

Courtney V Thompson[1], Steven D Webb[2], Peter E Penson[1], Judith C Madden[1]

[1]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, United Kingdom. [2]Syngenta, Product Safety, Early Stage Research, Jealott's Hill International Research Centre, Bracknell, RG42 6EY, United Kingdom

Abstract

In order for any chemical to elicit an effect on the body it must possess inherent activity and reach the site of action in sufficient concentration. Physiologically-based kinetic (PBK) models can be used to predict the time course of chemicals within the body at the organ level, facilitating prediction of the potential effects of xenobiotics. In recent years the number of PBK models being published in the literature has rapidly increased. Traditionally PBK models have been developed using software that required significant expertise to use (e.g. MATLAB). However, more generic modelling software is now available, increasing the accessibility of PBK modelling; examples include PKSim (Open Systems Pharmacology) and QIVIVE (http://www.qivivetools.wur.nl). Problems reproducing PBK models available in the literature arise due to significant variation in how models are reported as well as a lack of consistency in the level of detail recorded. Therefore, the aims of this study were: firstly, to assess the usefulness and accessibility of different software packages (e.g. MATLAB, PKSim and QIVIVE); and, secondly, to assess the reproducibility of published models. In the reconstruction of the models, multiple factors were considered including model description, accessibility of parameters, assumptions and the usability of the software. For simulation of concentration-time profiles, PKSim and QIVIVE were found to be more user-friendly than MATLAB, however, MATLAB provided greater functionality and transparency. Problems identified with regard to model reporting and potential solutions are discussed.

The funding of the European Partnership for Alternative Approaches to Animal Testing (EPAA) is gratefully acknowledged.

350
Application and evaluation of a tiered physiologically-based toxicokinetic modelling framework for mammals using empirical and QSAR-based biotransformation rate data

James Armitage[1], Liisa Toose[2], Lauren Hughes[3], Alessandro Sangion[2], Jon Arnot[2,4]

[1]AES Armitage Environmental Sciences, Ottawa, Canada. [2]ARC Arnot Research and Consulting, Toronto, Canada. [3]ARC Arnot Research and Consulting, Peterborough, Canada. [4]University of Toronto, Toronto, Canada

Abstract

Physiologically-based toxicokinetic (PBTK) models are required for many scientific and regulatory applications. PBTK model complexity ranges from relatively simple 1-compartment (1Co-PBTK) to more complex multi-compartment (MCo-PBTK) models. Biotransformation is a key process influencing TK, bioaccumulation (B). New Approach Methods (NAMs) for estimating biotransformation rate constants (or half-lives) include in vitro-in vivo extrapolation (IVIVE) of in vitro biotransformation rate data and Quantitative Structure Activity Relationships (QSARs). In vitro biotransformation rate data can be extrapolated to tissue (i.e., liver) or the whole-body level to parameterize TK models. QSARs have been developed and validated for predicting in vivo whole-body biotransformation half-lives to parameterize 1-CoTK models. The main objective of this study is to develop a tiered 1Co-PBTK and MCo-PBTK modelling framework for mammals that is consistent in terms of physiological processes and chemical distribution calculations. The TK models are parameterized

and simulated with a set of diverse organic chemicals using in vitro, in vivo and QSAR biotransformation rate estimates. The model predictions are compared against each other and to in vivo measurements, e.g., total elimination half-lives. Model output from the 1Co-PBTK and MCo-PBTK models using in vitro biotransformation rate constants is very similar across a wide range of property combinations. We highlight that for many model application contexts biotransformation rate constant uncertainty is a greater determinant of PBTK model uncertainty rather than PBTK model complexity.

202
Extrapolation of Blood/Gas Partition Coefficients across Species

Eugene Demchuk

Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Abstract

Blood-gas partition coefficients (*K*ba) of volatile chemical compounds (VCC) are empirical quantities that loosely follow physical-chemical trends. Therefore, their quantitative structure-activity relationship (QSAR) imputation remains a challenge, while their transferability across species remains unknown. In the present work, 528 coefficients of 101 VCCs measured in 7 species were compared. Significant differences in *K*ba across species were identified. On average, *K*ba decreased with increasing size of the species varying from rat to ox. The dependence was linear on the log-scale and identical to that of hemoglobin Bohr shifts. Thus, the observed correlation likely signifies the importance of VCC binding to peptides-proteins, rather than dependence upon species-specific water-lipid composition of the blood, which is often considered as the major descriptor in QSAR modeling. The established relationship can be used for extrapolation of *K*ba measured in one species to another. This way, multiple independent-study estimates of the human *K*ba may be obtained and then transformed to a meta-analytical value. A thus-derived *K*ba represents a meta-analytical estimate, reconciled with measurements in different studies-species, i.e. a self-consistent estimate with reduced dispersion as compared to a single study. Incorporating such estimate in a physiologically based pharmacokinetic (PBPK) model may be more representative of general population and likely to reduce experimental uncertainties and, consequently, increase the accuracy of modeling. Accurate modeling will improve the effectiveness of public health decisions, for which such modeling is performed. Thus, meta-analytical PBPK modeling may provide another computational-toxicology tool for assessing VCC exposures.

Disclaimer: aforementioned does not represent CDC-ATSDR determination or policy.

315
Advantage of read-across and pharmacokinetics modeling for the exposure assessment of persistent organic pollutants

Patricia Ruiz[1], Sydney Boone[1], David Ebbrell[2], Judith Madden[2], Moiz Mumtaz[1]

[1]ATSDR/CDC, Atlanta, USA. [2]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University., Liverpool, United Kingdom

Abstract

Persistent organic pollutants (POPs) are highly resistant to degradation in the environment, bio-accumulate in living organisms, and can cause adverse effects. In this case study, we tested the hypothesis that an adequately developed, parameterized and validated human pharmacokinetic (PK) model describing a source chemical (i.e. the chemical with an existing human PK model) can be used to simulate PK data for a target chemical (i.e. the chemical with no existing human PK model). We used a published PK model for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), as a template chemical. First, we identified target chemicals of TCDD using read across techniques which identified PCB 153, dichlorodiphenyldichloroethylene (p,p'-DDE), and hexachlorobenzene (HCB). We then used the TCDD model to parameterize it for target chemicals. Overall, there was a good agreement between the simulated and measured TCDD

concentrations using these new models. The models allow the estimation of TCDD concentrations using the HCB, p,p'-DDE and PCB 153 models for different exposure scenarios. Also presented is an application of the p,p'- DDE model for comparison with NHANES biomonitoring data. Hence, this series of PK models may be useful for interpreting human biomonitoring data as a part of an overall POPs risk assessment and demonstrate how existing PBK models can be used to inform the development of new PBK models where data may be lacking. *The findings and conclusions in this presentation have not been formally disseminated by the CCDC/the ATSDR and should not be construed to represent any agency determination or policy.*

342
In vitro biotransformation databases: data confidence evaluation for better QSARs and inter-species comparisons

Alessandro Sangion[1,2], Karen Foster[2], James Armitage[3], Michelle Embry[4], Linda Bertato[5], Ilaria Casartelli[5], Ester Papa[5], Jon Arnot[2,1,6]

[1]Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, Canada. [2]ARC, Arnot Research and Consulting Inc., Toronto, Canada. [3]AES, Armitage Environmental Sciences, Inc., Ottawa, Canada. [4]HESI, Health and Environmental Sciences Institute, Washington DC, USA. [5]Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy. [6]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada

Abstract

Biotransformation rate data are required to parameterize toxicokinetic (TK) and bioaccumulation models for various scientific and regulatory objectives. TK parameters can be estimated using *in vitro* assays coupled with *in vitro-in vivo* extrapolation (IVIVE) or directly by Quantitative Structure Activity Relationship (QSAR). Standardized *in vitro* methods have been approved by the OECD to quantify biotransformation rates from fish tissues. Similar methods have been developed and applied to mammalian species for decades, e.g., for pharmaceutical development. However, despite the availability of thousands of *in vitro* measurements, there is a high degree of variability in assay methods and the reporting of complementary data, which may impact data confidence and QSAR models.

This work summarizes preliminary explorations of similarities and differences in biotransformation rate databases obtained from various *in vitro* systems in fish and mammalian species. An extensive literature search was performed to review and compile existing *in vitro* biotransformation rates for fish (n>1000) and rodents (n>9000). A scoring system to evaluate the confidence and consistency of existing *in vitro* data with new standardized guidelines is developed and proposed to address variability and uncertainty in the datasets. Multi-variate analysis is applied to evaluate the statistical distribution of experimental responses. Preliminary QSARs are developed and tested following the "OECD guidelines on the Validation of (Q)SAR Models". Recommendations are provided for improving experimental data and future QSARs to expand the applicability domain of current estimation methods that can address uncertainty in a wide range of chemical assessment objectives.

208
Using metabolic similarity to justify analogues used for read-across. Application to human health endpoints

Darina Yordanova[1], Chanita Kuseva[1], Terry Schultz[2], Ovanes Mekenyan[1]

[1]Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria. [2]The University of Tennessee, College of Veterinary Medicine, Knoxville, TN 37996-4500, Tennessee, USA

Abstract

The reported work aims to demonstrate the utility of metabolism information that could aid in establishing metabolic (in)consistency between structurally similar analogues, such as ones used in read-across data gap filling. The lack of considerations on metabolism represents a major source of uncertainty in many read-across justifications. Thus, an important criterion that could be used in accepting or rejecting a read-across hypothesis is the assessment of the metabolic similarity. There are several aspects for assessing metabolic similarity, such as commonality between the metabolic transformation across pathways, reactivity pattern (e.g. common interaction mechanisms with biomacromolecules), etc. These and other metabolic criteria could be used to explain differences in the endpoint values for analogues chemicals or to identify better source chemical for read-across purposes. Due to the scarcity of toxicokinetic data for most of the organic chemicals, available *in silico* tools that simulate the (a)biotic transformations of the chemicals could be used to fill this information gap. Understanding the metabolism likeness is also important for confirmation of a negative read-across result, where more weights-of-evidence are required to attain the same level of certainty as a positive prediction. Examples demonstrating various scenarios for using the metabolic information will be demonstrated concerning human health endpoints.

212
Validating read-across analogues accounting for metabolic similarity. Application to environmental fate endpoints

Irina Dermen, Darina Yordanova, Nadezhda Dimitrova, Antonia Kesova, Todor Pavlov, Ovanes Mekenyan

Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria

Abstract

The metabolism of chemicals plays a central role in regulatory risk assessments. Currently, selection of analogues for read-across analysis is justified by three similarity layers: physicochemical, structural and mechanistic. So far the metabolism similarity has been ignored in the analogue selection process. However, the metabolic dissimilarity could explain cases where structurally similar substances have different properties. Due to difficulties in simulating metabolic maps and their complexity the similarity between chemicals is difficult to be estimated. Moreover, the comparison is a context-dependent issue. Thus, one could compare the metabolism of chemicals analyzing the commonality between molecular transformations. It is important to focus not only on the structural aspects, but also to estimate similarity accounting for the magnitude of metabolites (which is important for environmental metabolism). Implementation of the functionalities for assessing metabolic similarity provides transparency of the comparison process. The estimation of metabolic similarity will be illustrated with example of structurally very similar chemicals, which, however, cannot be used as analogues due to differences in their microbial metabolism in the environment.

220
Development of a QSAR model to predict comedogenic potential of some cosmetic ingredients

Sebla Oztan Akturk, Gulcin Tugcu, Hande Sipahi

Yeditepe University, Faculty of Pharmacy, Pharmaceutical Toxicology Department, Istanbul, Turkey

Abstract

Comedogenic cosmetic ingredients tend to cause blackheads or pimples by blocking the pores of the skin. Comedogenicity is a common adverse reaction, especially for acne-prone skin. Before animal testing was banned by European Commission in 2013, the comedogenic potential of cosmetics used to be tested on rabbits. However, full replacement of animal tests by alternatives is not yet applicable. Therefore, there is still a need for applying new approach methodologies. In this study, we aimed to develop a QSAR model to predict comedogenicity potential of cosmetic ingredients by using different machine learning algorithms and types of molecular descriptors.

The dataset of 124 cosmetic ingredients, including fatty acids, fatty alcohols, and pigments tested on rabbit ears, was obtained from the literature. 4516 molecular descriptors were calculated via various software. Different machine learning classification algorithms were used in modelling studies with Weka software. The model performance was evaluated by using 10-fold cross-validation. All models were compared by the means of classification accuracy, kappa statistic, precision, recall, MCC, F measure, ROC area, and the best model was chosen accordingly. The Random Forest model developed with MOLD2 descriptors gave the best results with 80% classification accuracy for test set. The model is the first step for the comedogenicity prediction with promising results. In the near future, advances in *in silico* modelling studies will provide us non-animal-based alternative modelling by regarding animal rights and ethical issues for the safety evaluation of cosmetics.

Keywords: comedogenic, *in silico*, QSAR, comedogenicity, random forest, machine learning, cosmetic ingredient

225
Prediction of Mitochondrial Toxicity using Machine Learning Technology

Frank Bringezu[1], Manuel Pastor[2], José-Carlos Gómez-Tamayo[2]

[1]Merck Healthcare KGaA, Darmstadt, Germany. [2]Pompeu Fabra University, Barcelona, Spain

Abstract

Mitochondria are intracellular organelles found in most eukaryotic cells. Mitochondrial function is complex and includes the generation of cellular energy, maintenance of cellular homeostasis, and metabolic processes. Mitochondrial functional impairment has increasingly been recognized as a contributor to drug-induced toxicity of a variety of drug classes. Early detection of mitochondrial toxicity employing in vitro assays was part of NTP Tox21 and is performed in drug development for candidate selection and to reduce risk for late failures.

The vast amount of existing data provides a suitable source of information to support the application of Machine Learning Technology enabling the prediction for large series of chemically diverse structures. We have employed Flame, an open source software for building predictive models using random forest (RF) and extreme gradient boosting (XGBoost) machine learning methods for the prediction of the in vitro outcome of the MMP and the GluGal assays. The applied technology allows the extension of the training data with further experimental data improving the predictive power of the models.

The results show good performance measures for the XGBoost model that can be further improved by combining individual models in an ensemble prediction for the mechanistic endpoints of mitochondrial toxicity.

237
Conformal prediction models to identify thyroid hormone disrupting chemicals

Elena Dracheva[1], Ulf Norinder[2], Patrik Andersson[1]

[1]Umeå University, Umeå, Sweden. [2]Stockholm University, Stockholm, Sweden

Abstract

Unknown toxic effects is a wide knowledge gap in understanding causes of various diseases related to exposure to manmade chemicals. Thyroid hormone system (THS) disruption includes interferences of the life cycle of the thyroid hormones and may occur in various organs. Over the past years, extensive research revealed a number of putative molecular initiating events (MIE) through which the THS can be disturbed, systemized in adverse outcome pathways (AOP).

In this study, we focus on putative MIEs in the AOP network related to thyroid disruption. For this purpose, we use high-throughput screening data available for the majority of them to identify and prioritize potential THS disrupters via assessing their predicted capacity to interact with the MIEs. Conformal prediction, using random forest as underlying basis algorithm, was chosen as modelling approach due to its strong mathematical evidence, control over error level and capacity to handle imbalanced data.

In total 19 predictive models were established for 14 biological targets where the vast majority of these models showed high efficiencies and balanced accuracies. The developed models were then applied to an in-house database of 499 chemicals found in human blood to assist selection for their further toxicity testing. The DIO1, NIS inhibition and TSHR antagonist models revealed 291, 149 and 298 chemicals of concern, respectively, with 85% confidence. Chemical classes triggering DIOs are PCBs, flame retardants and PFAS. Parabens, phthalates and their metabolites in the database were predicted as inactive DIOs inhibitors.

250
Model Development for Skin Sensitization using OChem

Leora Vegosen[1], Todd Martin[2]

[1]ORISE, Cincinnati, USA. [2]EPA/CCTE, Cincinnati, USA

Abstract

This study develops QSAR models for predicting skin sensitization as a binary toxicity endpoint, assesses the performance of different modeling methods and descriptor sets, develops consensus models, and assesses methods for defining applicability domain (AD). A local lymph node assay (LLNA) dataset of 1355 chemicals was compiled from the NICEATM LLNA Database, OECD QSAR Toolbox, and eChemPortal. Records were mapped to unique substances in the U.S. Environmental Protection Agency's (EPA) Distributed Structure-Searchable Toxicity (DSSTox) Database. Using 10 different modeling methods, models were developed in the Online Chemical Database with Modeling Environment (OCHEM). Models were built using 25 descriptor sets available in OCHEM and two additional descriptor sets: PaDEL descriptors and descriptors developed for EPA's Toxicity Estimation Software Tool (T.E.S.T.). Consensus models were developed using the best performing models in OCHEM. . The best-performing modeling methods, including Associative Neural Networks, Support Vector Machines, and WEKA-random forest, produced validation set balanced accuracies of 77%. T.E.S.T. and PaDEL descriptors performed comparably to the best-performing descriptor sets in OCHEM. Consensus models, achieving balanced accuracies of 79%, performed better than individual models. For the binary skin sensitization endpoint, the applicability domains in OCHEM generally did not improve the results (considering the tradeoff between balanced accuracy and prediction coverage) so other methods for defining AD should be explored. Models will be made publicly available in OCHEM and T.E.S.T., which will contribute to improving the performance and accessibility of new approach methodologies (NAMs) for predicting skin sensitization.

311
(Q)SAR evaluation of toxic and pharmacokinetic properties of autolysin E binders

Katja Venko, Janja Sluga, Marjana Novič

Laboratory for Cheminformatics, Theory Department, National Institute of Chemistry, Ljubljana, Slovenia

Abstract

Autolysin E (AtlE) is an enzyme of the pathogen *Staphylococcus aureus*. AtlE can be a good antibacterial target, because its inhibition leads to cell wall abnormalities of *S. aureus*, which reduces the ability of pathogen to enlarge during cell division and expand into mature morphology. Estimation of the toxic and pharmacokinetic properties of potential AtlE binders is a very important step in the drug development process. For this purpose, we used several (Q)SAR models available on different platforms (NIC, VEGA, Vienna LiverTox, Chembench, OECD Toolbox, TEST, admetSAR, pkCSM, SwissADME, Lazar). The dataset of 32 compounds was selected based on their high binding ability in the crystal structure of AtlE–ligand complexes (PDB ID: 4PI7, 4PI9). The aim of this study was to prioritise compounds that have the best drug-like and non-toxic profiles. Moreover, the comparison between the predictions from our in-house developed (Q)SAR models (NIC) and other publicly available models was performed and the agreement between the predictions was analysed (consensus approach). In this regard, we follow ECHA's recommendation to use as many available (Q)SAR models as possible for the endpoint of interest, as the agreement between predictions generated from multiple independent (Q)SAR models increases confidence in the predictions (ECHA, Practical Guide - How to use and report (Q)SARs 3.1). The compendium of (Q)SAR models for virtual chemical safety profiling used in this study can be practically implemented for any other substance of interest.

314
Improving Predictions of Hydrocarbon Biodegradation (DT50) in Aquatic, Soil, & Sediment Systems – Incorporation of system-specific parameterization and machine learning models

Craig Davis[1], Louise Camenzuli[2], David Brown[3], Chris Hughes[3], Delina Lyon[4], Alberto Martin[4], J. Samuel Arey[1], Aaron Redman[2]

[1]ExxonMobil Biomedical Sciences, Inc, Annandale, USA. [2]ExxonMobil Petroleum & Chemical, B.V., Machelen, Belgium. [3]Ricardo Energy & Environment, PLC, Oxon, United Kingdom. [4]CONCAWE, Brussels, Belgium

Abstract

Microbial biodegradation rates are utilized to assess a chemical's potential persistence and to inform risk assessment. For hydrocarbons, quantitative models (i.e., BioHCWin) exist to predict primary half-lives in aqueous media. While these models have been validated and benchmarked against experimental biodegradation rates, model performance for newer hydrocarbon datasets is mixed, with variation in experimental design, inoculum, and test conditions contributing to significant discrepancies between observed and predicted rates.

This work introduces a model framework which incorporates environmental conditions and test parameters, using updated aquatic, soil, and sediment biodegradation databases to improve predictions of hydrocarbon primary half-lives, leveraging a combination of molecular, structural, and system descriptors. For the aquatic (n=728) as well as soil/sediment (N=1,441) data sets, a novel model tree machine-learning algorithm (RMSE=0.24 and 0.36, R^2=0.71 and 0.75, respectively) utilizing ToxPrint structural fragments performed significantly better than BioHCWin for the expanded biodegradation datasets.

An approximate 3-fold reductions in predictive error as well as significant improvement in the ability of the models to explain variations in half-life behavior (R^2) were observed in both aquatic and soil/sediment systems. This improvement is accomplished with a comparable number of parameters (32 and 23, respectively, vs. 32 BioHCWin fragments). Finally, model tree rules and predictions are transparent and intuitively meaningful, can be easily communicated, and rely on freely-available, standardized chemical descriptors. Ultimately, the machine-learning model offers improved performance

and understanding of system effects on biodegradation in water, soil, and sediment with similar ease of application and communication of model results.

316
Aqueous solubility QSPR model development and application

Janja Sluga[1,2], Katja Venko[1], Viktor Drgan[1], Tihomir Tomašič[2], Marjana Novič[1]

[1]National Institute of Chemistry, Ljubljana, Slovenia. [2]Faculty of Pharmacy, Ljubljana, Slovenia

Abstract

Staphylococcus aureus is a widespread gram-positive pathogen in humans and animals. Autolysin E (AtlE) is an enzyme from *S. aureus* which catalyses the hydrolysis of the β-1,4-glycosidic bond between the *N*-acetylglucosamine and *N*-acetylmuramic acid units of bacterial peptidoglycan [Mihelič et al., 2017, *IUCrJ*]. We have applied *in silico* methods for the discovery of novel and optimizations of existing AtlE binders where we focused on the problem of solubility in water.

Aqueous solubility is one of the most important physicochemical properties that plays a significant role in various physical and biological processes and has a marked impact on the design and pharmaceutical formulation development. It is defined as the maximum amount of a chemical compound that dissolves in a given volume of water at a specified temperature and pressure [Sorkun et al., 2019, *Sci Data*]. A data set of drug-like compounds with experimentally determined solubility was collected from the literature. We have calculated molecular descriptors with Dragon software and selected influential descriptors using a combination of genetic algorithm based optimization method and mapping of molecular descriptors on Kohonen artificial neural network [Drgan et al., 2017, *J Cheminform*]. The internal and external model validation is performed. The predictive quantitative structure-property relationship (QSPR) models for aqueous solubility are presented. We believe that these QSPR models can be used to design water soluble ligands interacting with autolysines, which in turn can be a useful guidance for further development and optimization of this class of antibacterials.

222
Zebrafish AC_{50} Modelling: (Q)SAR models to predict Developmental toxicity in zebrafish embryo

Giovanna Lavado[1], Domenico Gadaleta[1], Cosimo Toma[1], Azadi Golbamaki[1], Andrey Toropov[1], Alla Toropova[1], Marco Marzo[1], Diego Baderna[1], Jürgen Arning[2], Emilio Benfenati[1]

[1]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [2]German Federal Environment Agency, Dessau-Roßlau, Germany

Abstract

Continuous and categorical QSAR models have been developed and validated for the prediction of half-maximal activity concentration AC_{50}. We focused on the development of *in silico* models for the evaluation of developmental toxicity (AC_{50}) of a set of data collected from the ToxCast™ Phase I chemical library on the freshwater zebrafish embryo, one of the most used model organisms in aquatic toxicology. We developed and validated two QSAR models for zebrafish embryo developmental toxicity using different strategies. Categorical and continuous QSAR models were built by means of gradient boosting machine learning and Monte Carlo technique, respectively. The models were built-up in accordance with OECD principles. The statistical quality of the models showed satisfactory results. In particular, classification model reached balanced accuracy BA = 0.89 and Matthews correlation coefficient MCC = 0.77 on test set. The regression model reached correlation coefficient R^2 = 0.70 in external validation and LOO cross-validation Q^2 = 0.73 in internal validation.

Poster Sessions Track 2

344
IN SILICO ADMET PROPERTIES OF METHOXY- PROPENYL-1,3-BENZODIOXOLES AND METHOXY-PROPENYL-BENZENES - QSAR STUDY

Milena Jadrijevic-Mladar Takac[1], Tin Takac[2]

[1]Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia. [2]Faculty of Chemical Engineering and Technology, University of Zagreb, Zagreb, Croatia

Abstract

Naturally occurring ethers from the group of methoxy-propenyl-1,3-benzodioxoles and methoxy-propenyl-benzenes are biologically active compounds, and those like myristicin and elemicin, the two main constituents of the nutmeg essential oil, are assumed to be responsible for the experienced psychoactivity as a result of nutmeg consumption. The metabolic conversion of these compounds into amphetamine similar 3-methoxy-4,5-methylenedioxy-amphetamine (MMDA), a precursor of ecstasy (MDMA), and 3,4,5- trimethoxyamphetamine (TMA), respectively, have been proposed as the mechanism for the psychoactivity of these compounds. In this QSAR study, the relationship between ADMET properties of methoxy-propenyl-1,3-benzodioxolones and methoxy-propenyl-benzenes (n =29) predicted by ADMET PredictorTM was evaluated. The MDMA was also included in this study. The majority of the investigated compounds were revealed as nonbiodegradable, except for several *mono*-methoxy-propenyl-benzenes. The bioconcentration factor of these molecules was predicted in a wide range, from 6.228 to 965.605. According to ECCS, all compounds belong to Class 2 (neutral or basic compounds with high permeability, predominantly cleared by metabolism). The main ADMET risk connected with CYP1A2 oxidation was revealed for all investigated compounds. However, the risk of mutagenicity was predicted for isomyristicin, croweacin, asaricin, apiol, isoapiol, and nothoapiol, and the risk of hepatotoxicity for piperonal, chavicol, eugenol, and isoeugenol. All molecules were predicted to be skin sensitizers. QSAR study revealed the best correlations between lipophilicity (MlogP) vs. CYP2C19_Km (R2 = 0.869), and vs. Andro_RBA (R2 = 0.735), as well as between permeability, S+Peff, vs. CYP2C19_Km (R2 = 0.717), vs. CYP3A4_Ki_testo (R2 = 0.720), and vs. Rat_Acute (R2 = 0.703).

199
Phenotypic profiling in planarians allows for distinction of classes of neuropsychiatric drugs

Danielle Ireland[1], Sagar Rao[1], Siqi Zhang[1], Zane Meyer[1], Christina Rabeler[1], Eva-Mari Collins[1,2]

[1]Swarthmore College, Swarthmore, PA, USA. [2]UC San Diego, La Jolla, CA, USA

Abstract

The integration of chemical high-throughput screening (HTS) using alternative models with innovative computational methods promises to revolutionize drug discovery and toxicology. Here, we evaluate the potential of phenotypic profiling for neuropsychiatric drug discovery using HTS in asexual freshwater planarians. This small aquatic invertebrate has a medium-sized nervous system with high molecular and functional homology to the vertebrate brain and a rich behavioral space that can be quantified using computer vision. We tested the acute effects of 3 classes of neuropsychiatric drugs - anti-psychotics, anti-depressants and anxiolytics - on planarian nervous system function using a HTS platform. Each drug was screened blinded at minimum 5 concentrations in half-log increments to evaluate dose-response over 3 experiments (n=24 total). Assay negative and positive controls were also tested. Each chemical concentration was assigned a quantitative phenotypic barcode based on 18 endpoints, spanning body shapes, locomotion and stereotypical behaviors induced by environmental stimuli. Using multidimensional scaling, we differentiated the drug classes based on their phenotypic barcodes. While small in scope, these results suggest that planarian HTS can identify neuroactive compounds without mechanistic information, which is generally complex and poorly understood for psychiatric disorders. A PhenoBlast approach could thus be used for rapid chemical screening in which the profiles of novel compounds are

compared to known neuroactive compounds. Identified hit compounds could then be substantiated using the similarity ensemble approach to identify putative target receptors. Using such a read-across based approach, we can better predict chemical effects to help streamline drug discovery and toxicology testing.

214
An integrated similarity-based workflow for automated chemical read-across

Domenico Gadaleta, Giovanna J. Lavado, Azadi Golbamaki Bakhtyari, Alessandra Roncaglioni, Emilio Benfenati

Laboratory of Environmental Chemistry and Toxicology, Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Abstract

Read-Across (RAX) is a popular data-gap filling technique that uses category and analogue approaches to predict toxicological endpoints for a chemical using experimental values of similar compounds (i.e., analog(s)). Despite its increasing relevance for regulatory purposes, RAX often relies on human expert judgement and lacks a subjective and automated protocol for the identification of suitable analog(s).

Here we propose a fully automated procedure for the selection of analog(s) for data gap-filling. Analog(s) were identified with a decision algorithm that integrates three similarity metrics that consider different toxicologically relevant aspects (i.e. structural, biological and metabolic similarity).

Each similarity metric was determined by mean of a tailored algorithm and implemented into a KNIME workflow that was used to automatically compile independent lists of candidate analogues. As a result, compound(s) included in multiple similarity lists are suggested as most suitable analog(s), and their activity is used to infer the activity of the target chemical. Structural filters based on the presence of maximum common substructures (MCS) and common functional groups were also applied to narrow the chemical space for the analog(s) search.

The procedure has been validated for its predictive power on a series of datasets relative to high-tier in vivo toxicological endpoints. The validation results confirmed the advantages of integrate multiple similarities with respect of the sole use of chemical similarity, and the benefit of the tool here presented to support regulatory decision-making.

A stand-alone GUI based application implementing the method above is currently under development.

216
Multi-scale comparative analysis of the mechanisms of organophosphorus pesticide developmental neurotoxicity

Danielle Ireland[1], Siqi Zhang[2], Veronica Bochenek[1], Christina Rabeler[1], Zane Meyer[1], Eva-Maria S. Collins[1,2]

[1]Swarthmore College, Swarthmore, USA. [2]University of California San Diego, La Jolla, USA

Abstract

Organophosphorus pesticides (OPs) are a chemically diverse class of commonly used insecticides. Inhibition of acetylcholinesterase (AChE) as the shared mechanism of acute OP neurotoxicity is well studied. However, it has been suggested that chronic low-dose exposure to OPs causes developmental neurotoxicity (DNT), via interactions with alternative targets. Because most studies have focused on chlorpyrifos, it remains unclear whether different OPs act through different mechanisms. We hypothesized that differences of OP DNT are due to differential effects on alternative targets. To test this, a comparative high-throughput screen of 7 OPs (acephate, chlorpyrifos, dichlorvos, diazinon, malathion, parathion and profenofos) across 10 concentrations in quarter-log steps was performed. Asexual freshwater planarians were used because this invertebrate system uniquely allows for testing of adult and developing specimen in parallel on an automated system. Twenty-two “mechanistic control compounds” known to target pathways suggested in the literature to be affected by OPs, and assay negative and positive controls were also tested. Neurotoxicity was

quantified across 29 (morphological and behavioral) readouts using automated image analysis. Phenotypic barcodes were created to quantify the holistic toxicological profile for each chemical concentration using the standardized, compiled (n=24 planarians) quantitative scores for each of the 29 endpoints. Multidimensional scaling revealed that the OPs separated into mechanistic clusters. The phenotypic profiles of adult vs regenerating planarians exposed to the OPs clustered differently, suggesting some developmental-specific mechanisms. This study provides new mechanistic insight into how OPs differentially damage the developing brain. Supported by NIH grant R15 ES031354.

231
Building a compendium of expert driven read-across cases to facilitate an analysis of the impact that New Approach Method (NAM) data can play in Generalized Read-Across (GenRA) performance

Willysha Jenkins[1,2], Tia Tate[1], Imran Shah[1], Grace Patlewicz[1]

[1]US EPA, Durham, USA. [2]ORISE, Oak Ridge, USA

Abstract

Read-across is a data-gap filling technique utilized to predict the toxicity of a target chemical using data from similar analogues. Read-across acceptance remains an issue, mainly due to the difficulties of addressing residual uncertainties and because read-across is still a subjective expert driven assessment. There have been many efforts to identify the sources of uncertainty in read-across, characterize them consistently and identify practical strategies to address and reduce those uncertainties. Notable have been the creation of frameworks to develop, assess and document read-across. Efforts also include transitioning to data driven approaches such as Generalized Read-Across (GenRA) (Shah et al., 2016) where uncertainties and performance can be quantified. GenRA affords opportunities for New Approach Method (NAM) data to be incorporated to provide mechanistic context. A key issue that remains is how to reconcile an expert driven approach with data driven approaches in terms of establishing scientific confidence in the use of NAM data. This study aims to explore these issues by building a database of expert driven read-across assessments. The data currently being extracted includes identifying the target being assessed, the candidate source analogues, which were carried forward as the preferred analogue, what toxicity endpoints were being read across, as well as all supporting information. This information will be used to identify which expert analogue groupings are similar, and which are insufficiently similar. The groupings will be cross referenced with existing NAM data available to facilitate new GenRA development. *This abstract does not reflect EPA policy.*

245
Influence of Transcriptomic Descriptors on the Generalized Read-Across (GenRA) Performance

Tia Tate, Grace Patlewicz, John Wambaugh, Imran Shah

Center for Computational Toxicology and Exposure, US Environmental Protection Agency, Research Triangle Park, USA

Abstract

Read-across is a data gap filling technique utilized to predict the toxicity of a target chemical using data from similar analogues. Recent efforts such as the Generalized Read-Across (GenRA) (Shah et al., 2016) approach facilitate automated read-across predictions for untested chemicals. GenRA makes predictions of toxicity outcomes based on “neighboring” chemicals characterized by chemical and/or bioactivity descriptors. This study utilizes a recently developed python package, genra-py, to investigate the impact of biological similarities (characterized by targeted transcriptomic data) on neighborhood formation and read-across performance in qualitatively predicting hazard (based on repeated-dose study outcomes from US EPA ToxRefDB v2.0). HepaRG™ cells were treated with eight concentrations of 1,060 chemicals and measured the expression of 95 transcripts, which

measure nuclear receptor activation, xenobiotic metabolism, cellular stress, cell cycle progression, and apoptosis. Transcriptomic similarity between chemicals was calculated using binary hit-calls from concentration-response data for each gene. GenRA performance in predicting ToxRefDB v2.0 hazard outcomes was evaluated using the area under the Receiver Operating Characteristic (ROC) curve (AUC) for baseline (chemical fingerprints) versus transcriptomic fingerprints, and hybrid (chemical and transcriptomic) fingerprints. An increase in read-across performance was noted for various toxicity endpoints when using either transcriptomic or hybrid fingerprints over baseline. Overall, the mean read-across performance increased by 0.01 (2.1% improvement) for all endpoints when utilizing transcriptomic descriptors and by 0.04 (7.3% improvement) with hybrid descriptors. Bioactivity descriptors or combined with chemical information offer significant benefits in predicting in vivo toxicity outcomes. This abstract does not reflect U.S. EPA policy.

269
Predicting molecular activity on nuclear receptors with deep and machine learning

Cecile Valsecchi[1], Francesca Grisoni[2], Viviana Consonni[1], Davide Ballabio[1], Roberto Todeschini[1]

[1]Milano Chemometrics and QSAR Research Group, Department of Earth and Environmental Sciences, University of Milano Bicocca, P.za della Scienza 1, Milan, 20126, Italy. [2]Department of Chemistry and Applied Biosciences, ETH Zurich, VladimirPrelog-Weg 4, Zurich, 8049, Switzerland

Abstract

Nuclear receptors (NRs) are a family of transcription factors involved in fundamental human health processes and are a relevant target for medicinal chemistry applications as well as for toxicological risk assessment. Although the ligand binding domain of ligand-activated NRs is a highly conserved domain, several nuclear receptors have been shown to be promiscuous targets, as demonstrated for instance by the endocrine interference exerted by several man-made compounds. In this study, we applied deep and machine learning methods to prioritize compounds for both pharmacological and toxicological applications. We used the recently published NUclear Receptor Activity (NURA) dataset, which contains annotations for 15,247 molecules and 11 NRs and integrates data from toxicological and pharmacological databases (i.e., Tox21, ChEMBL, NR-DBIND and BindingDB). As a benchmark, we built predictive models considering one receptor at a time, i.e., single-task classification. Then, to take advantage of information sharing among NR bioactivity data, we built multi-task Neural Networks, which allow simultaneous prediction of bioactivities for all the 11 NRs, but require extensive parameter tuning. On average, multitask Feedforward Neural Networks achieved the highest Balanced Accuracy of 90.1% and 93.0% on test and external validation sets. Although no approach systematically overperformed the others, task-specific differences were found, suggesting the benefit of multi-task learning for tasks that are less represented.

320
High-throughput phenotypic profiling to inform putative mode of action for environmental chemicals

Johanna Nyffeler[1,2], Clinton Willis[1], Grace Patlewicz[1], Imran Shah[1], Joshua Harrill[1]

[1]Center for Computational Toxicology and Exposure, Office of Research and Development, US Environmental Protection Agency, Durham, USA. [2]Oak Ridge Institute for Science and Education (ORISE) Postdoctoral Fellow, Oak Ridge, USA

Abstract

The EPA is exploring high-throughput profiling methods for rapid bioactivity screening and hazard evaluation of environmental chemicals. Phenotypic profiling is an imaging-based assay that measures morphological features of organelles at the single cell level. Here, we explore the use of phenotypic profiles to discern putative molecular mechanisms-of-action. We screened a set of 120 reference chemicals and toxicological model compounds as well as 462 environmental chemicals at 8 concentrations. U-2 OS cells were exposed for 24 h, fixed and labeled with fluorescent dyes to visualize multiple organelles: nucleus, nucleoli, endoplasmic reticulum, golgi, actin cytoskeleton, plasma membrane and mitochondria. Confocal images were acquired, and 1300 features extracted per cell. Cell-level data was normalized to

vehicle controls, aggregated to the well level, averaged across replicates and summarized across concentrations to derive a profile for each chemical. Biological similarity was computed by comparing profiles using Pearson correlation. Structural similarity was measured by comparing Morgan fingerprints using Tanimoto similarity. Overall, several distinct profile clusters were observed for different classes of pesticides (organochlorine, strobins, dinitroanilines). Reference chemicals with various DNA damaging mechanisms (alkylators, topoisomerase inhibitors, antimetabolites) clustered together along with a subset of environmental chemicals. Another example included three microtubule stabilizers with high biological similarity (>0.8): paclitaxel and docetaxel share high structural similarity, while epothilone B is structurally unrelated to the former two. We conclude that phenotypic profiling data can be used to identify chemicals with similar cellular effects, both among structurally diverse and structurally related chemicals. *This abstract does not reflect USEPA policy.*

293
Benchmarking recent Deep Learning methods on the extended Tox21 data set

Philipp Seidl, Christina Halmich, Andreas Mayr, Andreu Vall, Peter Ruch, Sepp Hochreiter, Günter Klambauer

Johannes Kepler University, Linz, Austria

Abstract

The Tox21 data set has evolved into a standard benchmark for computational QSAR methods in toxicology [1]. One limitation of the Tox21 data set is, however, that it only contains twelve toxic assays which strongly restricts its power to distinguish the strength of computational methods. We ameliorate this problem by benchmarking on the extended Tox21 dataset with 68 publicly available assays in order to allow for a better assessment and characterization. The broader range of assays also allows for multi-task approaches, which have been particularly successful as predictive models [2]. Furthermore, previous publications comparing methods on Tox21 did not include recent developments in the field of machine learning, such as graph neural and modern Hopfield networks [3]. Thus we benchmark a set of prominent machine learning methods including those new types of neural networks. The results of the benchmarking study show that the best methods are modern Hopfield networks and multi-task graph neural networks with an average area-under-ROC-curve of 0.91 ± 0.05 (standard deviation across assays), while traditional methods, such as Random Forests fall behind by a substantial margin. Our results of the full benchmark suggest that multi-task learning has a stronger effect on the predictive performance than the choice of the representation of the molecules, such as graph, descriptors, or fingerprints.

References:
[1] Huang, R., et al. (2016). Frontiers in Environmental Science, 3, 85.

[2] Mayr, A., et al. (2016). Frontiers in Environmental Science, 3, 80.

[3] Ramsauer, H., et al. (2021). 9th International Conference on Learning Representations.

309
Revisiting and Updating Chemical Categorizations using Chemical Fingerprint and High-Throughput Screening Data

Kellie A. Fay[1], Kamel Mansouri[2], John Prindiville[3], Grace Y. Patlewicz[4], Mark Lewis[5], Ann Richard[4], Mahmoud Shobair[4], Ellery Saluck[6], Daniel T. Chang[4]

[1]USEPA OCSPP/OPPT, Washington, DC, USA. [2]NIEHS NTP, Durham, NC, USA. [3]Environment and Climate Change Canada, Ottawa, ON, Canada. [4]USEPA ORD/CCTE, Durham, NC, USA. [5]Health Canada, Ottawa, ON, Canada. [6]Student Intern, USEPA OCSPP/OPPT, Washington, DC, USA

Abstract

Chemical categorization, or grouping, is employed to capture and report salient chemistry and toxicity correlations and identify analogs for chemicals with limited information. One prominent application of chemical grouping used by chemical

regulators is the Ecological Structure Activity Relationship (EcoSAR) model, which predicts the toxicity of classes of chemicals to various aquatic species. There is a need to update categories and models as new information on hazards becomes available, especially given that a large proportion of industrial substances are unclassifiable by EcoSAR. Hierarchical clustering approaches were applied to evaluate whether potential refinements could be made to current EcoSAR classes using chemical fingerprint and in vitro biological activity information. Refinements included building sub-categories for broad EcoSAR classes (e.g., neutral organics), and identifying new categories to address substances currently unclassifiable by EcoSAR. An ensemble tree-based classification model was developed to predict narcotic or specific-acting aquatic toxicity modes of action (MOA). The model was trained on chemical fingerprints, ToxCast and Tox21 biological activity, or both. It was then used to predict aquatic toxicity MOA for chemicals classified as neutral organics or unclassifiable by the current version of EcoSAR. Chemotype and activity enrichments for chemicals predicted to be specific-acting identified features useful for refining EcoSAR classes, including several bond chemotypes and in vitro assays. This approach identified gaps in the biological activity inventory and suggests specific in vitro assays that may be useful for informing reductions in animal testing. *Abstract does not reflect EPA policy.*

230

Harnessing 'Big Data' Toward the Design of Safer Pesticides: A Two-tiered In Silico Approach for Tuning Kinetics and Thermodynamics of Pesticide Photodegradation and Minimizing Their Ecotoxicity

Jessica Lewer, Jessica Huang, John Peloquin, Jakub Kostal

George Washington University, Washington D.C., USA

Abstract

Elucidating factors that contribute to ecotoxicity and persistence of agrochemicals in the environment is necessary in developing new, high-performing products with minimal adverse environmental impact. Chromophoric Dissolved Organic Matter in the triplet excited state (^{3}CDOM*) is known to play a key role in the degradation of pesticides in the environment. Here, we report a two-tier computational framework, developed to probe and predict both kinetics and thermodynamics of ^{3}CDOM*-pesticide interactions. In the first tier, our model is based on free energies, computed for the redox process using density functional theory, and fitted in linear models to experimental cell potentials and second-order rate constants. In the second tier, free energies and corresponding barriers of the redox process, determined in solution using Marcus Theory, are used to guide quick, yet accurate, predictions of photodegradation using Frontier Molecular Orbital (FMO) Theory. Since FMO metrics were previously shown effective in predicting chemical ecotoxicity, the second tier of our model integrates persistence and safety into a single environmental-impact metric. Being highly mechanistic and based on ca. 1,500 unique ^{3}CDOM*-pesticide interactions in the first tier and over 4 million interactions in the second tier, our approach is both robust and broadly applicable. Here, we outline the development and performance of our model as well as its incorporation into an open-source Pesticide Indirect Photodegradation (PIP) platform. Housing all computed as well as underlying experimental data, PIP can be used to assess novel pesticides and guide chemical design by integrating SMARTS-based substructure-matching and Tanimoto-coefficient similarity scoring.

201
New QSAAR model: Fish early life stage toxicity (FELS) from daphnid toxicity and quantum chemistry

Sebastian Schmidt, Daniel Faber, Jutta Hager, Michael Schindler

Bayer AG, Monheim, Germany

Abstract

Towards the goal of reduced animal testing, predictive in silico methods for the ecotoxicity of chemicals can play an important role, if they are reliable, interpretable and broadly applicable. This requires high-quality data, robust modelling approaches, and usually in-depth subject matter expertise to be successful.

We recently [1] compiled a large data set of fish early life stage (FELS) no observed effect concentrations (NOEC) based on published data sources and internal studies for 338 molecules. Furthermore, we developed a quantitative structure-activity-activity relationship (QSAAR) model to predict this endpoint using a combination of dimensionality reduction, regularization, and domain knowledge. We started from experimental daphnid acute data and a huge number of molecular descriptors ranging from topological to quantum chemical properties. Using a sparse partial least squares algorithm (sPLS) we pre-selected relevant variables for a subsequent manual refinement.

The final QSAAR model consists of 2 latent variables based on 8 molecular descriptors and experimental daphnid acute data (EC50, 48h). The model performs well on a test data set of chemically related molecules with experimental daphnid data (R^2 = 0.687, RMSE = 0.793 log units). It is broadly applicable, in particular across crop protection chemical space. We evaluated the model according to OECD principles and provide a mechanistic interpretation.

[1] S. Schmidt, M. Schindler, D. Faber, and J. Hager, SAR and QSAR in Environmental Research, *accepted for publication*, https://doi.org/10.1080/1062936X.2021.1874514

215
3D-SDAR classification models for large and diverse sets of opioid and cannabinoid receptors binders. Structural factors affecting binding to cannabinoid receptor type 1 and μ-, κ- and δ-opioid receptors.

Svetoslav Slavov, Richard Beger

FDA/NCTR, Jefferson, USA

Abstract

Addiction is a complex behavioral phenomenon in which naturally occurring or synthetic chemicals, through their binding to a variety of neuroreceptors, modulate the response of the reward system, resulting in compulsive substance-seeking. Among these, the opioid and cannabinoid systems play a critical role in substance addiction. Having in mind their profound effect on human behavior, properly validated, large scale models for binding to the mu, kappa and delta opioid receptors as well as cannabinoid receptor type 1 are surprisingly lacking.

Binary 3D-SDAR classification models for 3594, 2942, 2420 and 2817 MOR, KOR, DOR and CB1R binders were developed. The initial datasets were split into balanced modeling and “blind” prediction subsets. For each dataset, a total of 100 randomized PLS and KNN models splitting the modeling set into training and hold-out test sets were generated and used to predict the binding class of the chemicals in the prediction sets. The accuracy, sensitivity and specificity for the prediction subsets consistently exceeded 0.8 and were significantly higher after removal of the inconclusives near the cut-off. The AUC values for all prediction subsets exceeded 0.88. Morphinan and benzomorphan backbones were identified as universal and non-selective components of OR binders, whereas specific functional groups such as 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine, 3-pyrrolidinol and benzamide were found to result in substances that are selective to MOR, KOR

and DOR, respectively. On the other hand, in addition to the tricyclic terpenoid system specific to THC and its derivatives, CB1R also was selective to halogenated diarylpyrazoles and diaryl-(piperidinyl)purines.

360
KOWWIN Improvement on The Fly – Similarity-Based Error Correction Employing Atom-Centered Fragments

Gerrit Schüürmann[1,2], Ralph Kühne[1], Ralf-Uwe Ebert[1]

[1]UFZ Department of Ecological Chemistry, Helmholtz Centre for Environmental Research, Leipzig, Germany. [2]Institute of Organic Chemistry, Technical University Bergakademie Freiberg, Freiberg, Germany

Abstract

Hydrophobicity in terms of the logarithmic octanol/water partition coefficient, log *K*ow, is a key compound property for environmental chemistry and toxicology,1-3 addressing also chemoavailability2 and lethal body burdens.3 KOWWIN4 is the REACH method of choice to predict log *K*ow from molecular structure. For a curated EPISuite set of 15092 compounds with experimental log *K*ow data, KOWWIN yields an rms (root-mean-squared) error of 0.55 log units with maximum positive and negative deviations of 4.02 and –3.42 log units, respectively. To correct for local biases associated with substructural features, we have developed the following approach: For each target molecule, the KOWWIN prediction is corrected by the prediction error obtained for database compounds meeting a certain similarity threshold assessed through atom-centered fragments (ACFs). In this way, the global rms error reduces to 0.37 log units, and the largest positive and negative prediction errors to 1.96 and –2.00 log units, respectively. The new similarity-based error correction has been implemented in fully automatized form in our ChemProp software, and is available to the public through free-of-charge licenses.5

[1] Schüürmann G et al. 2007. In: Van Leeuwen K, Vermeire T (eds): Risk Assessment of Chemicals: An Introduction. 2nd Edition. Springer, Dordrecht, NL, pp. 375-426.

[2] Böhme A, Laqua A, Schüürmann G 2016. *Chem. Res. Toxicol.* 29: 952-962.

[3] Schüürmann G, Somashekar RK, Kristen U 1996. *Environ. Toxicol. Chem.* 15: 1702-1708.

[4] US EPA 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, KOWWIN, v 4.11.

[5] UFZ Department of Ecological Chemistry 2021. ChemProp 6.7.1 http://www.ufz.de/ecochem/chemprop.

198
Development of a water solubility dataset to establish best practices for curating new datasets for QSAR modeling

Charles Lowe, Chris Grulke, Antony Williams

US Environmental Protection Agency, RTP, USA

Abstract

The U.S. Environmental Protection Agency's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) hosts a plethora of environmentally relevant chemical information, including physicochemical property data suitable for QSAR/QSPR modeling. The development of these physical property datasets has generally involved the curation of publicly available experimental data. The ease of accessing these data, along with the overall quality of the dataset (i.e. machine-readable formatting, inclusion of experimental conditions, etc) is highly variable. This purpose of this work is to identify the challenges associated with the assembly of physicochemical property datasets, with a focus on obtaining high quality water solubility values for organic compounds. Common issues discovered during the process of assembling, integration and review of these data will be presented, along with solutions that can be easily implemented in a high-throughput

manner. Our intention is to develop standard workflows and provide guidance that can be used by researchers for the curation of physicochemical property datasets and ideally extended to environmental fate and transport data and other relevant chemical related datasets. The culmination of this work is a curated water solubility dataset for organic compounds from numerous sources, including both online databases and journal articles. Progress on modeling this dataset via machine learning methods (e.g. random forest, k-nearest neighbors) will also be reported. *This abstract does not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

361
Henry's Law Constant – A New Fragment Model to Predict Log K_{aw} From Molecular Structure

Gerrit Schüürmann[1,2], Ralph Kühne[1], Ralf-Uwe Ebert[1]

[1]UFZ Department of Ecological Chemistry, Helmholtz Centre for Environmental Research, Leipzig, Germany. [2]Institute of Organic Chemistry, Technical University Bergakademie Freiberg, Freiberg, Germany

Abstract

Henry's law constant in terms of the air-water partition coefficient *K*aw plays an important role for the environmental fate of organic compounds,1 and also for the compound partitioning between blood and the physiological gas-phase compartment.2 HENRYWIN from the EPISuite3 represents a current increment method of choice to predict log *K*aw from molecular structure. To explore room for improvement, we have collected a set of 2580 organic compounds with validated experimental *K*aw data, covering 1178 directly measured values and 1402 data calculated from experimental vapour pressure and water solubility. The rms (root-mean-squared) error of the new increment method is 0.53 log units, outperforming the respective HENRYWIN rms error of 1.23 log units. The discussion includes further comparisons with the performances of the quantum chemical COSMOTHERM4 and Abraham-type LSER (linear solvation energy relationship)1 models. Our new fragment model has been implemented in fully automatized form in the ChemProp software that is available to the public through free-of-charge licenses.5

[1] Schüürmann G et al. 2007. In: Van Leeuwen K, Vermeire T (eds): Risk Assessment of Chemicals: An Introduction. 2nd Edition. Springer, Dordrecht, NL, pp. 375-426.

[2] Salmina E, Wondrousch D, Kühne R, Potemkin VA, Schüürmann G 2016. *Sci. Total Environ.* 550: 586–597.

[3] US EPA 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, HENRYWIN, v 3.20.

[4] COSMOTHERM. http://www.cosmologic.de/products/cosmotherm.html.

[5] UFZ Department of Ecological Chemistry 2021. ChemProp 6.7.1 http://www.ufz.de/ecochem/chemprop.

195
Evaluation of EPI Suite KOCWIN performance on substances used for plant protection

Rodolfo Gonella Diaza[1], Antje Gerloff-Elias[2], Sebastian Schmidt[3]

[1]knoell Germany GmbH, Chemistry and Analytics, Mannheim, Germany. [2]knoell Germany GmbH, Environmental & Human Toxicology, Mannheim, Germany. [3]Bayer AG, Crop Science, Environmental Safety, Monheim, Germany

Abstract

According to the current European regulation for plant protection products (Regulation (EC) No 1107/2009), Quantitative Structure-Activity Relationship (QSAR) models are among the non-testing methods that may be used to generate data for the characterisation of active substances as well as their metabolites and impurities. These substances typically contain multiple functional groups; thus, being particularly challenging for structure-based *in silico* methods.

This poster provides results of an evaluation of the predictive power of two widely used QSAR models on substances used for plant protection. The EPI Suite (v4.11) KOCWIN (v2.00) log Kow-based and Molecular Connectivity Index (MCI)-based

models for prediction of the soil sorption coefficient (Koc) have been evaluated using a dataset of 199 molecules, including active substances and metabolites. For each molecule, experimental log Koc and log Kow data were available. We performed the evaluation on the whole dataset as well as by considering neutral and non-neutral (i.e. ionic and ionisable) molecules, separately.

The obtained results suggest that the log Kow-based method shows better performance than the MCI-based method for plant protection products. We observed clear trends between the experimental and log Kow-based estimated log Koc values, especially on neutral molecules. Furthermore, we demonstrated an increase of the reliability with a consistent implementation of the model's applicability domain.

Poster Sessions Track 3

185
Prediction of drug induced cardiotoxicity and liver toxicity using chemical structure and in vitro assay data

Lin Ye

NIH, Rockville, USA

Abstract

Drug-induced cardiotoxicity and liver toxicity (DILI) are major adverse effects encountered by many clinically important drugs especially antineoplastic agents. To provide an alternative to in vivo toxicity testing, the US Tox21 program has screened a collection of ~10K compounds, including drugs in clinical use, against ~70 cell-based assays in a quantitative high-throughput screening (qHTS) format. In this study, we evaluated the potential of Tox21 assay data in comparison with chemical structure information in building optimal prediction models for human in vivo cardiotoxicity and DILI. Models were built with a number of machine learning algorithms (e.g., random forest, SVM, MLP) and model performance was evaluated by area under the receiver operating characteristic (ROC) curve (AUC) and Matthews Correlation Coefficient (MCC). Chemical structure based models showed moderate predictive power for cardiotoxicity (AUC = 0.69±0.04) and better predictive performance for DILI (AUC = 0.77±0.05). Tox21 assay data alone only showed better than random performance with AUCs around 0.6. Combining assay data and structure information significantly improved the performance of the cardiotoxicity prediction model (AUC = 0.79±0.06) but did not have a positive impact on DILI prediction. The suboptimal predictive performance of the assay data is likely due to insufficient coverage of an adequately-predictive number of toxicity mechanisms. Tox21 is currently expanding the coverage of biological response space with additional assays that probe toxicologically-important targets and under-represented pathways that may improve the prediction of in vivo toxicity such as DILI and cardiotoxicity.

232
Generalised Read-Across (GenRA) Prediction: Updating the Dashboard implementation and using genra-py as a standalone application

Imran Shah[1], Tia Tate[1], Lionel Girardin[2], Sean Hamilton[2], Bhaskar Sharma[1], Terry N Brown[3], Kenta Baron Furuyama[1], Phuc Do[1], Grace Patlewicz[1]

[1]US EPA, Durham, USA. [2]GDIT, Falls Church, VA, USA. [3]US EPA, Duluth, USA

Abstract

Generalised Read-Across (GenRA) is a data-driven approach to estimate physico-chemical, biological, or eco-toxicological properties of chemicals from similar analogues. GenRA attempts to mimic the expert driven read-across workflow for filling data gaps using an interpretable and automated approach based on nearest-neighbours. A key objective of GenRA is

to systematically explore different choices of input data selection and neighbourhood definition to objectively evaluate predictive performance of automated read-across estimates of different chemical properties. Here we provide an update to the web application implemented as part of the EPA CompTox Chemicals Dashboard. The underlying databases supporting the Dashboard implementation have been updated and the user interface as been entirely rebuilt. We also present a new python package called genra-py that has been created that can be freely used for chemical safety analysis and risk assessment applications Automated read-across prediction in genra-py conforms to the scikit-learn machine learning library's estimator design pattern, making it easy to use and integrate in computational pipelines. Two examples of how genra-py can be used in different human health risk assessment problems namely: hazard identification and point of departure estimation are highlighted. The package is available from github.com/i-shah/genra-py. *This abstract does not reflect EPA policy.*

283
Comparative assessment of interpretability methods of deep activity models for hERG

Johannes Schimunek[1], Lukas Friedrich[2], Daniel Kuhn[2], Sepp Hochreiter[1], Friedrich Rippmann[2], Günter Klambauer[1]

[1]LIT AI Lab & Institute for Machine Learning, Johannes Kepler University Linz, Linz, Austria. [2]Merck Healthcare KGaA, Darmstadt, Germany

Abstract

Since many highly accurate predictive models for bioactivity and toxicity assays are based on Deep Learning methods, there has been a recent surge of interest in interpretability methods for Deep Learning approaches in drug discovery [1,2]. Interpretability methods are highly desired by human experts to enable them to make design decisions on the molecule based on the activity model. However, it is still unclear which of those interpretability methods are better identifying relevant substructures of molecules. A method comparison is further complicated by the lack of ground truth and appropriate metrics. Here, we present the first comparative study of a set of interpretability methods for Deep Learning models for hERG inhibition. In our work, we compared layer-wise relevance propagation, feature gradients, saliency maps, integrated gradients, occlusion and Shapley values. In the quantitative analysis, known substructures which indicate hERG activity are used as ground truth [3]. Interpretability methods were compared by their ability to rank atoms, which are part of indicative substructures, first. The significantly best performing method is Shapley values with an area under-ROC-curve (AUC) of ~0.74 ± 0.12, but also runner-up methods, such as Integrated Gradients, achieved similar results. The results indicate that interpretability methods for deep activity models have the potential to identify new toxicophores.

[1] Jiménez-Luna, J., et al. (2020). Nature Machine Intelligence, 2(10), 573-584.

[2] Preuer, K., et al. (2019). In Explainable AI: Interpreting, Explaining and Visualizing Deep Learning (pp. 331-345).

[3] Czodrowski, P. (2013). Journal of chemical information and modeling, 53, 2240–2251.

332
Beyond In Silico: Predictions based on Chemoinformatics and Highly Curated NOAEL Databases

Chihae Yang[1,2,3], Sunil Kulkarni[4], James Rathman[2,3], Aleksandra Mostrag[2], Tomek Magdziarz[1], Tara Barton-Maclaren[4], Mark Cronin[5]

[1]MN-AM, Nuremberg, Germany. [2]MN-AM, Columbus, USA. [3]Ohio State University, Columbus, USA. [4]Existing Substances Risk Assessment Bureau, Health Canada, Ottawa, Canada. [5]Liverpool John Moores University, Liverpool, United Kingdom

Abstract

Chemical safety assessment using QSAR, rule-based systems, or artificial intelligence approaches is becoming more acceptable. However, such approaches fall short when the underpinning data is weakly grounded in specific chemical-biological interactions. One example where a new paradigm is needed is for estimating a no-observed-adverse-effect level (NOAEL), as required in the assessment of systemic toxicity. When the NOAEL of a query compound is unavailable, it is often estimated from data for analogs, as in read-across. This study presents a novel method whereby a combination of statistically robust chemoinformatics analysis, based on highly curated NOAEL databases in COSMOS and Antimicrobial Threshold of Toxicological Concern (TTC) projects, and grouping of >1300 compounds by chemical categories are applied to estimate a NOAEL interval at a given confidence level. The central hypothesis is that similar compounds (structures, properties, biological effects) likely have similar toxicity profiles and, hence, similar NOAEL values. Analog quality (AQ), is quantified by physicochemical properties and ToxPrint chemotypes, defining coverage, diversity, local neighbors, and similarity measures. Within the database, distributions of all pairwise NOAEL differences are binned with respect to AQ. The confidence interval (CI) of the NOAEL for the query is then estimated from the distribution. The CI is dramatically narrowed when analogs are constrained to biologically related profiles including toxicity endpoints of nearest neighbors. This method can provide decision-support workflows and systems for new chemicals. Practical assessment cases are presented to demonstrate how this strategy goes beyond conventional in silico approaches. This abstract does not represent Health Canada policies.

191
Adverse Outcome Pathway Modeling from Big Data for Hazard Identifications by a Knowledge-Based Deep Neural Network Approach

Heather Ciallella[1], Daniel Russo[1], Lauren Aleksunes[2], Fabian Grimm[3], Hao Zhu[1,4]

[1]Center for Computational and Integrative Biology, Rutgers University, Camden, NJ, USA. [2]Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA. [3]ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA. [4]Department of Chemistry, Rutgers University, Camden, NJ, USA

Abstract

Traditional experimental testing to identify endocrine disruptors that enhance estrogenic signaling relies on expensive and labor-intensive low-throughput experiments. Existing computational models for predicting estrogenic potential are limited by presenting black-box predictions or requiring experimental data. Deep learning has unique advantages for processing the rapidly growing human and environmental health big data landscape. However, its application in the evaluation of heterogeneous data for toxicology is currently limited. We sought to design a knowledge-based deep neural network (k-DNN) approach to reveal and organize relevant public big data for compounds with nuclear estrogen receptor alpha and beta (ERα and ERβ) binding potentials. The target activity was rodent uterotrophic activity driven by ERα/ERβ activation. The input data for each of the 42 training chemicals included 43 high-throughput assay results, 1,027 chemical fragments, and expert knowledge to classify the input data based on toxicological mechanisms. After training, the network successfully inferred critical relationships among ERα/ERβ target assays, shown as weights of 6,521 edges between the k-DNN's 1,071 neurons. The network mimics an ERα/ERβ agonism adverse outcome pathway (AOP) for predicting estrogenic potential. The k-DNN's predictions for 88% of correctly-identified uterotrophic training chemicals were clearly based on the activation of neurons representing Key Events in the ERα/ERβ AOP. Therefore, this k-DNN model is a virtual AOP of rodent uterotrophic activity, capable of prioritizing new estrogenic chemicals (AUC=0.937). This k-DNN method is a potential universal computational toxicology strategy to utilize public big data to characterize hazards and prioritize potentially toxic chemicals.

200
Aligning data from public and proprietary sources to develop federated QSAR models

Adrian Fowkes, Robert Davies, Jeffery Plante, Thierry Hanser

Lhasa Limited, Leeds, United Kingdom

Abstract

One of the remaining challenges facing the development of QSAR models is leveraging the full breadth of relevant data. Despite the increase in publicly-available bioactivity databases, much data continues to reside in private data silos. This landscape hinders the development of useful models, by limiting arguably the key ingredient to model building: the data. Federated learning provides a mechanism to distil knowledge from multiple data sources, including proprietary ones, without loss of confidential information. This approach provides an attractive method to develop models which have learnt from a wide pool of data.

A consortium of pharmaceutical companies has been established to develop the infrastructure required for federated QSAR models for secondary pharmacology endpoints. To enable efficient model training, data curation guidelines were generated to align data throughout the consortium members. The approach requires an understanding of the assays used to identify activity and knowledge of how predictions are used in downstream decision making. These guidelines were also used to integrate distributed and heterogeneous data from the public domain (e.g. ChEMBL, ToxCast) into the federated learning approach. Using hERG inhibition as an example, a federated QSAR model outperformed all models trained from a single source of data, when challenged with an external test set. The consortium is demonstrating how data from a variety of partners can be used in a pre-competitive manner, to generate QSAR models with greater bioactivity knowledge for unexplored chemical space.

252

In silico and cheminformatics enrichment analysis to increase confidence in *in vitro* high-throughput screening results: Application to Tox21 thyrotropin-releasing hormone receptor (TRHR) assay

Mahmoud Shobair[1], Daniel Chang[1], Ryan Lougee[2], Katie Paul Friedman[1], Christopher Grulke[1], Jinghua Zhao[3], Ruili Huang[3], Menghang Xia[3], Ann Richard[1]

[1]Center for Computational Toxicology and Exposure, Office of Research and Development, US Environmental Protection Agency, Durham, NC, USA. [2]Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN, USA. [3]National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA

Abstract

Despite progress in applying high-throughput screening (HTS) technologies to toxicology, exemplified by the Tox21 and ToxCast programs, the challenge of relating biochemical outputs to molecular initiating events (MIEs) and adverse outcome pathways (AOPs) remains challenging. To increase confidence in HTS results for hazard evaluation, a structure-based data enrichment and knowledge contextualization workflow was developed to identify likely false positives and discriminate true receptor binders. The tiered approach was used to evaluate in vitro Tox21 assay quantitative HTS data for the thyrotropin-releasing hormone receptor (TRHR), an MIE in the thyroid hormone AOP. The tiered approach: 1) identifies structure-activity patterns using chemotype-enrichment analysis; 2) filters actives due to cytotoxicity and assay interference; and 3) uses 3D pharmacophore modeling to prioritize chemicals capable of binding to TRHR. Results from TRHR competitive binding literature studies were curated as a training set for pharmacophore modeling, the latter indicating that less than 11% of Tox21_TRHR actives contain TRH-like binding features. Results from these structure-based analyses were combined into a tiered, decision-tree workflow and applied to the Tox21_TRHR dataset, first to prioritize potential true positives within the agonist and antagonist “actives”, and second to identify a small set of potential false negatives with compelling structure-based evidence for true activity. The presented workflow is grounded by structural determinants directly related to relevant signals in experimental results and can be generalized to other HTS datasets to increase the value of in vitro data for chemical prioritization. This abstract does not reflect EPA policy.

256
OrbiTox – A Platform for Translational Discovery and Cheminformatics Applications

Alexander Sedykh[1], Austin Ross[1], Ruchir Shah[1], Kristine Witt[2], Warren Casey[2], Vijay Gombar[1]

[1]Sciome LLC, Research Triangle Park, USA. [2]National Institute of Environmental Health Sciences (NIEHS), Division of the National Toxicology Program (NTP), Research Triangle Park, USA

Abstract

OrbiTox has been developed as a translational discovery platform projecting high-dimensional data from different domains (chemical, gene, pathway, species) in concentric 3D globes to enable interactive viewing of data and inter-relationships among them. With special emphasis on predictive toxicology, OrbiTox houses tens of millions of experimental and modelled data-points and data gap-filling predictive models for *in silico* profiling and read-across assessments.

The current version of OrbiTox contains ~900,000 substances, ~ 25,000 fully annotated human genes, ~2000 pathways with functional annotation, and 36 species on which toxicity tests have been done. This unique arrangement of data and connections made across data domains in OrbiTox enables knowledge extraction previously very onerous to get. For example, for a given disease pathway one can easily identify participating genes and investigate chemicals that impact the functions of such genes.

OrbiTox also has 41 QSAR models for Tox21 assays, which have been built using recursive partitioning (RP) and our recently developed interpretable 834 molecular features (*Saagar*) to provide chemistry-backed reasoning of each prediction (DOI: 10.1021/acs.chemrestox.0c00464). For these RP-*Saagar* models, the AUROC in 5-fold cross-validation was 0.58 – 0.94 (mean 0.72) at 10uM, and 0.55 – 0.91 (mean 0.70) for 100uM threshold models. In comparison, these models are better or as good as those developed with Mordred descriptors (the average absolute difference in AUROC = 0.02) but have a unique advantage of directly relating chemical substructures and motifs to the predicted outcome providing structural clues that are responsible for key interactions with Tox21 assay targets.

260
Toxicity Prediction using Locality-Sensitive Deep Learning

Xiu Huan Yap, Michael Raymer

Wright State University, Ohio, USA

Abstract

Predicting chemical toxicity from molecular descriptors and fingerprints using QSAR models is well-approximated on a 'small-scale', local level of similar chemicals derived from the same base structure, but not on a global level spanning a chemical library. Nevertheless, a global model may be desirable as it has a wide applicability domain and can be applied to many classes of chemical compounds. We hypothesize that a machine learning model which recognizes location-dependent feature-target relationships will apply well to this problem. Hence, we propose a feed-forward neural network with an attention mechanism (Vaswani et al., 2017), which we refer to as Locality-Sensitive Deep Learner, that is designed to implicitly recognize local feature-target relationships.

After validating the Locality-Sensitive Deep Learner on carefully constructed synthetic data, we compared its performance against a feed-forward neural network with similar complexity in terms of depth and number of trainable parameters, on the Tox21 chemical toxicity dataset. In our preliminary tests, we observed a marginal increase in test AUC score of 0.44% averaged over 12 toxicity labels, with a maximal improvement of 5.2% for PPAR-gamma. Distances between attention scores also correlated with tanimoto distances ($R=0.098$, $p<1E-32$), suggesting that attention scores are related to locality and proximity between chemicals. Besides its potential predictive capacity, this global model may be a data-driven tool for prospectively identifying relevant chemicals for further QSAR modeling.

Vaswani et al., 2017. Attention Is All You Need. arXiv:1706.03762 [cs.CL]

262
Atomic contribution mapping and exploration with reverse fingerprinting (ACME-RF): Assigning toxicological endpoints to chemical structure at atomic resolution

Rocky Goldsmith[1], Chris Williams[2]

[1]US-Environmental Protection Agency, RTP, USA. [2]Chemical Computing Group ULC, Montreal, Canada

Abstract

Purpose: In silico tools and models for assessing activity are usually defined by endpoints and quantitative structural metrics. Although it is useful to obtain categorical/continuous estimates of activity, traditional SAR provide limited guidance as to the molecular moieties giving rise to the endpoint. Reverse-fingerprinting (RF), provides a useful marriage between discretized endpoints and feature-based molecular fingerprint. RF produces both a quantitative and visual representation of atomic contribution to an endpoint, mapped on to structure (Williams C, 2009 PMID: 19442069). Here we introduce the concept of atomic contribution mapping and exploration (ACME) using the RF framework.

Method: Using public datasets, we explore three different ACME-RF examples. First, we demonstrate the rapid identification of a class of pyrethroid acaricide that is not-toxic to honeybees while still being toxic to the varroa mite using very basic insecticide-class information of 80 pyrethoids as inputs. Second, we used the ToxCast NVS_NR_hER dataset (165/2645) to build a RF model that was used to identify the toxicophore of hER-a that directly map to known crystal structures. Finally, we explore photostability half-lives (Blum, Kristin M. 2013) and identify critical photolabile moieties.

Results/Conclusions: Using ACME-RF we identified and visualized moieties of molecules that resulted in (I) apical endpoints across species (II) chemical-biological interactions and (III) photodegradation liabilities. The method can be used to identify toxic chemicals and critical toxicophore fragments or sub-structures essential for molecular discovery and de-risking.

[This abstract solely represents the views of the authors and not the view of the Agency.]

305
Computing Fingerprints for PubChem Bioassays to Enable Clustering, Better Searching and Mechanistic Insights in Chemical Toxicities

Suman Chakravarti

MultiCASE Inc, Beachwood, USA

Abstract

We are reporting computational techniques to generate dense, continuous fingerprints for about a million PubChem bioassays using Word Embedding techniques borrowed from the natural language processing (NLP) field. These fingerprints allow a variety of useful and interesting operations, e.g., computing similarity between two assays, searching for bioassays using approximate and conceptual keywords, clustering and visualizations to identify assays that target similar biological or toxicological events. Word embedding connects keywords that are otherwise computationally difficult to spot, e.g., carrageenan and antianalgesic. Similarity between assays help in the identification of discriminatory in-vitro assays for complex toxicological end points, e.g., drug induced liver toxicity, phospholipidosis etc. We will present techniques that use a set of chemicals, accompanied by activity in an apical toxicological endpoint, to find PubChem bioassays that discriminate toxic and non-toxic chemicals. We hope that these methods will help fill data gaps, enhance read across and provide mechanistic insights.

343
Dynamic Classification for Chemoinformatics and Materials-Informatics

Abraham Yosipof

College of Law & Business; Faculty of Information Systems and Computer Science, Ramat Gan, Israel

Abstract

The ever-growing data acquisition speed represents a challenge for data analysis in Chemoinformatics and Material-informatics. This is because many unsupervised and supervised learning algorithms require model re-derivation when presented with new samples that are markedly different from those used for model construction. Dynamic segmentation addresses this problem by continuously updating the clusters structure, for example, by splitting old clusters or opening new ones, as new samples are presented. In this work, we present the application of a Dynamic Classification Unit (DCU) to the study of the chemoinformatics and Material-informatic space. Using different databases we demonstrate that the DCU algorithm when initiated with a small training set (~10% of the database) correctly classified ~80% of the remaining, ~90% samples. At the same time, the algorithm unveiled the presence of interesting trends, outliers, and activity cliffs.

285
Assessing and Improving Confidence in a Novel Scheme to Group Chemicals for Ecotoxicological Endpoints

David Ebbrell[1], Franklin Bauer[2], Bruno Campos[3], James Firman[1], Steve Gutsell[3], Geoff Hodges[3], Judith Madden[1], Jayne Roberts[3], Maria Sapounidou[1], Paul Thomas[2], Mark Cronin[1]

[1]Liverpool John Moores University, Liverpool, United Kingdom. [2]KREATiS SAS, L'Isle d'Abeau, France. [3]Unilever Safety and Environmental Assurance Centre, Sharnbrook, United Kingdom

Abstract

A novel approach to assess the confidence in structural alerts for (eco)toxicology has recently been developed. This study has applied this approach to a recently published scheme for the classification of mode of action for environmental toxicity (https://doi.org/10.1021/acs.est.0c06551). The classification scheme unifies and extends existing schemes through linkage to AOPs and taxonomic level being based on three broad domains of toxic action representing narcosis, reactive and specific mechanisms. The scheme is organised at three further levels of detail to separate out mechanistic group, specific mechanism and the Molecular Initiating Events (MIEs) responsible. The purpose of the study was to determine the level of evidence that is associated with an alert that may be used for grouping of a chemical, and hence support the justification of grouping for environmental effects. In total over 230 structural alerts based on experimental ecotoxicological studies, for the 63 MIE groups, were coded in SMARTS strings for the classification of the environmental effects of compounds across multiple species. Alerts were assessed against twelve criteria in order to assess uncertainty associated with structural alerts for toxicity based around: the definition of the alert, the supporting toxicity data and evidence, species relevance, mechanistic interpretation, metabolism, coverage and performance. The scheme enabled a succinct evaluation of alerts demonstrating confidence that may be associated with them, as well as areas where further information could strengthen their use for a particular purpose.

206
New SAR modelling approach accounting for the kinetics of metabolism and adduct formation with Proteins/DNA

Hristiana Ivanova[1], Sabcho Dimitrov[1], Petko Petkov[1], Gergana Dimitrova[1], Elena Kaloyanova[1], Chanita Kuseva[1], Terry Schultz[2], Ovanes Mekenyan[1]

[1]Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria. [2]The University of Tennessee, College of Veterinary Medicine, 2407 River Drive, Knoxville, TN 37996-4500, Tennessee, USA

Abstract

Current (Q)SAR models for predicting chemical toxicity are based on presence/absence of alerts, i.e. the positive effect is assigned only if alerts for the interaction of chemicals with macromolecules are identified in the parent molecule or in some of the metabolically activated products. Such systems, do not consider the kinetics of metabolism and formation of protein/DNA adducts. As a result, the concept of presence/absence of alert produces false positive predictions for classes of chemicals. The aim of the current work is to introduce a new modeling concept for predicting hazard endpoints, and specifically skin sensitization and mutagenicity. In turn, this requires building of kinetic models for predicting metabolism and magnitude of formed adducts over time. According to this new concept to estimate the potency of the effect along with the presence/absence of reactive functionalities, one should also estimate the amount of protein/DNA adducts formed. Based on the estimated amounts, empirically-defined thresholds for positive effect associated with the alerts are introduced to separate chemicals with different potency, e.g. positive vs. negatives. Thus, despite the presence of alert, if the amount of the adducts is below the quantity threshold, chemicals will be predicted with low potency, i.e. negatives. Hence, in the new modelling concept presence of alert is necessary but not sufficient reason for predicting positive effect. The performance of skin sensitization and mutagenicity predictions after implementation of the new modeling concept will be demonstrated.

213
Automated read-across workflow for predicting acute oral toxicity

Stela Kutsarova, Daniela Nedelcheva, Aysel Mehmed, Marin Georgiev, Todor Petkov, Stoyanka Stoeva, Ovanes Mekenyan

Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria

Abstract

The *in silico* prediction of acute oral toxicity (AOT) is a difficult task due to the biologically complex nature of the studied endpoint and the variability of experimental data. Earlier we developed TIMES AOT model v.13 for predicting acute oral toxicity based on a category approach [1]. This model provides high accuracy of the predicted LD50 value and mechanistic transparency of the predictions. However, due to the conservative application of the structural similarity criteria for analogue search the model is characterized by a restricted applicability domain. In the current work an automatic workflow for predicting AOT is developed using the OECD QSAR Toolbox platform, a workflow editor functionality and available profiling tools. The array of reactivity mechanisms was identified using a training set with over 10 000 chemicals. Here, the primary categorization of chemicals is based on the protein binding mechanisms [2] and other reactivity mechanisms which are specific to AOT, such as receptor-mediated effects and mitochondrial uncoupling. A step-wise logic is applied dividing the database into local training sets based on the presence of alerts for protein binding or specific AOT reactivity mechanisms found in the parent chemicals or after their abiotic or *in vivo* (rat) activation. The model provides predictions for fast hydrolysing chemicals. The applicability domain of the model, assessed by the total coverage of the training set, is 96 %, whereas its read-across predictability is 89 %.

1. Nedelcheva D. *et al*., *Comp Toxicol*, 2019, 12, 100-109
2. Wilson D. *et al.*, *Applied in vitro Toxicology*, 2018, 4 (2), 214-219

299
Application of Open-Source PBPK Models in Rat-to-Human Pharmacokinetic Extrapolation of Oral Nicotine Exposures

Jingjie Zhang[1], David Hines[2], Xiaoqing Chang[2], Shannon Bell[2], Armin Salehi[1], Kyeonghee Lee[1]

[1]Altria Client Services LLC, Richmond, USA. [2]Integrated Laboratory Systems, Research Triangle Park, USA

Abstract

Physiologically based pharmacokinetic (PBPK) models developed based on animal data can be used to predict chemical specific kinetics in humans considering interspecies differences in physiology or exposure scenarios. In this study, we first utilized an open-source PBPK model to simulate rat plasma nicotine profiles following 7-day gavage dosing of nicotine formulation (18% nicotine up to 8mg/kg/day). We used the rat-parameterized PBPK model to predict human-relevant nicotine plasma concentrations from oral nicotine product (gum) exposures. For human exposures, the rat-optimized gavage model underpredicted the maximal plasma concentration (C_{max}) of nicotine as measured during human gum use. Lacking experimental data from rat "buccal" dosing, we simulated human kinetic profiles using the rat model with gut absorption adjustment ("oral-absorption adjusted"). The simulated results showed a nicotine C_{max} ~3-5 times higher in the human nicotine gum users than in the gavaged rats for the same daily dose. We hypothesized that this discrepancy in C_{max} and absorption rate is due to the difference in the route of nicotine uptake between the rat gavage dosing and human oral product use. To approximate the impact of bypassing initial liver metabolism in the human exposure route, we used the "IV-buccal adjusted" model to correct for partitioning of nicotine directly from the mouth to the plasma. The "IV-buccal adjusted" model results were comparable to a custom nicotine-specific model and approximated the human data. These results suggest understanding species-specific nicotine product characteristics, dosing routes and uptake mechanisms are critical in estimating human relevant exposure from animal experiments.

370
QsarDB – new features for organizing and accessing in silico models

Geven Piir, Sulev Sild, Uko Maran

Institute of Chemistry, University of Tartu, Tartu, Estonia

Abstract

QSAR DataBank (QsarDB) provides an open digital data exchange standard and associated tools that enable research groups, project teams and institutions to share and represent (Quantitative) Structure-Activity Relationships ((Q)SAR) data and models. QsarDB is a practical resource and tool for the QSAR community and is designed for models produced with all statistical and mathematical algorithms that qualitatively or quantitatively express the relationship between the chemical structure and the propertie(s) of a compound or material. These properties can belong any of the wide group of endpoints: physical and chemical properties, ecotoxicity, environmental fate, human health and toxicokinetics endpoints. QsarDB advances QSAR best practices in collecting, systematizing, and reporting data, thereby reducing the time to decision. QsarDB makes the results of in silico modelling work transparent, reproducible and accessible. QsarDB is comaptibel with QSAR reporting guidelines as recommended by OECD and EU REACH regulations (QMRF and QPRF). The models are represented in the QsarDB data format and can be browsed, searched and downloaded. In addition, it offers integrated services, such as model analysis and visualization and making predictions. QsarDB unlocks the potential of descriptive and predictive in silico (Q)SAR models by allowing new and different types of collaboration between model developers and model users. QsarDB makes data and models FAIR (Findable, Accessible, Interoperable, Re-usable) by giving access to over 500 QSAR-s. The poster presentation gives overview of recent developments: new models, new applicability domain features, integration of descriptor calculators, integration with other tools (e.g. OECD QSAR Toolbox, etc).

June 8th, 2021

Development, Evaluation and Application of QSARs and Thresholds of Toxicological Concern (TTC)

329
Enhancing Carthew's inhalation TTC – developing an exposure-based waiving approach for inhalation exposure safety evaluation

Nikaeta Sadekar[1], Kaushal Joshi[1], Mihir Date[1], Manoj Kumar[1], Jane Rose[2], Anne Marie Api[1]

[1]RIFM, Woodcliff Lake, USA. [2]Proctor and Gamble, Seattle, USA

Abstract

Safety evaluation of inhaled substances is challenged by limited existing inhalation data and limitations in generating new data. However, the current *in vivo* inhalation exposure data may be valuable as a combined resource. One such combined dataset, published by Carthew et al. in 2009, has been accepted as a part of the RIFM's safety assessment process, specifically for the local respiratory toxicity endpoint. With the absence of *in vivo* inhalation toxicity data and standardized and validated *in vitro* models, this exposure-based waiving approach is recognized as an effective alternative to animal testing. Due to its strategic importance, RIFM is working to enhance Carthew's inhalation TTC by increasing the number of materials in the inventory and refining the approach. The inventory consists of 200+ inhalation studies, over two times the amount of Carthew's. This dataset excluded certain chemical classes such as heavy metals, inorganics, organophosphates. The studies were evaluated considering the species, exposure concentrations, mode and duration of exposure, effect levels identified, and include detailed observations in the respiratory tract and evaluations for systemic endpoints. Categorization of the current inventory was based on the Cramer classification system, similar to Carthew's approach. Considering that the Cramer decision tree was designed using the systemic effects, evaluating local respiratory effects may require a different categorization process. Machine learning techniques offer an alternative way of categorizing chemicals specifically for local respiratory toxicity effects. The renewed interest in inhalation TTC indicates the need for a broader collaborative approach to establishing relevant inhalation thresholds.

275
Extension of the Carcinogen Dose-Response Database to Support Threshold of Toxicological Concern (TTC) Analyses

Mark Cronin[1], Samuel Belfield[1], Sylvia Escher[2], James Firman[1], Jie Lieu[3], Cyril Marsaux[4], Aleksandra Mostrag[3], Katarzyna Przybylak[1], James Rathman[3,5], Aleksey Tarkhov[5], Chihae Yang[3,5]

[1]Liverpool John Moores University, Liverpool, United Kingdom. [2]Fraunhofer Institute for Toxicology and Experimental Medicine, ITEM, Hanover, Germany. [3]Altamira LLC, Columbus, OH, USA. [4]ILSI Europe a.i.s.b.l., Brussels, Belgium. [5]Molecular Networks GmbH, Nuremberg, Germany

Abstract

A freely available and well curated database of carcinogenicity potency has been developed. The new database has extended the existing compilation by the addition of new data for more than 60 compounds from the National Toxicology Program (NTP), EFSA DARS and other publicly available sources. There was thorough curation and quality control of existing and new data to a common standard. The new database is intended to support the development of Thresholds of Toxicological Concern (TTC) for carcinogens. Compounds were evaluated based on potential genotoxic or non-genotoxic carcinogenicity using either existing *in vitro* and *in vivo* genotoxicity (mutagenicity or clastogenicity) data (where available)

or *in silico* models using structural alerts and QSARs for DNA reactivity. Points of Departure were calculated as both TD50 and benchmark dose levels (BMDL). Using data extracted from the database, TTC values were explored to demonstrate the conservative nature of the existing thresholds. Further the database has been made available for other initiatives to further explore TTC values for non-genotoxic carcinogenicity. The funding of CEFIC Project LRI-B18 is gratefully acknowledged.

364
Are Non-Genotoxic Tumorigenic Substances Adequately Covered in the Current TTC Approach?

Monika Batke[1], Fatemeh Moradi-Afrapoli[1], Rupert Kellner[1], Mark T. Cronin[2], Chihae Yang[3], James Rathman[4], Sylvia E. Escher[1]

[1]Fraunhofer ITEM, Hanover, Germany. [2]Liverpool John Moores University, Liverpool, United Kingdom. [3]Molecular Networks, Nuremberg, Germany. [4]Altamira LLC, Columbus OH, USA

Abstract

This study aimed to identify the most sensitive dose descriptor after chronic oral exposure for non-genotoxic carcinogens. Using the recently extended Cancer Potency Database, 232 compounds were classified as non-genotoxic carcinogens, using a straightforward decision tree. Following a detailed review of peer-reviewed publications, experimental and predicted data, the dataset was reduced to 137 organic compounds, excluding non-carcinogens, inorganic and genotoxic compounds.

NOAEL values were derived from 689 studies with repeated oral exposure (483 chronic and 206 subchronic studies) using high quality data from the RepDose, ToxRef and COSMOS databases or literature. NOAELs were compared based on either the most sensitive i) adverse apical effect in the entire study; ii) non-neoplastic lesions; or iii) neoplastic lesions. Study quality was considered as one potential confounder.

To distinguish the most sensitive point of departure for risk assessment, the study NOAELs were plotted against the effective tumour dose (ETD_{10}) and the benchmark dose level ($BMDL_{10}$) calculated by model averaging. The comparative analysis between NOAEL/EDT_{10} and $BMDL_{10}$ values revealed that bioaccumulating substances and steroids were among the 5% most toxic compounds. Exclusion of these compounds led to comparable 5th percentiles for chronic NOAELs/$BMDL_{10}$ values, whereas the 5th percentile EDT_{10} is about three times higher. A statistical significant difference was, however, not detected.

These results were evaluated with regard to the current threshold of toxicological concern (TTC) supporting the application of Cramer Class thresholds to non-genotoxic tumorigen substances. This work received funding from the CEFIC LRI B18_2 project.

312
Predicting N-Nitrosamine Activity from Structure-Activity Relationships

Kevin Cross[1], David Ponting[2]

[1]Leadscope, Inc., Columbus, USA. [2]Lhasa Limited, Leeds, United Kingdom

Abstract

N-Nitrosamine impurity levels in pharmaceutical drug substances and products is guided by the ICH M7 guideline stating that the Threshold of Toxicological Concern (TTC) may be used to generate a toxicity limit, or a class-specific limit may be applied depending on the type of structural alert. The EMA, U.S. FDA and other regulatory agencies around the world have set provisional daily acceptable intake (AI) limits for *N*-nitrosamines based upon rodent carcinogenicity TD_{50} values for experimentally measured *N*-nitrosamines; where no experimental data exist, close analogs may be used or a class-specific

TTC. To address whether *N*-Nitrosamine carcinogenicity can be better predicted for regulatory purposes, an *ad hoc* workgroup of over 20 companies and universities has been established to address several scientific and regulatory issues. These include: identification of *N*-Nitrosamine mutagenicity and carcinogenicity reaction mechanisms, collection of all relevant experimental data, development of structure-activity relationships (SARs) consistent with mechanisms, identification of *N*-Nitrosamine carcinogenicity potency categories from SARs, and more precise methods for calculating acceptable intake limits for *N*-Nitrosamines based upon mechanistic analogs. This presentation will describe this collaboration and review our progress made towards development of mechanistically robust structure-activity relationships. Additionally, we propose an alternative approach in order to make the risk assessment of *N*-Nitrosamines more precise by first establishing the dominant reaction mechanism prior to retrieving an appropriate set of close analogs. The TD50 of the most relevant analog from this set may be used for calculating acceptable intake limits. Barring that, an established default TD50 value for the analog group may be used.

282
IN SILICO NETWORK ASSEMBLY OF LITERATURE DATA TO SUPPORT HAZARD IDENTIFICATION OF CARCINOGENS

Bernice Scholten[1], Laura Guerrero Simón[1], Roel Vermeulen[2], Jelle Vlaanderen[2], Anjoeka Pronk[1], Benjamin M. Gyori[3], John A. Bachman[3], Shaji Krishnan[1], Rob Stierum[1]

[1]Research Group Risk Analysis for Products in Development, The Netherlands Organisation for applied scientific research (TNO), Utrecht, Netherlands. [2]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands. [3]Laboratory of Systems Pharmacology, Harvard Medical School, Boston, USA

Abstract

Hazard identification of chemicals can be supported by mechanistic data. However, the volume and variety of the data is large, challenging its use in risk assessment. Here, we studied if evidence building for hazard identification can be made more efficient through automated machine reading of biomedical publications with network visualization. We focused on the 10 key characteristics (KCs) of carcinogens concept as these are supported by well-described literature search terms (Guyton et al., 2018). 10 compounds were selected for which the carcinogenicity hazard has been identified by IARC, including a mechanistic evaluation considering KCs. We used the Reach natural language processing system with Integrated Network and Dynamical Reasoning Assembler framework to extract knowledge from publications and assemble biological networks. From the retrieved literature, causal relationships were extracted and transformed into statements. Per chemical *plus* KC combination, the statements were assembled into networks and compared to the expert evaluation on the KCs. Seventy networks were generated. In general, larger networks with higher belief scores (a measure indicating more evidence supporting a statement) were obtained for those KCs that were evaluated to have strong evidence of being activated. Our methodology likely improves the efficiency for the evaluation of mechanistic data for hazard identification (here KCs). The approach could potentially be used to prioritize KCs and underlying biological processes for further review, and create an inventory of available studies to be further evaluated by an expert committee.

Guyton et al., (2018). Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification. https://doi.org/10.1093/carcin/bgy031.

Emerging Issues

261
Inverting the SAR paradigm: Applications of a Chemotype-Enrichment Approach within EPA's Computational Toxicology Programs

Ann Richard[1], Ryan Lougee[2], Christopher Grulke[1], Jun Wang[1], Mahmoud Shobair[1], Grace Patlewicz[1], Chihae Yang[3]

[1]US EPA, Durham, NC, USA. [2]ORISE Fellow, Durham, NC, USA. [3]MN-AM, Nürnberg, Germany

Abstract

Traditional structure-activity relationship (SAR) approaches to modeling in toxicology are determined and bounded by the chemical-activity test set, the chemical descriptors used, and the modeling method employed, resulting in models with limited applicability or comparability outside the test set and its bounding conditions. Thus, SAR models in toxicology are effectively siloed into a multitude of separate, non-overlapping applications and fail to effectively build on each other's limited successes. Overcoming the profound data limitations, structural diversity, and mechanistic complexity challenges in this field requires new ways of thinking. The "Comparative QSAR" approach, promoted by the late Corwin Hansch, extracted mechanistic insights by examining patterns of regression coefficients across thousands of fixed-format, linear-regression QSAR models of biological potencies. In effect, diverse QSAR models were compared by projecting them onto an aggregation layer comprised of a small "basis set" of Hansch/Free-Wilson type QSAR descriptors (s.a., logP). A somewhat analogous chemotype-enrichment approach is being applied to a wide variety of binary activity datasets and problems in EPA's ToxCast, Tox21, and computational toxicology research programs. The approach uses a standardized enrichment algorithm and a fixed "basis set" of ToxPrint chemical features to create an aggregation layer on which chemical enrichments across diverse activity datasets can be projected and compared. A series of examples will be presented illustrating the power of the approach to provide chemically intuitive results whereby weak chemical-activity signals are amplified within local chemical domains, and global patterns are extracted from diverse activity datasets. *Abstract does not represent EPA policy.*

328
QSAR approaches for safety assessment of nanomaterials: how FA(I)R are we?

Cecilia Bossa[1], Cristina Andreoli[1], Martine Bakker[2], Flavia Barone[1], Isabella De Angelis[1], Nina Jeliazkova[3], Penny Nymark[4,5], Chiara Laura Battistelli[1]

[1]Istituto Superiore di Sanità, Rome, Italy. [2]National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands. [3]Ideaconsult Ltd., Sofia, Bulgaria. [4]Misvik Biology, Turku, Finland. [5]Karolinska Institutet, Stockholm, Sweden

Abstract

QSAR methodologies are widely applied to predict the (eco)toxicological effects of chemicals, and their use is envisaged in different regulatory frameworks for filling data gaps of untested substances. However, their application to the risk assessment of nanomaterials is still limited, also due to the scarcity of large and curated experimental datasets. Despite a great amount of nanosafety data having been produced over the last decade, their interpretation, integration and reuse has been hampered by several obstacles, such as poorly described (meta)data, non-standard terminology, lack of harmonized reporting formats and criteria (Jeliazkova-2021).

Recently, the FAIR (Findable, Accessible, Interoperable, and Reusable) principles have been established to guide the scientific community in good data management and stewardship (Wilkinson-2016). Different international projects and initiatives, among which the EU-H2020 Gov4nano project (https://www.gov4nano.eu/), are addressing the challenge of improving nanosafety data FAIRness, for maximizing their availability, understanding, exchange and reuse. Being a relatively young and highly multidisciplinary research area, standardization in nanoscience is particularly challenging.

Although many experimental data on characterization and effects of nanomaterials are produced, the methods, protocols and parameters driving their generation are not fully mature. These efforts are largely supported by the creation of a common Nanosafety data interface (https://search.data.enanomapper.net/) through the eNanomapper database (Jeliazkova-2015).

Critical issues and challenges analysed within the Gov4nano project, on the reuse of genotoxicity data for QSAR approaches, will be illustrated.

Wilkinson M.J. et al. 2016 https://doi.org/10.1038/sdata.2016.18

Jeliazkova N. *et al.* 2021 *submitted*

Jeliazkova N. et al. 2015 http://doi.org/10.3762/bjnano.6.165

Work performed within H2020-Gov4Nano, Grant Agreement-814401.

247
Guidance on the Application of *In Silico* Tools for Benign by Design

Ann-Kathrin Amsel[1,2], Stefanie Lorenz[1], Neele Puhlmann[1], Oliver Olsson[1], Klaus Kümmerer[1,2]

[1]Institute of Sustainable and Environmental Chemistry, Leuphana University of Lüneburg, Lüneburg, Germany. [2]Research and Education Hub, International Sustainable Chemistry Collaborative Centre (ISC3), Lüneburg, Germany

Abstract

The globally increasing chemicalization comes along with increasing pollution of the environment with toxic and persistent chemicals. Therefore, there is the need for combined approaches, tools and metrics to investigate fate, effects and risks of chemicals and pharmaceuticals in the environment for already existing compounds but even more for compounds of the future to meet requirements set by planetary boundaries and upcoming legal frameworks (e.g. Chemicals Strategy for Sustainability towards a Toxic-Free Environment by the European Commission). An important building bloc in this context is that chemicals and pharmaceuticals, which can enter the environment, should be designed at the very beginning to be mineralizable in the environment (Benign by Design, BbD). *In silico* tools have been successfully applied for BbD[1,2,3]. However, there is no guidance for the application of *in silico* tools in BbD approaches, yet. Therefore, the aim of this study is to provide an innovative workflow to help practitioners to make faster and better-informed decisions using *in silico* tools and to apply these in a consistent and confident way in the BbD process. Literature on BbD approaches and *in silico* tools was consulted. Based on these findings, a recommendation how to implement *in silico* tools into a BbD workflow was developed, which helps to better understand and evaluate properties of chemicals and to implement those insights into the benign design of chemicals.

[1]Kümmerer et al., *WO 2019/072905 A1,* (2019).

[2]Leder et al., *Sustainable Chemistry and Pharmacy* **2**, (2015).

[3]Rastogi et al., *Chemosphere* **111**, (2014).

207
Predicting explosive properties of chemicals analyzing thermodynamics and kinetics of the process.

Chanita Kuseva[1], Valentin Marinov[1], Todor Pavlov[1], Todor Petkov[1], Sarah Mullen-Hinkle[2], Tobias Wombacher[2], Wisdom Zhu[2], Michael Siebold[2], Ovanes Mekenyan[1]

[1]Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria. [2]Merck KGaA, Darmstadt, Germany

Abstract

Substances which pose high risk to health, safety, property or the environment when transported are known as “Dangerous goods” and are subject of regulation with main purpose of making transport feasible and safe by reducing risks to a minimum. In this respect, assessing explosive properties of substances is of high concern for many industries. An explosive substance is capable of undergoing exothermic chemical reaction at extremely fast rates. This work is presenting a QSAR model for predicting explosive properties of chemicals consisting of three layers. The first one addresses presence of chemical groups which are necessary but not sufficient condition for bringing explosion. This layer defines the structural domain of model. The second layer addresses thermodynamics of the process and includes simulation of decomposition products, enthalpy of the decomposition reaction and volume of released gases (V). They are used to calculate Power index (PI) – a parameter discriminating explosive from non-explosive chemicals. The third layer addresses kinetics of the process and discriminates chemicals which can explode with less amount of external energy (sensitive chemicals) as compared to the chemicals which need much more energy to explode (non-sensitive). The sensitivity modeling uses impact sensitivity (IS) data which are modeled by quantum chemical indexes associated with the activation barrier of the explosion. Deriving the model and its validation are based on experimental data for heat of formation, heat of explosion, V and IS as found in the literature. The model correctly discriminates explosive from non-explosive substances taking into account decomposition energy for PI.

324
Improving and Updating the Population Life-course Exposure to Health Effects Model (PLETHEM): An Online Tool for PBPK Modeling

Jeremy Fitzpatrick, Salil Pendse, Alina Efremenko, Eric Hack, Marjory Moreau, Patrick McMullen

Scitovation, Durham, USA

Abstract

An outstanding challenge in the acceptance of alternatives to animal testing is the systematic incorporation of computational models into risk-based decision-making pipelines. This can be achieved by linking exposure estimation methods, physiologically based pharmacokinetic (PBPK) modeling, and computational systems biology pathway modeling tools into a standardized framework. To that end, we have developed the Population Life-course Exposure to Health Effects Model (PLETHEM) suite, a modular open source modeling platform that provides users the ability to create, run, share, and audit PBPK models. The platform consists of a database of chemicals, QSAR models, life-stage specific physiological and metabolic parameters needed to parameterize PBPK models, an R-based engine to perform model simulations, and an interactive user interface to define and select parameter sets for the models. PLETHEM implements easy to use interfaces for a generic PBPK model and a high-throughput IVIVE model. The PLETHEM database also incorporates ontogeny profiles for key metabolic enzymes that can be used to calculate in vivo metabolic clearance using measured in vitro clearance. In addition, PLETHEM has an ability to link to several EPA and OECD exposure estimation programs. These models, which estimate exposures in the workplace and the general populations, can be used to drive PBPK model-based estimates of resulting internal exposures to support risk assessments. Recently we have focused on updating the software to include models for several fish species. However our main focus of the update has been to make the online version of PLETHEM (https://www.scitovation.com/plethem/) more user friendly.

Keynote – Dr. Russell Thomas

368
Can toxicology by any NAM be as sweet?

Russell S Thomas

US EPA, Durham, USA

Abstract

The challenges associated with chemical safety testing remain largely the same - tens of thousands of chemicals are currently in commerce, hundreds of more are introduced every year, and only a small fraction of chemicals fully evaluated for potential human health risks. To date, the scientific community has struggled to integrate new approach methods (NAMs) that incorporate technological and computational advances to address these challenges due to the potential public health and regulatory implications of the underlying science, differences across regulatory jurisdictions and societal pressures, and the lack of clear standards for success. To address the challenges in chemical safety, EPA released a comprehensive NAM work plan that integrates regulatory, scientific, and communication strategies and objectives. The talk will provide an overview of the short-and long-term strategies being used by the Agency as well as highlight the on-going multi-disciplinary research being performed to realize the future vision of chemical safety testing. *This abstract does not necessarily reflect U.S. EPA policy.*

Poster Sessions Track 4

274
Is the bacterial reverse mutation assay an accurate predictor for N-nitrosamine carcinogenicity?

Rachael Tennant, Andrew Thresher, David Ponting

Lhasa Limited, Leeds, United Kingdom

Abstract

In light of the discovery of N-nitrosamine impurities in several marketed pharmaceuticals, there is a requirement for further investigation into their mutagenic and carcinogenic activity. Recent regulatory requirements necessitate marketing authorisation holders for human medicines, containing chemically synthesised active substances, to review their products for the possible presence of genotoxic nitrosamines and test extensively where there is a risk.

Mutagenicity data is a core component of the safety assessment data required by regulatory agencies for acceptance of new drug compounds. The OECD-471 bacterial reverse mutation (Ames) assay is the most widely used primary screen to assess drug impurities for potential mutagenic risk to patients and is a first screen for carcinogenic potential. The ICH M7 guideline allows an impurity, even one in the cohort of concern, to be managed by establishing appropriate levels that are expected to pose negligible carcinogenic risk.

Previous literature reports indicated that the Ames test might not be sensitive enough to detect the mutagenic potential of N-nitrosamines in order to accurately predict a risk of carcinogenicity. To explore this hypothesis, public Ames and rodent carcinogenicity data pertaining to the N-nitrosamine class of compounds was collated for analysis. Here we present how variations to the OECD 471-compliant Ames test, including type of metabolic activation, solvent type and pre-incubation/plate incorporation methods, may impact the predictive performance for carcinogenicity. An understanding of optimal conditions for testing of N-nitrosamines may improve both the accuracy and confidence in the ability of the Ames test to identify potential carcinogens.

233
Evaluating the utility of the Threshold of Toxicological Concern (TTC) and its exclusions in the safety assessment of extractable substances from medical devices

Grace Patlewicz[1], Mark Nelms[1,2,3], Diego Rua[4]

[1]US EPA, Durham, USA. [2]ORISE, Oak Ridge, USA. [3]RTI International, Durham, USA. [4]US FDA, Silver Springs, USA

Abstract

The Threshold of Toxicological Concern (TTC) is a pragmatic approach used to establish safe thresholds below which there can be no appreciable risk to human health. Here an inventory of ~45,000 substances was profiled through the Kroes TTC decision module within Toxtree v3.1 to assign substances into their respective TTC categories. 4002 substances were found to be not applicable for the TTC approach. Closer examination of these substances uncovered a number of issues: substances represented in their salt forms were automatically assigned as not appropriate for TTC when many of these contained essential metals as counter ions which would render them applicable for TTC. High Potency Carcinogens and dioxin-like substances were not entirely captured based on the rules implemented in the Toxtree software. Phosphorous containing substances were considered exclusions when many organophosphates would be appropriate for TTC. Refinements were made to the exclusion rules to address these issues. The second component of the study sought to extend the exclusion rules to address application to the many compounds released from medical devices the lack of toxicity data. Additional structural rules were collated to address a broader set of substances for which TTC should not be applicable. The refined rules were applied to the large inventory and the TTC assignments were compared. This case study demonstrated the importance of evaluating the software implementation of established workflows, identified as well as addressed certain limitations and explored potential refinements when applying these concepts to medical devices. *This abstract does not reflect any Agency position*

259
A TTC for acute fish toxicity.

Hans Plugge[1], Nihar Das[1], Jakub Kostal[2]

[1]Verisk 3E, Bethesda, USA. [2]George Washington University, Washington, USA

Abstract

Threshold of Toxicological Concern (TTC) is a concept that has been around for decades in human health sciences and applied here to the entirety of acute fish toxicity data, i.e. establishment of an exposure level below which there would be minimal probability of acute fish toxicity for any chemical. We calculated TTC values for a number of groups using various approaches. These approaches were evaluated using data from a cohort of 69,999 acute fish toxicological assays. This database was normalized for units, exposure duration, QA/QC and duplicates which reduced it to 47,694 assays. Data were not normally but log-normally distributed making geometric means the most appropriate statistical parameter. Thus we developed descriptive statistics using geometric means with 95, 99, and 99.9 % confidence intervals. Similar to PNEC (Predicted No Effect Concentration) derivation, another form of TTC, various safety/assessment/uncertainty factors were applied. Other approaches employed were the calculations of y=0 intercepts, development of 95 and 99.75 percentile cutoff of cumulative data and MUST (Modular Uncertainty Scoring Tool) analysis. The data described here would be most useful in making a binary testing/no testing required decision. For acute fish toxicity, the TTC value of 2 ug/L was most appropriate, based on 95% percentile of data distribution without any assessment factor.

325
Human Relevant Potency Threshold and CompTox Approach for Risk Assessment

Lyle Burgoon[1,2], Satinder Sarang[3], Christopher Borgert[4,5]

[1]Raptor Pharm & Tox, Ltd, Apex, USA. [2]Michigan State University, East Lansing, USA. [3]Shell International, Houston, USA. [4]Applied Pharmacology and Toxicology, Inc, Gainesville, USA. [5]University of Florida, Gainesville, USA

Abstract

Right now, our cellular receptors are bombarded by thousands of chemicals competing for binding to their active and modulatory sites. Most of these chemicals are endogenous ligands, i.e., natural products of our own metabolism. This means that to produce effects through stimulation, inhibition, or modulation of receptor pathways, exogenous chemicals must compete against endogenous ligands for access to those binding sites. Molecular affinity and chemical concentration at the receptor sites are the key determinants of ligand-receptor interactions, including activation/inactivation of the receptor, subsequent signaling, and the resultant potential benefit or adverse effect. Mathematically, affinity and concentration of the chemical are related to chemical occupancy of the receptor site through Michaelis-Menten mechanics. Based on Michaelis-Menten mechanics, there is a threshold potency below which exogenous chemicals are simply unable to compete with the endogenous ligands. This principle has been demonstrated for estrogen receptor alpha where the human relevant potency threshold (HRPT) is 1E-4 relative to 17β-estradiol. The HRPT can be extended to other receptors as well. Here we discuss ways of establishing an HRPT for receptors with endogenous ligands of known tissue/blood concentrations using the Michaelis-Menten model and provide an update on our ongoing work in establishing HRPTs for various receptors. We will also demonstrate how computational toxicology predictions of receptor affinity, as well as bona fide affinity values, are used with the HRPT to make a determination about the potential hazards of a chemical given particular use and exposure scenarios.

330
QSTR Modeling for Quantitative Toxicity Prediction using DFT for Carbamate Compounds

Emma Herenis Acosta, Julián Cruz Borbolla, Rosa L. Camacho Mendoza, Simplicio González Montiel

Universidad Autónoma del Estado de Hidalgo, Mineral de la Reforma, Mexico

Abstract

In this work we proposed a new model using a genetic algorithms method based on a multiple linear regression analysis, this model predicts the toxicity of carbamate compounds, applying the B3LYP exchange-correlation energy functional with the 6-311G** basis set. The reactivity descriptors such as hardness, chemical potential and electrophilicity are calculated to measure stability and reactive nature of the carbamates. The best model explains 82% of the training set variance (R^2), 72% in terms of Leave-One-Out (LOO), variance (Q^2), and 75% for test set variance (prediction quality, R^2_{pred}). This model might be applicable for determination of toxicity in environment organic compounds, in the case of new or untested chemicals falling within the applicability domain of the model.

331
Expert Review of Cramer Class Predictions under three Toxtree modules.

Rachel Chang[1], Ian Hadley[2], Alexander Alverson[2], Joel Cohen[2]

[1]Gradient, Seattle, USA. [2]Gradient, Boston, USA

Abstract

The Cramer decision tree categorizes chemicals into three structural classes with corresponding hazard potential and established thresholds of toxicological concern (TTC) for systemic toxicity (excluding mutagenic carcinogenicity). These

TTC values represent exposure levels with no appreciable risk to human health. Therefore, Cramer classification is often used for the purposes of risk assessment to establish safe exposure levels for chemicals lacking comprehensive toxicological data packages. Toxtree is a widely used in silico tool for predicting chemical hazard. In its current version (3.1.0), there are three different modules that each apply the Cramer decision tree:s: "Cramer rules," "Cramer rules, with extensions," and "Revised Cramer Decision Tree.". Here we present five case-study chemicals with varying structural characteristics, and divergences in Cramer classications predicted across the three Cramer decision tree modules. These chemicals are citric acid (CAS No 77-92-9), laurolactam (CAS No 947-04-6), propanoic acid, 2-propenyl ester (CAS No 2408-20-0), 2-pentanone, 4-hydroxy-4-methyl- (CAS No 123-42-2), and cyclohexanone (CAS No 108-94-1). For each chemical we conducted an expert review of the diverging Cramer classifications across the three modules, and compared our conclusions (*e.g*. Class I, II, or III) to existing toxicity data (*e.g*. no observed adverse effect levels from repeat dose toxicity studies). Our findings suggest that no single Cramer decision tree model is more accurate or conservative than another for assessing chemical toxicity. Thus, a multi pronged approach using multiple Cramer decision tree modules followed by expert review is recommended for interperating diverging toxicological hazard predictions made by QSAR tools.

354
New approach methods for developing iTTCs for human health safety assessment

Jon Arnot[1,2], Alessandro Sangion[1], Liisa Toose[1], James Armitage[3], Alexandra Looky[1], Rick Becker[4]

[1]ARC Arnot Research and Consulting, Toronto, Canada. [2]University of Toronto, Toronto, Canada. [3]AES Armitage Environmental Sciences, Ottawa, Canada. [4]American Chemistry Council, Washington, USA

Abstract

The Threshold of Toxicological Concern (TTC) can be used to address hazard data gaps. In absence of chemical-specific toxicity data, the TTC approach provides an estimate for a level of exposure in which no appreciable human health risk is expected. Most current TTCs are derived from exposure-route specific toxicity experiments, e.g., oral (ingestion) based TTCs. However, humans can be exposed to chemicals from multiple exposure routes simultaneously, i.e., aggregate exposure. Internal TTCs (iTTCs) have been proposed to address this limitation. The objective of this study is to develop and apply a method for estimating iTTCs. We apply a toxicokinetic (TK) model to calculate steady-state whole body and blood concentrations corresponding to oral exposures. As a case study we apply the method to the No Observed Effect Levels (NOELs) used to develop the “Munro TTCs”. The model is parameterized using measured in vivo total elimination rate constants (k_T /day) from rodents (preferentially) or from humans when they are available. In absence of in vivo k_T data, in vitro biotransformation rates and in vitro-in vivo extrapolation (IVIVE) methods are used to parameterize the TK model. In the absence of experimentally based TK data, Quantitative Structure Activity Relationships (QSARs) for predicting biotransformation rates are used to parameterize the TK model. Internal whole body concentrations predicted from the NOELs range from about 10^{-6} to 1 mmol/kg. Predicted blood concentrations range from about 10^{-7} to 1 mmol/L. Tentative iTTCs are calculated from the cumulative distributions. Recommendations for addressing uncertainty in the estimated iTTCs are provided.

322
Skin Permeability Profiler to classify chemicals into categories using structural features and physicochemical properties

Aleksandra Mostrag[1], Tomasz Magdziarz[2], James Rathman[1,3], Chihae Yang[1,3,2]

[1]MN-AM, Columbus, USA. [2]MN-AM, Nuremberg, Germany. [3]Ohio State University, Columbus, USA

Abstract

Skin permeability, irritation and sensitization are key dermal toxicity endpoints important for evaluating risk/safety of topically applied chemicals. Aligned with efforts to reduce animal testing (EU Cosmetics Directive, California Cruelty-Free Cosmetics Act), we present the Skin Permeability Profiler, an in silico tool to classify chemicals according to their ability to permeate human skin into categories (low, medium, high) by applying rules devised to reflect both structural features and physicochemical properties. A training set of 270 chemicals with in vitro Kp data was curated from regulatory sources, databases, and literature. Using ToxPrints, structural features were identified that tend to be associated with structures having low (e.g., phthalates), medium (e.g., carbamates), or high (e.g., phenyl halides) skin permeability. Final rules are defined by these fragments and relevant physical/chemical properties identified via statistical analyses/expert evaluation. For example, the rule set for compounds containing “fused ring – steroid” structural moiety uses the physicochemical properties XlogP and TPSA (topological polar surface area) to predict the skin permeability class. Rules are encoded as new chemotypes using the Chemical Subgraphs and Reactions Markup Language (CSRML) enabling representing both structural and physicochemical information within one object. The Profiler is available via ChemTunes.ToxGPS and can be applied within in silico workflows for holistic assessment of dermal toxicity

323
Mutagenicity potential of substituted quinolines – expert review of in silico predictions

Joel Cohen[1], Rachel Chang[2]

[1]Gradient, Boston, USA. [2]Gradient, Seattle, USA

Abstract

Expert review of *in silico* predictions are considered best practice for making informed hazard and risk conclusions. We present here an ICH M7 compliant mutagenicity assessment for 2,6-dimethylquinoline (2,6-DMQ; CAS No. 877-43-0), highlighting the value in incorporating multiple lines of evidence to justify an overall hazard conclusion. *In silico* mutagenicity predictions were generated using expert-rule programs (Toxtree, Derek Nexus) and statistical based programs (VEGA QSAR, US EPA's TEST, Leadscope). We also conducted a literature review to contextualize *in silico* predictions in order to make an overall conclusion. *In silico* predictions indicate 2,5-DMQ to be a class 4 mutagen (alerting structure in at least one program). However, one pre-GLP Ames assay indicates 2,6-DMQ is not mutagenic, though study details are limited (exposure concentrations are not reported). Furthermore, the mechanism of genotoxic action suggests substitution at certain positions on the quinoline structure can sterically hinder the formation of an electrophilic enamine epoxide, thereby reducing mutagenic potential. This mechanism of genotoxicity (and the possibility for steric hindrance) is supported by experimental findings showing a range of potency across a number of substituted quinoline structures, with reduced mutagenic potential arising from substitution at the 2- and 6-positions. Overall we consider this mechanistic evidence, combined with negative experimental findings for mutagenicity (limited as they may be), support a potential non-mutagenic classification for 2,6-DMQ. This case study highlights the value in expert review of *in silico* predictions, applying multiple lines of evidence to reach a weight of evidence conclusion.

336
QSAR modeling for in vitro human NIS inhibition with blinded external validation and screening of 80,086 REACH substances

Ana C.V. Martins[1], Nikolai G. Nikolov[1], Tammy E. Stoker[2], Jun Wang[2], Eva B. Wedebye[1]

[1]Division of Diet, Disease Prevention and Toxicology, National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark. [2]Neurological and Endocrine Toxicology Branch, Public Health and Integrated Toxicology Division, Center for Public Health and Environmental Assessment, Office of Research and Development, Research Triangle Park, USA

Abstract

Inhibition of the sodium/iodide symporter (NIS) can lead to learning and memory impairment in humans and rats (AOP 54 under development). The aim of this study was to develop global binary QSAR models that can be applied for screening purposes and single-compound identification of possible NIS antagonists. For this purpose, we processed the HTS assays results from U.S EPA's ToxCast Program phases I and II for NIS inhibition to develop the first QSAR model for this endpoint adopting a new curation procedure including tautomer treatment and accounting for volatility and lipophilicity, resulting in a training set of 579 substances (64 actives and 515 inactives). Two models were developed and robustly cross-validated, one with high sensitivity and another with high overall accuracy. The models were subjected to external validation with ToxCast NIS inhibition results blinded to the QSAR developers for 740 E1K substances. The external validation set underwent the same processing as the training set. Next, the training set was expanded with the E1K dataset and two final models were developed and cross-validated, applying the same methods as for the first versions. The final models were used to screen 80,086 REACH substances for NIS inhibition. These QSAR predictions will be published in the free online Danish (Q)SAR Database (https://qsar.food.dtu.dk). Furthermore, the models will be published in the free online Danish (Q)SAR Models, accessible from the Danish (Q)SAR Database, for real-time prediction of user-submitted structures and download of detailed results in the QSAR Prediction Reporting Format.

238
Are (Q)SAR models fit-for-purpose for predicting the mammalian acute oral toxicity of chemicals from the plant protection product industry?

Richard Marchese Robinson, Surya Hari Lal, Katy Bridgwood, William Masinja, Karina Clifford, Sarah Whalley

Syngenta Crop Protection, Product Safety Department, Jealott's Hill International Research Centre, Bracknell, United Kingdom

Abstract

Mammalian acute oral toxicity (AOT) is a major concern informing regulatory decisions regarding plant protection product (PPP) registration and transport of chemicals. Currently, there is no accepted alternative to rodent *in vivo* studies, from which Global Harmonized System (GHS) hazard categories are assigned using LD50 thresholds. However, in early stage research (ESR), it is not feasible to assess all candidate active ingredients using *in vivo* studies. Moreover, for ethical reasons, there is increasing regulatory interest in finding a suitable non-animal alternative, whilst ensuring protection of human health. This presentation examines whether (Q)SAR models implemented in various commercial and freely available software programs are fit-for-purpose to (i) guide ESR projects and (ii) support regulatory submissions, possibly as part of a weight-of-evidence involving expert review. Preliminary results were obtained using a dataset of 657 marketed and proprietary compounds from the PPP sector, associated with a well-defined GHS category (1 – 5 or not classified). Initial results obtained using a commercially available global consensus (Q)SAR model were encouraging. Excluding 21 compounds with out of domain or indeterminate predictions, the average percentage across all categories which were (i) correctly classified (45%, compared to 17% expected from random assignment) or (ii) assigned to the correct or a more conservative category (90%) suggested the models might (i) be useful in ESR and (ii) support a weight-of-evidence approach to assess AOT in a regulatory context. More recently, the test dataset has been updated and in-depth analysis will be presented of predictions from various (Q)SAR models.

255
Chemistry-backed Reasoning of Bacterial Mutagenicity Prediction from *In Silico* Models

Vijay Gombar[1], Alexander Sedykh[1], Ruchir Shah[1], Kristine Witt[2], Warren Casey[2]

[1]Sciome LLC, Research Triangle Park, USA. [2]National Institute of Environmental Health Sciences (NIEHS), Division of the National Toxicology Program (NTP), Research Triangle Park, USA

Abstract

Application of predictive models for profiling chemicals for their toxicity is critical to transition away from animal-based toxicity assessment. In this work we present quantitative structure-activity (QSAR) models to predict Ames mutagenicity using *Saagar* features - our recently published set of 834 substructures designed to facilitate structural interpretation (DOI: 10.1021/acs.chemrestox.0c00464).

The modeling dataset was extracted from the CCRIS Assay ID 1259407 compilation. To better identify intrinsic structural features related to mutagenicity, we only chose compounds assayed in the absence of metabolizing media and on OECD-recommended (Guideline 471) *Salmonella* and *E. coli* strains. Extensive cleaning and harmonization resulted in 3,681 unique compounds (37.6% mutagens). We randomly selected 370 compounds (36.5% mutagens) as the hold-out test set for evaluating model robustness. Models were developed with five-fold cross-validation using popular rule-learning methods, recursive partitioning (RP) and random forest (RF), with default feature selection from *Saagar* substructures and motifs.

Cross-validation yielded an average negative prediction rate of 80.4%, positive prediction rate of 75.2%, specificity of 87%, and sensitivity of 64.9%. The consensus predictions for the hold-out set resulted in similar statistics of 81.1%, 70.1%, 83.8%, and 65.9%, respectively, in line with cross-validation performance and confirming models' robustness. The average ranking performance (by ROC AUC) was 0.793 (0.743 - 0.842; $\alpha = 0.05$).

Saagar features SGR10052 ([OH0]~N) and SGR10039 ([#6;X3]) were found as primary differentiators between mutagens and non-mutagens implicating nitroso and nitro groups, especially as aromatic substituents. This *Saagar*-RP model is a robust predictor of mutagenicity in the absence of any metabolic medium.

288
Permeability prediction models for assessing and grouping the absorption of chemicals in the gastrointestinal tract

Mare Oja, Sulev Sild, Uko Maran

Institute of Chemistry, University of Tartu, Tartu, Estonia

Abstract

Gastrointestinal absorption is one of the most important properties for toxicokinetics and pharmacokinetics. The biopharmaceutical classification system (BCS) is used to evaluate absorption in the gastrointestinal tract (GIT). The BCS makes decisions according to solubility and permeability, which both are influenced by the wide pH-range (3 to 8) in the GIT. Experimental solubility and permeability data in a wide pH-range is scarce and thus computational tools are a suitable alternative to fill the data caps. Such prediction tools are available to predict solubility of a compound over a wide pH-range, but there is no such tool for permeability.

The lack of prediction tools for permeability is caused by missing systematic experimental data in a wide pH-range. The easiest way for obtaining such data is *in vitro* cell-free method, like a parallel artificial membrane permeability assay (PAMPA). Therefore, the caps in experimental permeability data were filled by measuring PAMPA values at pH 3, 5, 7.4 and 9 for 238 compounds. Based on this data, we have developed qualitative and quantitative models, which enable precise prediction of permeability in a wide pH-range. By combining models at different pH-s into a decision tree, 91% of the U.S. FDA reference drug substances can be correctly classified for permeability classes in the BCS, showing the importance of weighted decision over different pH-s. This concludes that the proposed models are an alternative way to fill permeability data caps at wide pH-range, which can be applied for regulatory purposes to describe gastrointestinal absorption for toxicokinetics and pharmacokinetics.

292

First models to predict thermal decomposition properties of possible self-reactive substances based on industrial datasets

Guillaume Fayet[1], Klaus Dieter Wehrstedt[2], Annett Knorr[2], Patricia Rotureau[1]

[1]Ineris, Verneuil-en-Halatte, France. [2]BAM, Berlin, Germany

Abstract

Self-reactive substances are unstable chemical substances which can easily decompose and may lead to explosion. For this reason, their thermal stability properties are required within regulatory frameworks related to chemicals in order to assess their hazardous properties. Due to the fast development and availability of computers, predictive approaches like QSPR models are increasingly used in the evaluation process of hazardous substances complementary to experiments.

In that context, the HAZPRED project (2015-2018) aimed to develop QSPR models to predict physical hazards of substances to fill the lack of knowledge on these hazardous substances quickly.

An experimental campaign, based on 50 samples provided by Industrial producers, was carried out on potential self-reactive substances, for which no QSPR model already existed. Their heats of decomposition were characterized using differential scanning calorimetry in homogeneous experimental conditions.

QSPR models were derived using the GA-MLR method (using a genetic algorithm and multi-linear regressions) using molecular descriptors calculated by Dragon software based on both 3D molecular structures from density functional theory (DFT) optimizations, to access three-dimensional descriptors, and SMILES codes, favoring the access to simpler models, requiring no preliminary quantum chemical calculations. All models respected the OECD validation guidelines for regulatory acceptability of QSPR models. They were tested by internal and external validation tests and their applicability domains were defined and analyzed.

If improved models should be expected with larger database (and a better ratio between size and chemical diversity), these first models already represent a screening tool capable to access early reactive hazards.

334

Predicting liver toxicity and potency using *in silico* chemistry profilers derived from molecular initiating events

James Firman[1], Mark Cronin[1], Aleksandra Mostrag[2], James Rathman[2,3], Chihae Yang[2,3]

[1]Liverpool John Moores University, Liverpool, United Kingdom. [2]Altamira LLC, Columbus, OH, USA. [3]Molecular Networks GmbH, Nuremberg, Germany

Abstract

Chemical-induced liver toxicity represents an area of particularly notable concern, owing both to its potential lethality and to the challenges associated with the early detection of compounds liable to induce it. Many such issues arise from the inherent complexity of the endpoint – a factor which may be addressed through expansion of mechanistic understanding of the pathways underlying emergence of adverse effects. Integral within this is the framing of the molecular initiating event (MIE) – the key primary interaction between xenobiotic chemical and biological system preceding emergence of toxicity. Appreciation of this enables the construction of mechanistically-based *in silico* profilers linking compound structure to definitive adverse outcome. As part of a broader initiative to capture liver toxicity with reference to the MIE, we have recently reported the development of such a set of 15 structural alerts relating specifically to hepatic cholestasis (DOI: 10.1021/acs.chemrestox.0c00465). The purpose of this investigation was to expand upon this basis, incorporating quantitative analysis in order to derive a wider series of potency-based liver toxicity alerts permitting assignment of

NO(A)EL values to matched compounds. It is intended that such a tool may be of use both in the identification of hazard and in the construction of chemical grouping for purposes such as read-across.

319
Predicting dermal absorption for ingredients in personal care products: preliminary validation of IH SkinPerm© model for use in safety assessments

Charlotte Marsh, Jhanel Chew

Gradient, Boston, USA

Abstract

Dermal absorption is a critical yet often overlooked component of safety assessments for topically applied personal care products. Despite the progress made in the area of dermal absorption modeling, no relevant agency has formally accepted QSAR modeling as a valid method to estimate dermal absorption in this context. Instead, prominent regulatory bodies recommend the use of experimental data or the use of conservative default values (e.g. 50%, 100%). We evaluated the IH SkinPerm© v2.0 dermal absorption model as an alternative approach to these default values. In addition, we compared the results from IH SkinPerm to default categories proposed by Kroes et al. (2007), which are based on predicted maximum flux (J_{max}). In this preliminary analysis (n=14), we selected ingredients based on known use in personal care products and availability of relevant experimental dermal absorption data. Ingredients of different functional classes (*e.g*. colorants, preservatives) were included to investigate the applicability of the model across varying physicochemical properties. For IH SkinPerm, duration and loading rate (mg/cm^2) were matched to the approximate test duration and loading rate from the experimental data. We found that in general, IH SkinPerm under-predicted dermal absorption for ingredients with low experimental absorption values and over-predicted absorption for ingredients with higher experimental dermal absorption values. As a conservative screening approach, the Kroes *et al*. (2007) default values consistently over-predicted dermal absorption for all but one ingredient. Future model validation efforts should expand the test set and investigate effects of test vehicle/formulation on dermal absorption.

359
Read-across Prediction of Mutagenicity – In Silico Model Derived From a Data Set of 7719 Organic Compounds

Gerrit Schüürmann[1,2], Ralph Kühne[1], Ralf-Uwe Ebert[1]

[1]UFZ Department of Ecological Chemistry, Helmholtz Centre for Environmental Research, Leipzig, Germany. [2]Institute of Organic Chemistry, Technical University Bergakademie Freiberg, Freiberg, Germany

Abstract

Industrial chemicals produced at or above 1 t/a require assessment of their mutagenic potential. Besides the Ames test as regulatory method of choice, in silico tools often focus on structural alerts alone or in combination with expert systems,1-3 and are recommended for the early drug development phase.4,5 Here we present a new read-across model derived from 7719 organic compounds with Ames test results, featuring 4079 experimentally active and 3640 experimentally non-active substances. The computerized approach is based on atom-centered fragments (ACFs) built from chemical structures, enabling the assessment of chemical similarity in the toxicological context.6 The new model with an overall concordance of 81% outperforms prominent structural alerts. It can be tuned through thresholds for reference similarity and activity variation, yielding up to 94% concordance with reduced application domains. Thus, the model appears promising for both screening-level applications and in order to arrive at predictions with particularly high confidence for chemical compounds sufficiently ACF-similar to substances with sufficiently homogenous test results.

[1] Benigni R, Bossa C 2011. *Chem.* Rev. 111: 2507-2536.

[2] Hsu K-H, Su B-H, Tu Y-S, Lin, OA, Tseng YJ 2016. *PLoS One* 11: e0148900.

[3] Verheyen GR, van Deun K, van Miert S 2017. *J. Genet. Genome Res.* 4: 029.

[4] Amberg A et al. 2016. *Regulat. Toxicol. Pharmacol.* 77: 13-24.

[5] Wichard JD 2017. *Food Chem. Toxicol.* 106: 595-599.

[6] Schüürmann G, Ebert R-U, Kühne R 2011. *Environ. Sci. Technol.* 45: 4616-4622.

Poster Sessions Track 5

304
EPA ORD NaKnowBase (NKB): Nanomaterial Database Development for Access and Collaboration

Bradley Beach[1], weston Slaughter[1], Gayle Chan[2,3], William Boyes[4], Paul Harten[5], Antony Williams[6], Holly Mortensen[4]

[1]US EPA/ORD/CPHEA -ORISE, RTP, NC, USA. [2]Evans School of Public Policy and Governance, University of Washington, Seattle, Seattle, WA, USA. [3]US EPA/ORD/CPHEA -ORISE, RTP,NC, USA. [4]US EPA/ORD/CPHEA, RTP, NC, USA. [5]US EPA/ORD/CPHEA, Cinncinati, OH, USA. [6]US EPA/ORD/CCTE, RTP,NC, USA

Abstract

Engineered nanomaterials (ENM) are being developed for use in a wide variety of consumer and industrial applications. They can exhibit significantly different properties compared to their macro counterparts due to a high surface-area-to-volume ratio, enabling surface properties to dominate over bulk properties. The development and application of these particles is currently outpacing the ability of scientists to test their environmental and human health effects. US EPA has collected its research on nanomaterials into a database, NaKnowBase (NKB), that is currently under development. It is a primary objective of this database to facilitate open science and help fill gaps in understanding of the health impacts of nanomaterials. NKB data focuses primarily on documenting nanomaterial studies including nanomaterial material chemistry. For this data to be useful in exploring the health, environmental, and biological impacts of these nanomaterials, it needs to be easily interoperable with databases that focus on biological and environmental context of materials. The lack of a consistent nomenclature across sources for ENM exacerbates difficulties in efficiently and accurately integrating data from separate data sources. To overcome these barriers EPA ORD has developed a standardized of terminology and data structure system for NKB. Here, we describe recent improvements in consistency and accessibility in Linked Open Data (LOD) formats for NKB, recent updates to an EPA established nomenclature for NaKnowBase nanomaterials, integration with the EPA CompTox Dashboard, and ontological mapping efforts being performed for semantic integration with external datasets. *This abstract does not reflect EPA Policy.*

183
Quantitative Molecular Activity Calculation Using Bayesian Learning Neural Networks

Timothy Allen[1], Alistair Middleton[2], Jonathan Goodman[3], Steve Gutsell[2], Predrag Kukic[2], Paul Russell[2]

[1]MRC Toxicology Unit, University of Cambridge, Cambridge, United Kingdom. [2]Unilever Safety and Environmental Assurance Centre, Sharnbrook, United Kingdom. [3]Department of Chemistry, University of Cambridge, Cambridge, United Kingdom

Abstract

A risk assessment involves comparing the hazard associated with a chemical to the exposure an individual can have to it for the calculation of a margin of safety. Therefore, understanding the numerical values and uncertainty associated with molecular activity is key to producing a robust risk assessment. Currently many predictive *in silico* toxicology algorithms

are based on classification tasks, and hence can only be used for hazard identification. The ability to produce robust numerical activity estimates will be key to the further use of *in silico* methods in the future.

Bayesian learning neural networks have the capacity to help answer this question. By replacing point values at the weights and biases throughout the network with probability distributions, the network can produce a probability distribution as the output prediction. By appropriate training, the output distribution can provide information on the aleatoric and epistemic uncertainty in the prediction. This accounts for both how close the new example is to the existing data and how much variation exists within the training set. These networks produce quantitative activity estimates with errors within one log unit, even on external validation data, and helps distinguish between molecules similar to and different from the training data.

These algorithms can help move computational toxicology towards the requirements for risk assessment. Understanding the uncertainty gives additional benefits, as a lack of knowledge around uncertainty is often cited as an issue in new approach methods. As such, Bayesian learning provides major benefits for the future of *in silico* toxicology.

184
Systematic identification of molecular targets and pathways related to human organ level toxicity

Tuan Xu[1], Leihong Wu[2], Menghang Xia[1], Anton Simeonov[1], Ruili Huang[1]

[1]National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), Rockville, USA. [2]National Center for Toxicological Research, US Food and Drug Administration, Jefferson, USA

Abstract

Mechanisms leading to organ level toxicities are poorly understood. In this study we applied an integrated approach to deduce molecular targets and biological pathways involved in chemically-induced toxicity for eight common human organ level toxicity endpoints (carcinogenicity, cardiotoxicity, developmental toxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, reproductive toxicity, and skin toxicity). Integrated analysis of in vitro assay data, molecular target and pathway annotations from the literature, and toxicity-molecular target associations derived from text mining, combined with machine learning techniques, were used to generate molecular targets for each of the organ level toxicity endpoints. A total of 1,516 toxicity-related genes were identified and subsequently analyzed for biological pathway coverage resulting in 206 significant pathways (p-value < 0.05), ranging from 3 (e.g., developmental toxicity) to 101 (e.g., skin toxicity) for each toxicity endpoint. This study presents a systematic and comprehensive analysis of molecular targets and pathways related to various in vivo toxicity endpoints. These molecular targets and pathways could aid in understanding the biological mechanisms of toxicity and serve as a guide for the design of suitable in vitro assays for more efficient toxicity testing. In addition, these results are complementary to the existing adverse outcome pathway (AOP) framework and can be used to aid the development of novel AOPs. Our results provide abundant testable hypotheses for further experimental validation.

192
Information loss of adverse outcome pathways network in the drug space.

Qier WU[1,2], Youcef Bagdad[1,2], Olivier Taboureau[1,3,4], Karine Audouze[1,2]

[1]University of Paris, Paris, France. [2]Inserm UMR S-1124, Paris, France. [3]Inserm U1133, Paris, France. [4]CNRS UMR 8251, Paris, France

Abstract

Background: Many complex systems in the real word reflect binary nature. In toxicology and pharmacology, bipartite graphs are regarded as a tool to understand the interactions of two sets of elements. Furthermore, bipartite network could be transferred into two monopartite networks depending on the layer of interest. However, the step of keeping as much as

possible information from a bipartite network during monopartite projection remains a tremendous challenge. One way to solve this challenge is to quantify the network reduction, i.e. loss information. Two techniques have been previously developed for network pharmacology, that are “increase of uncertainty” and “loss of coverage”.

Method: In our study, we applied both techniques to explore Adverse Outcome Pathway (AOP) events within the drug space. Drug-AOP event associations were extracted from various data sources to create a bipartite drug-AOP graph. Then key event relationships (KER) were included to enrich the network, allowing to identify more linkage between the AO events, that are molecular initiating event (MIE), key evens (KE) and adverse outcome (AO). Finally, the loss information of the monopartite network of AOP events was quantified.

Result: Our network shows that MIEs and AOs had high information loss during monopartite projection. As examples the event “Activation, 5HT2c” had a high value of loss of coverage, and the AO, the “Cognitive Function, Decreased” had a maximum increase in uncertainty, reflecting the need to be caution for any conclusion from a monopartite projected network due to the limitation of retaining original information.

193
Skin Sensitization Potency of Fragrance Materials Assessed using Kinetic Direct Peptide Reactivity Assay

Mihwa Na, Anne Marie Api

Research Institute for Fragrance Materials, Inc. (RIFM), Woodcliff Lake, USA

Abstract

Currently, several validated non-animal methods are available to assess the skin sensitization potential of chemicals. Each of these assays addresses a specific key event in the adverse outcome pathway (OECD, 2012). The direct peptide reactivity assay (DPRA) and amino acid derivative reactivity assay (ADRA) are validated to test the chemical’s ability to activate the molecular initiating event (OECD TG442C). When used in combination with other non-animal methods, DPRA has been shown to be valuable in hazard identification of skin sensitizers. However, determining the potency of skin sensitizers using non-animal methods remains a challenge. Recently, it was suggested that kinetic DPRA (kDPRA) could be utilized to assign the skin sensitization potency class of a chemical (Wareing et al., 2017). In this modification from the standard DPRA, the chemical’s reaction with a model peptide are measured at multiple concentrations and multiple time points. A rate constant for this reaction has been shown to be a good predictor of the skin sensitization potency (Natsch et al., 2020). Herein, we report data and analysis of 60 fragrance ingredients (49 sensitizers and 11 non-sensitizers) in the kDPRA method, in comparison with existing animal and human data. For this dataset, 12 of the 49 sensitizers and 2 of the 11 non-sensitizers exhibited peptide reactivity. The 14 materials that have shown peptide reactivity were predicted as stronger sensitizers, when compared to the animal and human data for this dataset.

194
Skin Sensitization Potential of Fragrance Ingredients Assessed Using the U-SENS™ Assay

Isabelle Lee[1], Mihwa Na[1], Nathalie Alepee[2], Walter Westerink[3], Irene Eurlings[3], Anne Marie Api[1]

[1]Research Institute for Fragrance Materials, Inc. (RIFM), Woodcliff Lake, USA. [2]L'Oréal, Aulnay-sous-Bois, France. [3]Charles River Laboratories, Den Bosch, Netherlands

Abstract

Ethical considerations and the European Union’s legislative ban of animal testing on cosmetic products have accelerated the development of several *in vitro* methods to characterize the skin sensitization potential of chemicals. The U-SENS™ assay was developed to address the third key event of the skin sensitization adverse outcome pathway (AOP) (OECD, 2012), dendritic cell (DC) activation, and is described in OECD test guideline 442E (OECD, 2017). U-SENS™ quantifies the change in the expression of a cell surface marker, CD86, associated with monocyte and DC activation in the human

histiocytic lymphoma cell line U937. A dataset of 68 fragrance ingredients comprising of 8 non-sensitizers and 60 sensitizers was tested in the U-SENS™ assay. We aimed to determine how well U-SENS™ predicted the sensitization potential of fragrance ingredients when compared to weight of evidence (WoE) from combined historical human and animal data. Of the non-sensitizers, 3 were predicted to be negative while 5 were predicted to be positive. Of the sensitizers, 49 were predicted to be positive, while the remaining 11 were negative. Positive and negative predictive values were 91% and 21%, respectively. No specific chemical property (e.g., solubility and interference) could account for the misclassified ingredients. As a general agreement within the scientific community, that one single NAM would not be sufficient to replace the animal-based methods for skin sensitization, combining complementary in silico and in vitro methods to the U-SENS™ data should be integrated to define the hazard classification of fragrance ingredients and therefore perform the risk assessment.

196
In silico methods for the assessment of endocrine disruptors (ED) in the EU

Antje Gerloff-Elias, Martina Duft

knoell Germany GmbH, Environmental & Human Toxicology, Mannheim, Germany

Abstract

The assessment of potential endocrine disrupting (ED) properties of substances has recently become a major topic in the EU. Since 2018 an ED assessment according to the respective EU ED Guidance is mandatory for active substances, safeners and synergists under Regulation 1107/2009 and active substances and co-formulants under Regulation 528/2012. Other European regulatory frameworks currently discuss the implementation of information requirements with regard to potential endocrine disrupting properties of chemicals as well.

Given the few options of alternative test methods to replace the requested higher tier studies required for assessing potential endocrine disrupting properties of chemicals, the extended information requirements will inevitably lead to an increase of laboratory tests connected with a massive use of animals and resources. To avoid this, New Approach Methodologies (NAMs) including *in vitro* and *in silico* methods are being explored and developed.

Due to the complex mechanisms of the endocrine system, standard *in silico* models focusing on merely one mechanism alone are not sufficient for the identification of endocrine disrupting chemicals (EDCs). However, they can provide an insight into possible mechanisms of action. Corroboration by molecular modeling methods predicting interaction mechanisms of chemicals with 3D-biomacromolecule complexes can further support the analysis of potential mechanisms.

In this presentation, we provide an overview of *in silico* models and tools that can be used in a weight of evidence approach to support decision-making processes for assessing the endocrine potential of chemicals. Furthermore, we address the challenges and limitations related to the application of these *in silico* methods.

218
Chemical Exploration: Providing Biological Context for NAMs

Bethany Cook[1], Jaleh Abedini[1], Shannon Bell[1], Eric McAfee[2], Jason Phillips[2], David Allen[1], Nicole Kleinstreuer[3]

[1]ILS, Research Triangle Park, USA. [2]Sciome, Research Triangle Park, USA. [3]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, USA

Abstract

New approach methodologies (NAMs) use in vitro and in silico models to predict toxicity based on a chemical's bioactivity and molecular properties. The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods' (NICEATM) Integrated Chemical Environment (ICE) provides easy access to data and tools needed

to explore and contextualize chemical bioactivity profiles. ICE Search provides summary-level information, curated reference data, and bioactivity details for chemicals and mixtures. Bioactivity can be further examined using the Curve Surfer tool to explore concentration-response relationships of curated high-throughput assays. ICE's IVIVE tool allows users to translate in vitro bioactivity profiles to estimated equivalent in vivo doses for different exposure routes. The new physiologically based pharmacokinetics (PBPK) tool predicts tissue-level concentrations resulting from in vivo doses. A new ICE feature allows users to explore ICE's database of >800,000 chemicals through a SMILES similarity search, providing information on target chemicals and those with similar structures. These similar chemicals can then be piped into any ICE tools, expanding available information. Additionally, ICE links to the NTP's Chemical Effects in Biological Systems and the U.S. Environmental Protection Agency's Chemical and Products Database, expanding ICE's capacity to examine and compare chemicals based on physicochemical properties, bioactivity, and product use categories. This presentation will use case studies to provide an overview of the tools and features available in ICE for chemical analyses and comparisons. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

241
Bayesian Network Integrated Testing Strategy for Skin Sensitization Potency Determination

Petra Kern[1], Els DeConinck[1], Greg Dameron[2], James Rathman[3,4], Vinnie Ribeiro[3,4], Chihae Yang[3,4,5], Aleksandra Mostrag[3], Tomasz Magdziarz[5], Cindy Ryan[2,6]

[1]Procter & Gamble Services NV/Sa, Strombeek-Bever, Belgium. [2]Procter & Gamble, Mason, OH, USA. [3]MN-AM, Columbus, OH, USA. [4]Ohio State University, Columbus, OH, USA. [5]MN-AM, Nuremberg, Germany. [6]ToxTechSolutions, Milan, IN, USA

Abstract

We present an update of the original Bayesian Net integrated testing strategy (BN-ITS3) (Jaworska et al, 2015) and recent developments in how to use this for assessing skin sensitization potential of chemicals. The BN-ITS enables a quantitative weight-of-evidence (WoE) prediction of skin sensitization potency using diverse information available for a compound of interest, including *in vitro* AOP assays, physicochemical properties, and *in silico* results. Bayesian networks offer several distinct advantages over conventional methods. First, Bayesian networks do not assume individual evidence sources to be independent. Second, unlike simplistic consensus approach, they provide probabilistic predictions taking into account the reliabilities of the different inputs. Third, Bayesian networks are adaptive, meaning that predictions can be obtained from the available evidence, which may vary from one test compound to the next. Missing data are easily handled and it's possible, for example, to determine whether collecting additional data from a particular assay would be worthwhile. Finally, Bayesian network models offer transparent interpretability and mechanistic insights. Using examples where the AOP pathways are well understood, we can develop methods to suggest possible pathway connections and interpret the latent nodes for deeper mechanistic interpretations. Although a data-greedy method, Bayesian networks provide a clustering technique supported by robust statistics. The new BN ITS model is coded in a platform-free language using a broader training set, updated input data and offers a simplified data integration process. The potency prediction will be converted into a point of departure for sensitization safety assessment through a realistic case study.

253
Collaborative Modeling Project for Predicting Acute Oral Toxicity (CATMoS)

Kamel Mansouri[1], Agnes Karmaus[2], Jeremy Fitzpatrick[3,4], Grace Patlewicz[3], Prachi Pradeep[3,4], Dave Allen[2], Warren Casey[1], Nicole Kleinstreuer[1]

[1]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, USA. [2]ILS, Research Triangle Park, NC, USA. [3]CCTE/EPA, Research Triangle Park, NC, USA. [4]ORISE, Oak Ridge, TN, USA

Abstract

In order to fulfill the pressing need to accurately assess chemicals for acute oral toxicity potential, NICEATM and the ICCVAM Acute Toxicity Workgroup organized the Collaborative Acute Toxicity Modeling Suite (CATMoS) project to develop in silico models as alternatives to predict LD50 and bridge data gaps. Participants from 35 international groups submitted a total of 139 predictive models built using a dataset of 11,992 chemicals split into training (75%) and evaluation sets (25%). Crowdsourced models were developed for five endpoints identified as relevant to regulatory decision frameworks: LD50 value, EPA hazard categories, GHS hazard categories, very toxic (LD50 < 50 mg/kg), and non-toxic (LD50 > 2000 mg/kg). Predictions within the applicability domains of the submitted models were evaluated, then combined into consensus predictions based on a weight-of-evidence approach. The resulting consensus model, forming CATMoS, leverages the strengths and overcomes the limitations of individual modeling approaches. The consensus predictions are fully reproducible and performed as well as independent replicate in vivo acute oral toxicity assays. The CATMoS consensus model can be applied to any new chemical via the free and open-source tool OPERA (Open Structure-activity/property Relationship App), a comprehensive standalone suite of QSAR models including chemical structure standardization workflow and molecular descriptor processing, in addition to applicability domain and accuracy assessments. CATMoS predictions processed by OPERA for the DSSTox ~850k chemical structures are made publicly accessible via NTP's Integrated Chemical Environment and subsequently at the EPA's CompTox Chemicals Dashboard. *This abstract does not necessarily reflect NIEHS and EPA policy.*

254
Mechanistically driven identification of novel structural alerts for mitochondrial toxicity

Charles Gong[1], Katarzyna Przybylak[2], Jonathan Goodman[1]

[1]Center for Molecular Informatics, Yusuf Hamied Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom. [2]Unilever Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, United Kingdom

Abstract

Mitochondrial toxicity is a problem of growing concern in modern society, resulting in several serious adverse health effects. The adverse outcome pathway provides a model for a mechanistic understanding of toxicology, but most existing mitochondrial toxicity models do not account for the mechanism of action of potential toxicants. In a recent study by Hallinger et al.[1], the Seahorse respirometric assay provides assignments about the mechanism of action. This makes possible, for the first time, the development of structural alerts linked to mechanisms. By using a substructure searcher and Bayesian statistical analysis, we have discovered 11 alerts associated with different mechanisms of action. Eight of these are completely novel. By incorporating the mechanisms into the structural alerts, more information can be gained about the molecular initiating events involved and build toward a more complete adverse outcome pathway for mitochondrial toxicity.

1. Hallinger et al., 2020, Toxicol Sci 176:175–192.

277
An Integrated Screening Method Based on Quantitative Structure Activity Relationships Predicting Molecular Initiating Events of Neurotoxicity

Domenico Gadaleta[1], Nicoleta Spinu[2], Alessandra Roncaglioni[1], Mark T. Cronin[2], Emilio Benfenati[1]

[1]Laboratory of Environmental Chemistry and Toxicology, Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [2]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, United Kingdom

Abstract

Developmental and adult/ageing neurotoxicity is an area needing alternative methods for chemical risk assessment. Formulation of a strategy to screen chemicals is extremely relevant because people are daily exposed to large amounts of compounds that may have long-term adverse health consequences to the nervous system. Adverse Outcome Pathways (AOPs) are a resourceful tool for toxicologists. Compounds of unknown hazard can be assigned to various levels of concern according to the activated molecular initiating events (MIEs) and their extent to activate downstream key events.

Here we propose a screening method based on the integration of Quantitative Structure-Activity Relationship (QSAR) models. The MIEs of AOP networks as published in the literature were modelled to predict neurotoxicity. Random Forests and data available from public available chemical databases (ChEMBL) were used to develop models for each MIE of neurotoxicity. Predictions returned by models were integrated and evaluated for their capability to predict neurotoxicity. In particular, MIE predictions were used to develop various classifiers and compared with other reference standards (chemical descriptors and structural fingerprints) to benchmark their predictive capability. Overall, classifiers based on MIE predictions returned predictive performance (BA = 0.73 - 0.77) comparable to those based on chemical descriptors and structural fingerprints, with the additional advantage of providing a mechanistic rationale and indication of the biological targets responsible of the onset of the apical toxicity.

The integrated computational approach described will be beneficial for large-scale screening and for prioritization of chemicals as a function of their potential to cause long-term neurodegenerative effects.

279
Two in silico NAMs combined to accurately Identify potential for Endocrine Disrupting Modalities of chemical substances

Paul Thomas[1], Franklin Bauer[1], Zlatomir Todoroov[1], Satinder Sarang[2], Carole Charmeau[1]

[1]KREATiS, L'Isle d'Abeau, France. [2]Shell International, Shell Health, Houston, USA

Abstract

There is a need for new approach methodologies (NAMs) to identify endocrine disrupting chemicals (EDC) involved in key events of endocrine pathways including binding to receptor proteins. Regulatory authorities in the EU and the US are using data generated from NAMs for prioritization, classification and labelling, and risk assessment processes. The purpose of our program was to develop new *in silico* methods which accurately estimate the potential of chemicals for endocrine disruption. Two in-house tools are developed: iSafeRat® ED SAR (a set of 2D structural alerts) and *the iSafeRat® ED* docking tool "SESAME": (a workflow for molecular docking). The 2D model was curated and validated using a diverse set of chemicals from the USEPA Comptox and other databases. The docking workflow relies on third party software for its major modeling stages and on an X-ray crystallographic dataset as input of protein targets. Its key features include: automation and high-throughput, an open architecture allowing to build up consensus-problem-solving strategy. Currently, using both our tools we are able to investigate and test a ligand affinity for EATS target proteins. We tested a diverse set of chemicals composed of petrochemicals and consumer products and the predictions generated from our i*n silico* platform agreed with the published endocrine properties. The outcomes suggest that the 2D SAR is amenable for screening a large set of potential EDCs. The *ED* docking module, while longer to perform, provides useful mechanistic information on ligand-receptor interactions.

339
Biotransformation rates in humans: from *in vitro* data to QSAR models

Alessandro Sangion[1,2], Ester Papa[3], Linda Bertato[3], Karen Foster[2], James Armitage[4], Alexandra Looky[2], Liisa Toose[2], Michelle Embry[5], Jon Arnot[2,1,6]

[1]Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, Canada. [2]ARC, Arnot Research and Consulting Inc., Toronto, Canada. [3]Department of Theoretical and Applied Sciences, University of Insubria, Varese, Italy. [4]AES, Armitage Environmental Sciences, Inc., Ottawa, Canada. [5]HESI, Health and Environmental Sciences Institute, Washington DC, USA. [6]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada

Abstract

Biotransformation is a key toxicokinetic (TK) process relating external and internal exposures, half-life, and bioaccumulation potential. Biotransformation rates can be measured from *in vitro* tests which can then be scaled to tissue and whole-body levels using *in vitro-in vivo* extrapolation (IVIVE) models. We have previously developed and validated QSARs for predicting *in vivo* whole-body biotransformation half-lives in humans.

This presentation describes new methods to address data gaps in biotransformation rates through the development of validated QSARs using *in vitro* data. Approximatively 12,000 *in vitro* human TK data are collected and critically evaluated. A scoring system is developed and applied to evaluate *in vitro* data confidence and consistency using new standardized guidelines developed for *in vitro* assays for fish. This data confidence scoring method seeks to identify high-quality data that are most appropriate for QSAR development and for other potential applications (e.g., prioritization). Case studies are presented to illustrate how the variability in the existing experimental data can be addressed. In addition, QSAR models are generated using multiple training sets created on the basis of similar reactivity patterns. The *in vitro*, *in vivo* and QSAR estimates are then compared to evaluate different IVIVE models.

Given the significant role that biotransformation rates have in determining the bioaccumulation of organic chemicals there is a critical need to develop integrated testing strategies and high-quality *in silico*, *in vitro* and *in vivo* biotransformation rates data. The results derived in this study using complementary approaches provide opportunities to address uncertainty in IVIVE models and TK parameters.

326
Machine learning models for predicting lung toxicity of metal oxide nanoparticles

Yang Huang[1], Xuehua Li[1], Shujuan Xu[2], Huizhen Zheng[2], Jingwen Chen[1], Ruibin Li[2]

[1]Key Laboratory of Industrial Ecology and Environmental Engineering, School of Environmental Science and Technology, Dalian University of Technology, DaLian, China. [2]State Key Laboratory of Radiation Medicine and Protection, Collaborative Innovation Center of Radiological Medicine of Jiangsu Higher Education Institutions, School for Radiological and Interdisciplinary Sciences (RAD-X), Soochow University, Suzhou, China

Abstract

Lung toxicity caused by inhaled nanoparticles is an endpoint of high concern yet there are major ethical and financial limitations to *in vivo* bioassay. Development of *in silico* models can fill gaps in lung toxicity data, avoid testing of each new nanoparticle formulation from scratch and facilitate safe nanotechnology. In this study, machine learning models were built to relate metal oxide nanoparticle (MeONPs)' physicochemical properties to their toxicity in an alveolar-macrophage-like cell (THP-1), which is the main route to remove inhaled insoluble fine particulates. The endpoints to be predicted were inflammatory potential based on a pro-inflammatory cytokine (IL-1β) release and cytotoxicity based on cell viability. Dataset for each endpoint consists of 240 toxicity data (30 MeONPs tested at 8 serial dilutions), with 9 physicochemical properties and 59 quantum-mechanical attributes (input parameters). The *in vitro* toxicity data were validated in mouse lungs by oropharyngeal instillation of six representative MeONPs. Inflammatory potential and cytotoxicity were correctly predicted with predictive accuracy (*ACC*) exceeding 90% and further validated experimentally with *ACC* reaching 86% and 75%, respectively. The structure–activity relationship extrapolation indicated that electronegativity, ζ-potential, and cation charge were key properties responsible for inflammatory effects of MeONPs; while size, dissolution and electronegativity of MeONPs could be used to determine their cytotoxicity. DFT computations further revealed the underlying mechanisms: MeONPs with lower metal electronegativity and positive ζ-potential were more likely to cause lysosomal

damage and substantial inflammation or cytotoxicity. The insights derived are useful to consider when developing future (non-)testing approaches to address regulatory purposes.

327
Supervised SOMs in evaluating drug potential for liver injury

Viktor Drgan, Benjamin Bajželj

National Institute of Chemistry, Ljubljana, Slovenia

Abstract

Information on the potential of drugs to cause liver damage is important both for the development of new drugs and when a trade-off is to be made between the beneficial effects of the drug and its side effects during treatment. Some of the adverse effects of drugs may not be known until late after their extensive use, so in silico tools play an important role in evaluating drug safety.

In this study, we conducted several computational experiments to evaluate the efficiency of different learning algorithms based on self-organising maps (SOMs) in predicting the hepatotoxic potential of drugs. Drug likelihood scores describing the potential of a drug to cause liver injury were obtained from the LiverTox database (https://livertox.nih.gov). Drugs with known hepatotoxic potential were classified into a hepatotoxic or non-hepatotoxic class and used in QSAR modelling with 0-2D descriptors. Neural network models were developed using genetic optimization of counter-propagation neural networks (CPANNs), X-Y fused self-organising maps, and a newly developed modification of the counter-propagation artificial neural network learning algorithm.

X-Y fused SOMs and a new modification of the CPANNs training algorithm showed better modelling capabilities than standard CPANNs in terms of accuracy and clustering. A comparison of the results is given. Some views on the relationship between the training algorithm used and the interpretation of the neural network results are presented.

351
QSAR and molecular docking studies on succinate-cytochrome c reductase inhibitors for the prediction of drug-induced mitochondrial dysfunction

Alicia Rosell Hidalgo[1], Anthony Moore[1], Taravat Ghafourian[2]

[1]University of Sussex, Brighton, United Kingdom. [2]University of Bedfordshire, Luton, United Kingdom

Abstract

Increasing evidence links mitochondrial dysfunction with organ toxicity, which demonstrates the need for the development of efficient predictive tools to predict drug-induced mitochondrial dysfunction early in the drug discovery. However, there are currently very limited structure-activity models in the literature for the prediction of mitochondrial toxicity, more specifically, with regards to the interaction of compounds with the electron transport chain. This investigation focused on the inhibition of succinate-cytochrome *c* reductase (SCR) (respiratory complexes II and III).

First, SCR inhibition by a collection of 34 drugs was measured to expand the currently available literature data. The IC_{50} values for additional 26 compounds were obtained from the literature (same experimental condition). This dataset was used for molecular docking and QSAR studies to enable a mechanistic link between inhibition of the mitochondrial respiratory chain complexes II+III and chemical characteristics of compounds.

Molecular docking was performed against the ubiquinone site of both complex II and III (PDB entries 3SFD and 1PPJ). Docking scores showed moderate linear correlations with the pIC_{50} values. Protein-Ligand Interaction Fingerprinting (PLIF) analysis identified the most important interactions for strong inhibition (*e.g.* His 161 sidechain H-acceptor in complex III).

Stepwise regression analysis using hundreds of molecular descriptors computed by ACD Percepta and Molecular Operating Environment (MOE) as independent variables resulted in QSAR with good prediction accuracy for the external

test set (R^2 = 0.82, Q^2 = 0.73). This investigation shows potential for molecular docking and QSAR to achieve local models for individual mitochondrial mechanisms that may guide the identification of mitochondrial toxicants.

335
Advanced Models for the Fate and Transport of Aqueously Dissolved Hydrophobic Organic Compounds through Porous Geologic Media Using QSAR Approaches

Kennly Weerasinghe[1], William Blanford[1,2], Adam Kapelner[1]

[1]Queens College, City University of New York, Flushing, USA. [2]The Graduate Center, City University of New York, New York, USA

Abstract

Advanced QSAR methods have been under applied to solute transport in porous geologic media. In this field, the *Advection Dispersion Equation* (ADE) is widely employed to simulate the fate and transport of aqueous species. In practice, those ADEs-based models are commonly populated with basic expressions for processes that contain parameters related to basic system attributes (eg porosity, bulk density, linear velocity). However, they underutilize common physiochemical relationships for solute parameters such as diffusion and sorption which are based on basic solute, solvent, or porous media properties (eg aqueous solubility, salinity, grain coating composition) or system attributes (eg temperature, pressure). Further, advanced ADE models rarely examine the fate and transport of extended series of homologous compounds and thus do not develop and cannot exploit quantitative structural retention relationships (QSRR) that may better constrain their parameters and findings.

In our work, we have taken a widely employed ADE analytical solution for 1D systems with a constant flux and dispersion boundary condition through a model geologic media (Berea Sandstone). To that, we have examined the utility of published expanded hydraulic parameters linked to porous media properties, diffusion equations based on solute and solvent properties and thermal states of core floods. We have further developed and evaluated correlations among solute properties of a homologous series of chemicals (mononuclear aromatic hydrocarbons) to develop equations for sorption of such hydrophobic organic compounds (HOCs) based on these attributes. Our preliminary results show great promise for expanded ADEs where QSAR approaches are able to improve transport parameter values.

Poster Sessions Track 6

204
Grouping Naturally Complex Substances (NCS) for Safety Assessment through Multi-component SPR Analysis

Mihir Date[1], Manoj Kumar[1], Terry Schultz[2], Daniel Liebler[3], Trevor Penning[4], Anne Marie Api[1], Daniel Salvito[1]

[1]Research Institute for Fragrance Materials, Woodcliff Lake, NJ, USA. [2]The University of Tennessee, College of Veterinary Medicine, Knoxville, TN, USA. [3]Protypia, LLC, Nashville, TN, USA. [4]Center of Excellence in Environmental Toxicology, The University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA

Abstract

Grouping of naturally complex substances (NCS) is a valuable approach for rapid data analysis, identification of read-across analogs, and an efficient safety assessment process. An inventory of 120 essential oils extracted from species under the *Rutaceae* family and *Citrus* genus, categorized as NCS, has been grouped by building a multi-component structure-property relationship (SPR) between NCSs. Our approach begins with conventional agglomerative hierarchical clustering (AHC) to build a hierarchy of NCS groups. In AHC, the concentration of each component is considered as an independent variable. In the second step, RIFM discrete fragrance chemical clustering is applied to overall components,

accounting for their structure-property relationship (SPR). In the last step, to further refine NCS groups, a decision tree is applied, which is based on similarities in plant part, processing for oil extraction, and RIFM discrete fragrance clusters. Consequently, these steps build a multi-component SPR analysis between the NCSs to achieve groups of NCS with similar toxicological properties. Efforts are underway to confirm the grouping achieved using this approach by comparing genotoxicity data on the components and the whole oil whenever available. We plan to apply this approach to over 1200 NCS in the RIFM database across 81 families and 203 genera.

223
QSAR modelling of fish toxicity and algae inhibition by cationic polymers using available molecular features

Kunal Roy[1], Pathan Mohsin Khan[2], Hans Sanderson[3]

[1]Drug Theoretics and Cheminformatics Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India. [2]National Institute of Pharmacetical Education and Research, Kolkata, India. [3]Aarhus University, Dept Env Sci, Roskilde, Denmark

Abstract

Polymers are macromolecules made up of multiple repeating units, i.e. monomers, connected by covalent bonds. They are used extensively in several industrial fields representing a growing multi-billion dollar industry covering several 1000s of materials and billions of metric tons used globally every year. However, polymers have until recently been considered of low environmental concern. Therefore, they have been subject to exemptions or reduced regulatory requirements in all jurisdictions worldwide. However, these exceptions are expected to be revised in the coming years in several geographies. Cationic polymers are assessed to be the class of highest environmental concern in the portfolio of polymers. This presentation will demonstrate new Quantitative Structure-Activity Relationship (QSAR) models for cationic polymers' acute aquatic toxicity to fish and growth inhibition to algae. Both models showed optimistic statistical quality in terms of several internal and external quality and validation parameters such as determination coefficient R2 (0.703 and 0.676), cross-validated leave-one-out Q2 (0.638 and 0.516) and predictive R2pred or Q2ext (0.776 and 0.703) for fish (Ntrain = 72, Ntest = 23) and algae (Ntrain = 40, Ntest = 14) toxicity datasets, respectively. The study revealed that higher charge density results in an increase in the toxicity against both the response endpoints. However, a higher percentage of oligomers with molecular mass less than 1000 Daltons results in a decreased toxicity towards both the studied endpoints. Similarly, primary amines in the molecular building block result in a reduction in the toxicity against the algal species.

224
Aquatic ecotoxicity interspecies Quantitative Structure Toxicity-Relationship (i-QSTR) models for cationic polymers

Pathan Mohsin Khan[1], Kunal Roy[2], Hans Sanderson[3]

[1]National Institute of Pharmacetical Education and Research, Kolkata, India. [2]Drug Theoretics and Cheminformatics Laboratory, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India. [3]Aarhus University, Dept Env Sci, Roskilde, Denmark

Abstract

Polymers are macromolecules used extensively in several industrial fields representing a growing multi-billion dollar industry covering several 1000s of materials and billions of metric tons used globally every year. Despite widespread use of cationic polymers were generally considered of low concern compared to other low molecular weight compounds. However, this pragmatic approach to dealing with environmental concerns linked with polymers is coming under an increased scrutiny in recent years and they are expected to be included under the European REACH regulation in the coming few years. The amount of publicly available, high-quality environmental toxicity data on industrial polymers such as

cationic polyquaterniums is low. In the present study, we have proposed interspecies models utilizing *D. magna* experimental toxicity data as a predictor for i-QSTR model development against fish and algae in order to predict the toxicity of polymeric compounds of the *D.magna* dataset whose toxicity data was missing for fish and algae species. We have developed intercorrelation models utilizing the fish and algae experimental toxicity data as independent variables for i-QSTR model building against *D. magna* with the prime goal to predict *Daphnia* toxicity based on the fish and algae dataset, since the toxicity data for *D. magna* did not support building independent *Daphnia* toxicity models using only molecular features. Finally, we have also proposed the intercorrelation models between fish and algae. The proposed models can be used for intial regulatory screening and data gap filling for new or untested polymers falling within the applicability domain of the models.

243
Developing a list of per- and polyfluoroalkyl (PFAS) chemicals from public domain databases

Antony Williams, Charles Lowe, Chris Grulke, Grace Patlewicz, Ann Richard

US Environmental Protection Agency, Research Triangle Park, USA

Abstract

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals that have been used in a variety of industries around the globe. These chemicals persist in the environment and the human body and there is evidence that exposure to certain PFAS chemicals can lead to adverse health effects, including reproductive and developmental, liver and kidney, and immunological effects in laboratory animals. The aggregation and curation of a list of PFAS chemicals sourced from literature data, public databases and our own laboratory studies has been undertaken. During the assembly of the list, a wide range of data have been assembled, including toxicity data, physicochemical and fate and transport properties, reference mass spectra, and external identifiers allowing for mapping to other online databases. Where structures can be assigned, the effort has been bounded by definitive substructure elements that are being used as the basis of further expansion of a PFAS structure list. Certain PFAS chemicals that cannot be represented by a unique structure can be represented with ambiguous structure forms, so-called Markush structures, as well as mapped to building block elements such as polymeric units. This presentation will provide an overview of the processes for data assembly and curation and provide representative examples of data quality issues. The overall master list of PFAS chemicals maps to a set of segregated lists supporting various research projects underway at the US-EPA as well as to specific regulatory lists. *This abstract does not represent the EPA policy.*

244
Establishing and Using a Reference Mixture in Assessing Botanical Oils: A Case Study

Terry Schultz

University of Tennessee, Knoxville, USA

Abstract

Essential oils are mixtures of volatile organic substances extracted from various plant taxa, various plant parts and various processes. Earlier work has revealed all these factors can affect similarity/dissimilarity analysis of different oils. Thus, the multidimensionality of essential oils provides a unique set of problems for conducting safety assessments. This study aims to use GC/MS-derived literature data on lavender oils and establish a ‘reference mixture’ that reduces the complexity of its safety assessment by standardizing some dimensions and simplifying others. Data on the % mass contribution of the discrete components of various oils extracted by steam distillation of flowering tops of *Lavandula angustifolia* were harmonized to produce a reference *L. angustifolia* essential oil. Based on molecular structure, the vast majority of the 61 constituents are highly similar – mono- and sesqui-terpenes, many of which are oxygen-containing. Sixty-nine % of the components individually contribute < 2% to the total mass of the oil. It was determined that 75 ± 15% of the region lavender oils consist of only 6 key chemicals – linalool, linalyl acetate, borneol, camphor, eucalyptol and terpinen-4-

ol. Results from using information and experimental *in vivo* data for metabolism and repeated-dose effects of specific components (i.e., C10O1 derivatives) the assessment of subchronic toxicity of the reference mixture will be discussed.

271
Applying computational toxicology for early identification of genotoxic pyrrolizidine alkaloids in plant-based ingredients

Elena Lo Piparo, Nicolas Christinat, Marion Ernest, Thomas Bessaire, Flavia Nagy

Nestlè Research, Lausanne, Switzerland

Abstract

The objective of this work was to investigate a new avenue to exploit computational toxicology to safety assessment of plant-based materials. Even though modeling is considered a valid alternative to mutagenicity testing for substances with known structure, it is not commonly used for plant-based ingredients of unknown composition. Considering that in the absence of toxicological information, an important early consideration is whether any substance present may be mutagenic, we tried to establish a correspondence between mutagenicity structural alerts (SAs) and fragments in the mass spectrum from a chromatographic peak (so called signature fragment alerts). Indeed, if this correspondence is established, chromatograms could be screened for chemical features associated with mutagenic alerts. Pyrrolizidine alkaloids (PA), a large group of natural toxins synthesized by different plant species were used as a case study. Since several PAs are known to be carcinogenic and mutagenic, their early identification through mutagenicity SAs would bring significant benefits and it is of high importance. The method was built using 56 PAs pure standards, resulting in the characterization of signature fragment alerts. Finally, the approach was verified in real plant-based samples such as herbal tea and alfalfa, where the screening of signature fragment alerts allowed highlighting the presence of PAs in plant-based mixtures at safety relevant levels.

281
Implementing analytics to investigate combined exposures to endocrine-disrupting chemicals (EDCs) in consumer products in South Korea

Jiwon Choi, Sunmi Kim, Jongwoon Kim

Chemical Safety Research Center, Korea Research Institute of Chemical Technology (KRICT), Daejeon, Korea, Republic of

Abstract

Worldwide, endocrine disruption effects of synthetic chemicals are growing concern. Since some studies reported that several compounds used in consumer products such as air fresheners, detergents, etc. might cause endocrine disruption, public concerns regarding the chemical safety of consumer products have been raised [1,2]. Most of scientific studies relating to the EDCs have been focused on single EDCs rather than their mixtures, although their cocktail effects can be caused by toxicological interactions among chemicals. In practice, different EDCs can be used in the same consumer products. Therefore, in this study, an implementing analytics was carried out to investigate combined exposures to endocrine-disrupting chemicals (EDCs) in consumer products in South Korea. We found different combinations of EDCs simultaneously used in 1,125 consumer products of which components were voluntarily provided from chemical companies. To derive combined exposures to those EDCs, major exposure routes (e.g. oral, dermal, and inhalation) were also taken into account. This study highlights that the investigated combined exposures to EDCs in the consumer products can facilitate and support further studies for more reliable mixture risk assessment of EDCs.

References

1. Dodson, Robin E., et al. "Endocrine disruptors and asthma-associated chemicals in consumer products." *Environmental health perspectives* 120.7 (2012): 935-943.

2. Meeker, John D. "Exposure to environmental endocrine disruptors and child development." Archives of pediatrics & adolescent medicine 166.10 (2012): 952-958.

296
Representation and Enumeration of UVCB Substances to enable QSAR Predictions for Substances with Structural Uncertainty

Christopher Grulke[1], Antony Williams[1], Brian Meyer[2], Ann Richard[1]

[1]US EPA - Center for Computational Toxicology and Exposure, Durham, NC, USA. [2]US EPA - Senior Environmental Employment Program, Durham, NC, USA

Abstract

Many chemicals regulated by the US EPA fall in the class of substances referred to as Unknown, Variable composition, Complex reaction product or Biological origin substances (UVCBs). These chemicals cannot be represented with a single structure and, therefore, pose a significant challenge when attempting to apply QSAR models for in silico risk prioritization. Additionally, public chemical databases often include a single representative structure for UVCBs, leading to non-unique substance-structure mappings and potentially erroneous estimations of substance properties and activities based on representative structures. To enable computational estimation of UVCB properties and activities, particularly for inventories of high-interest to EPA, EPA's DSSTox project has begun to more thoroughly document the relationships between UVCBs and their potential components through use of manual relationship annotations or Markush/query structures. The use of Markush and query structures within a database presents new challenges, including difficulty with determining substance uniqueness (since Markush lack InChIs), storage format limitations, and inconsistent (or lack of) handling of the representations by different software packages. On the other hand, Markush structures offer powerful capabilities for programmatic structure-enumeration, enabling enhanced search capabilities and detection of related substances, as well as the prediction of the range and boundaries of the properties and activities associated with a UCVB substance. Such predictions, in turn, can help to identify cases where a single, or a small number of manually annotated structure representatives would be insufficient to properly understand the potential risks associated with the UVCB. *This abstract does not necessarily represent U.S. EPA policy*.

310
Building Structure-Hazard Relationships for Aromatic Polymeric Polyisocyanate Prepolymer (P3) Substances

Robert West[1], Scott Arnold[2], Anne Chappelle[1], Martha Ehlers[3], Timothy Feeley[4], Cynthia Graham[5], Travis Gulledge[6], Shannon Krieger[2], Astrid Neuhahn[3], Patrick Plehiers[1]

[1]International Isocyanate Institute Inc., Mountain Lakes, NJ, USA. [2]Dow Inc., Midland, MI, USA. [3]CURRENTA GmbH & Co OHG, Leverkusen, Germany. [4]Covestro LLC, Pittsburgh, PA, USA. [5]Huntsman, The Woodlands, TX, USA. [6]Burleson Research Technologies, Morrisville, NC, USA

Abstract

Diisocyanate (DII) substances are associated with the potential to cause skin and/or respiratory sensitization. By reacting DII monomers with polymeric polyols, polymeric polyisocyanate prepolymer (P3) substances can be produced that enable custom-tailored polyurethane applications which have decreased exposure and hazard potentials. However, due to perceived potential for conversion to polycationic polymers in the environment, the P3 substances are excluded from consideration as polymers of low concern. This study investigated relationships of structure features and physical-chemical properties to skin sensitization potency and to aquatic hazard, and revealed an improved basis for read-across of P3 hazard properties. Ten generic P3 substances were designed and tested for skin sensitization potency (OECD 429; Mouse LLNA), and for aquatic exposure (OECD 120; water extractability) and hazard potential (OECD 202; *D. magna*

immobilization). The results support the hypothesis that skin sensitization potency depends on isocyanate equivalent weight, but also showed contributions of polyol structure features and hydrophobicity to sensitization potency and to aquatic exposure potential. In the LLNA, an ~100-fold span in dose-normalized stimulation indices was observed across P3 substances having average MW of 750 – 4,500 g/mole and calculated log Pow of -5 to 45. Multivariate regression analyses revealed structure features and properties which distinguish sensitizing from non-sensitizing P3. The percentage of P3 loadings (100; 1,000 mg/L) which was soluble after 96h stirring in water ranged from < 0.1 to 30 %; however, no acute toxicity to *D. magna* was observed. These results show promise for development of new QSAR tools to predict P3 hazard properties.

276
Deriving waveform parameters from calcium transient measurements in human iPSC-derived cardiomyocytes and their applications to cardiotoxicity prediction

Hongbin Yang[1], Will Stebbeds[2], Jo Francis[2], Amy Pointon[3], Olga Obrezanova[3], Kylie Beattie[4], Peter Clements[4], James Harvey[4], Graham Smith[3], Andreas Bender[1,3]

[1]University of Cambridge, Cambridge, United Kingdom. [2]GlaxoSmithKline, Stevenage, United Kingdom. [3]AstraZeneca, Cambridge, United Kingdom. [4]GlaxoSmithKline, Ware, United Kingdom

Abstract

Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have been established to detect dynamic calcium transients by fast kinetic fluorescence assays, as well as subsequently been applied to understand and predict aspects of functional cardiotoxicity. However, how to precisely derive and use waveform parameters to predict cardiac activity is poorly understood. Hence, in this study, we derived, evaluated, and applied 38 waveform parameters in a novel Python toolkit, including (among others) peak frequency, average amplitude, peak widths, rise time, decay time, and shoulder-tail ratio. Firstly, parameters were derived from concentration-response data for 63 compounds with clinical cardiac risk annotations. Applying correlation analysis, we found that Average Peak Amplitude, PW10 (peak width at 10%), and shoulder-tail ratio have high correlation with cardiac activity, especially at higher compound concentrations. Subsequently, the distributions of the most correlated 25 parameters were selected and analysed in more detail, corroborating their capability of identifying cardiac active compounds, especially at concentrations above 1 µM. Finally, we trained a Random Forest model to predict cardiac activity based on the same set of 25 parameters and found that for a leave-one-compound-out cross validation the AUC obtained is 0.86 while overall accuracy is 0.81, thereby improving predictions beyond molecular (ECFP4) fingerprint alone, for which the AUC is 0.6 and the accuracy is 0.71. The current work shows that this novel analytical approach increases the predictivity of in vitro calcium transient data and the translatability to clinical cardiac activity.

290
A Streamlined, Fragment-Based Approach to Categorizing Large Chemical Inventories Based on Structural Similarity

Catherine Rudisill, Christina Coley, Courtney Hard

SRC, Inc., Syracuse, USA

Abstract

A top-down approach for categorizing (or clustering) large chemical inventories of heterogeneous chemicals based on structural similarity using the fragment-based software ChemACE was developed and evaluated. In the relevant literature, case studies tend to focus on identifying analogs for a specific chemical of interest. Less attention has been paid in the literature to categorizing large inventories of chemicals. However, inventory approaches are being implemented in several chemical management initiatives. Regulatory agencies will likely use categorization approaches to prioritize and assess

PFAS. Commercial sustainability initiatives such as the Chemical Footprint Project and the Zero Discharge of Hazardous Substances (ZDHCs) requires companies to compile a complete inventory of chemicals in their supply chains to identify hazardous substances. As such, there is a need for an efficient, streamlined approach to categorizing these large chemical inventories for the purposes of prioritization and toxicological read across. Recent literature suggests the use of Tanimoto similarity scores for the purposes of categorization is best applied to small, homogeneous sets of chemicals. This presentation will focus on evaluating the fragment based ChemACE software program for categorizing large, heterogeneous inventories of chemicals. Three case studies covering sets of PFAS, fragrances, and dyes with SMILES inventories of 800 to >3500 unique substances will be presented. The results will be focused on evaluating the validity, efficiency, and adaptability of this tool for clustering large data sets.

300
Assessing safety concern of food packaging chemicals using in silico toxicology

Serena Manganelli, Benoit Schilter, Gabriele Scholz, Elena Lo Piparo

Nestlé Research, Lausanne, Switzerland

Abstract

There is an increasing alarm about potential toxicological effects of food packaging chemicals since most of them lack experimental data. There have been already initiatives to screen food contact chemicals using *in silico* toxicology, but many of them use qualitative approaches, mainly mutagenicity predictions, suitable for hazard identification. However they do not provide information about hazard characterization and even less about health risks. We are currently refining and applying an *in silico* approach, previously developed in a pilot study, on a large set of ~3,400 curated food packaging chemicals to assess rapidly, cost-efficiently and without animal toxicity testing, their safety concern. A number of toxicity endpoints relevant for risk assessment have been sequentially screened using *in silico* models, i.e. mutagenicity, developmental, reproductive and chronic toxicity [lowest-observed-adverse-effect level (LOAEL)]. Individual predictions have been integrated in order to identify the most relevant toxicological value to be compared with exposure through a margin of exposure approach (MoE, the ratio between predicted toxicity value and exposure estimate). For non-mutagenic chemicals, the lowest quantitative predicted toxicity values were compared to exposure resulting from a theoretical migration level in food of 10 ppb and a food intake of 1 kg for a 60 kg individual. Based on the application of this approach more than 95% of chemicals investigated in the present study were compatible with safety when present in food at a level of 10 ppb. The remaining ones deserve a deeper analysis to confirm or discard the presence of concern.

318
An interdisciplinary analysis of computational tools for analogue identification in chemical hazard assessment

Mary Kawa[1], Savannah Sierco[2], Ramsey Hanna[2], Heather Carlson-Lynch[3], Julie Melia[3], Laura Morlacci[2]

[1]SRC Inc., North Syracuse, NY, USA. [2]SRC Inc., Arlington, VA, USA. [3]SRC Inc., Scarborough, ME, USA

Abstract

Experimental toxicity, metabolism, and environmental fate and transport data from chemical analogues are often needed when data for a chemical of interest are not available. Analogue data may be used to fill data gaps and provide read-across values, support modeled results, or more broadly provide additional lines of evidence when performing a chemical assessment or identifying safer substances. Identification of relevant analogues is a critical initial step in these initiatives that can be facilitated with computational tools. A practical implementation and streamlined approach for analogue identification was developed by an interdisciplinary team of toxicologists, chemists, and environmental scientists with expertise in identifying and curating analogues in support of regulatory assessments. The process begins with analogue collection based on chemical structure, using fragment and similarity score methods, from publicly available tools and

datasets including EPA's Analog Identification Methodology, CompTox Chemicals Dashboard, OECD QSAR Toolbox, PubChem and ChemIDPlus. Additional analogues can be identified based on similarity in their presumed mechanism of action, and include chemicals with common metabolites, metabolic precursors, and bioactivity as demonstrated in high-throughput screening assays. The comprehensive list of structural and targeted analogues is screened to identify CASRN, names, and mixtures, and then reviewed by the team. Experimental data specific to the project goal is then mined to further refine and finalize the list of candidate analogues. Application of this approach to several case studies demonstrates that computational tools can greatly inform the initial selection of analogues, while expert judgment is required for data integration from multiple sources.

298
Abstract Sifter: A literature informatics tool for computational toxicology

Nancy Baker[1], Thomas Knudsen[2]

[1]Leidos/EPA, Hillsborough, USA. [2]EPA, Durham, USA

Abstract

The biomedical literature contains an abundance of information about the activity of chemicals in biological systems. The goal of literature informatics research at the EPA's Center for Computational Toxicology and Exposure is to use the literature more effectively in computational toxicology and new approach methods. To this end, we have developed a novel approach to article retrieval in our Abstract Sifter application. The Abstract Sifter is a document retrieval tool that integrates the richness of PubMed and other bibliographic sources with the powerful data-handling capabilities of Microsoft Excel. Results from searches are imported directly into an Excel sheet where the end-user can then use a novel "sifting" methodology for quick, agile relevance ranking of articles. The tool also enables article triage capabilities through easy tagging and noting functionality. Triaged citations can be exported to external software such as reference management tools. The Abstract Sifter can also provide a high-level view of a corpus of literature for a defined set of entities such as chemicals. This "landscape" view helps researchers assess the volume of literature in any given subject area to help with project scoping and chemical ranking and prioritization. Queries developed from the OECD Adverse Outcome Pathway (AOP) project connect key events in AOPs to the literature for chemicals on the Landscape sheet, offering evidence for inferring and investigating a chemical's mechanisms of action. The Excel format of the tool provides ease of use and facilitates collaboration. *This abstract does not necessarily represent U.S. EPA policy.*

295
Defining Applicability Domains of Analogues and Categories for Read-Across with New Approach Methodology Data

Cynthia Pestana, James Firman, Nicoleta Spinu, Mark Cronin

Liverpool John Moores University, Liverpool, United Kingdom

Abstract

Read-across predictions for data gap filling can be supported by a variety of New Approach Methodology (NAM) data and other existing information. These have been shown to be essential in increasing the confidence associated with a read-across prediction in line with ECHA's Read-Across Assessment Framework and published criteria for uncertainty assessment (doi: 10.1016/j.yrtph.2020.104855). This study has investigated the possibility of using NAM data, including estimates of similarity, in silico profiling for ADMET, existing data e.g. for ToxCast etc., to help define the applicability domain of a read-across. For an analogue approach the domain demonstrates how close the target and source molecules are within a specific group. This is illustrated with reference to bioactive triazole compounds. Statistical analysis of the group, for instance using K nearest neighbours and cluster analysis, provides a quantification of the applicability domain. This approach to defining applicability domain quantitatively allows for an appropriate selection of analogues, confirmation

of the validity of analogues and is adaptable to the mechanism of action and context of the read-across scenario. The definition of applicability domain could be standardised for specific (regulatory) use or be used in a bespoke manner in a context dependent manner.

240
Accessing bulk predicted QSAR data via batch search functionality in the CompTox Chemicals Dashboard

Antony Williams[1], Chris Grulke[1], Todd Martin[1], Kamel Mansouri[2]

[1]US Environmental Protection Agency, Research Triangle Park, USA. [2]NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Research Triangle Park, USA

Abstract

There are a myriad of public free access chemistry databases now accessible to the community to source various types of data to support, for example, drug discovery, environmental chemistry and materials research. The US EPA CompTox Chemicals Dashboard is a web-based application providing access to ~900,000 chemical substances and diverse data types including physicochemical property, toxicity and bioactivity data. While the application supports users with the expected single chemical search (based on CASRN, chemical name, InChI Key etc) one of the most powerful pieces of functionality is the batch search that allows a user to search of thousands of chemicals at a time. Batch searching using each of, or a combination of chemical names, CAS RNs, InChIs, masses or formulae as inputs facilitates downloads of data *en masse* into either Excel spreadsheet, comma or tab-separated value files, or into an SDF file containing thousands of chemicals. Data that can be exported includes data from QSAR prediction models, specifically TEST (Toxicity Estimation Software Tools) and OPERA models. This poster presents an overview of the batch search capability in the dashboard and the rich data streams that are made accessible by this functionality and available for exchange with other systems. It will also review the Open data that has been made available for download from the site so that it can be reused and repurposed in other systems. *This abstract does not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

340
QSAR Models for Prediction of the Influence of Cyclodextrin on the Distribution and Remediation of Hydrophobic Organic Compounds in Environmental Systems

William Blanford

Queens College, City University of New York, Flushing, USA. The Graduate Center, City University of New York, New York, USA

Abstract

Cyclodextrins (CD) are cyclic oligosaccharides with a unique truncated conical structures consisting of a hydrophobic cavity into which inclusion complexes with low-polarity molecules of appropriate size and shape can form. This property has been exploited in numerous fields including remediation of hazardous waste sites. In this presentation, QSAR relationships are able to aptly predict the partitioning coefficients between aqueous and CD-complexed states for numerous Hydrophobic Organic Compounds (HOCs) that are commonly found at environmental hazardous waste sites. These relationships are significantly stable that they are able to be extended in more complex models for the phase distribution and transport of chlorinated solvents, aromatic compounds, and other HOCs in batch and column experiments with additional environmentally relevant third phases such as granular activated carbon, soil, and air. While inherently less-controlled, the models show decent correlations and predictions of the results of field studies where CDs have been applied for aquifer remediation at sites with single and multiple HOCs. As a result, QSAR models are functional tools for

prediction of the effect on cyclodextrin on multiple aspects of aquifer remediation systems including aquifer flushing and treatment of extracted fluids.

June 9th, 2021

Application of Tools

303
New developments in the Danish (Q)SAR Database

Nikolai G. Nikolov, Eva B. Wedebye

Technical University of Denmark, National Food Institute, Copenhagen, Denmark

Abstract

The Danish (Q)SAR Database (https://qsar.food.dtu.dk) is one of the most comprehensive freely available (Q)SAR tool with predictions for 650,000 substances in hundreds of QSAR models for a wide range of physical-chemical properties and hazard-related endpoints for human health and environment. It can be used for e.g. single substance evaluations, large-scale complex screenings and to contribute to read-across hypothesis generation and identification of structural analogs. The database was developed by the DTU National Food Institute with financial support from Danish EPA and the Nordic Council of Ministers, as well as support from ECHA.

Since its launch in November 2015, multiple new developments were added:

- Expansion with around 10,000 structures, including 7,000 REACH registered and/or pre-registered substances with predictions in all models.
- Searchable information added on EU CLP harmonized classification, DK EPA / DTU QSAR-based Advisory list classification, and REACH registration cumulated tonnage.
- Expansion with predictions from a number of new DTU-developed QSAR models for: TPO inhibition, PXR binding and activation, CYP3A4 induction, AhR activation, CERAPP ER activation, CoMPARA AR activation, inhibition and binding, CAR activation and inhibition.
- Expansion with predictions from many OECD QSAR Toolbox profilers: genotoxicity, ER binding and skin sensitization.
- Link with the OECD QSAR Toolbox, so predictions can be retrieved on-the-fly by Toolbox users.
- A new website, Danish (Q)SAR Models, for prediction generation in 42 models from the database and export of detailed QPRF reports.

The database has been used by over 10,000 unique IP addresses from regulatory bodies, industry, academia, NGOs etc. worldwide.

347
New approach methods for high throughput risk-based screening and prioritization for ecosystem health

Jon Arnot[1,2], Liisa Toose[1], James Armitage[3], Alessandro Sangion[1], Li Li[4], Mark Bonnell[5]

[1]ARC Arnot Research and Consulting Inc., Toronto, Canada. [2]University of Toronto, Toronto, Canada. [3]AES Armitage Environmental Sciences, Ottawa, Canada. [4]University of Nevada Reno, Reno, USA. [5]Environment and Climate Change Canada, Ottawa, Canada

Abstract

Current chemical assessment methods categorize and prioritize chemicals using various “bright-line” pass/fail criteria for Persistence, Bioaccumulation and Toxicity (PBT). The RAIDAR mass balance model combines environmental fate and toxicokinetic models for aquatic and terrestrial organisms to simulate exposure and risk. The objective of this study is to demonstrate how new approach methods (NAMs) for holistic high-throughput screening and prioritization compare to PBT methods. We conduct a case study comparing RAIDAR exposure- and risk-based metrics to PBT classifications for 12,000 organic chemicals. Model input data were compiled from various sources, including QSARs. The RAIDAR calculated risk assessment factors (RAFs) for the 12,000 chemicals span approximately 14 orders of magnitude thus providing a relatively simple means for prioritizing the chemicals based on potential risks to a range of ecological receptors. Chemicals classified in this example as “PBT” and “not PBT” show an overlap of approximately 14 orders of magnitude when compared based on RAFs. In other words, many chemicals classified as “no concern” using PBT methods have risk estimates comparable to or greater than chemicals classified as “PBTs” and vice versa. This indicates the potential for a high degree of “false negatives” and “false positives” for risk-based prioritization efforts using PBT classifications. The results suggest significant effort and resources can be spent assessing chemicals that present negligible risk in the environment (i.e., not of concern under current use patterns), primarily due to a wide margin of exposure, while other chemicals with high potential risk are overlooked for further evaluation.

221
More than predictions: OECD QSAR Toolbox as an integrated platform in support of chemical hazard assessment

Andrea Gissi[1], Stanislav Temelkov[2], Yordan Karakolev[2], Atanas Chapkanov[2], Todor Pavlov[2], Tomasz Sobanski[1], Ovanes Mekenyan[2]

[1]European Chemicals Agency (ECHA), Helsinki, Finland. [2]Laboratory of Mathematical Chemistry, “Prof. As. Zlatarov” University, Bourgas, Bulgaria

Abstract

With almost 25,000 registered users and thousands of REACH registrations including it, the OECD QSAR Toolbox is one of the most used tools by industry, governments and academia for the prediction of chemical properties. The Toolbox, originally conceived to focus on predictions, has evolved to serve as an integrated platform in support of chemical hazard assessment.

To this end, development efforts are focusing on the Toolbox ability to interact with other systems creating synergies. Existing Toolbox resources and functionalities including chemical searches (such as queries that combine structural and chemical properties), data (over 55 databases), profilers (encoding “knowledge” to e.g. predict possible mode of actions), metabolic simulators and QSAR models can be used in combination with third-party tools. An example is the dedicated plug-in being developed to improve Toolbox access to IUCLID (a database for data on chemicals becoming the standard worldwide), enabling IUCLID users to use Toolbox to perform structural searches and scientific operations in their IUCLID data. Toolbox also features a rich WebAPI that allows Toolbox features to be integrated into pipeline systems and workflows for batch processing of data for e.g. screening purposes. Finally, a web client is under development to enable users of various operating systems and platforms to run the Toolbox in a simplified environment.

As freely available tool rich of resources and functionalities for chemical hazard assessment and being able to communicate with other systems, the Toolbox is an invaluable resource for the regulatory application of in-silico tools in support of chemical hazard assessment.

242
US-EPA CompTox Chemicals Dashboard providing access to QSAR predictions

Antony Williams, Chris Grulke, Todd Martin, Imran Shah, Grace Patlewicz

US Environment Protection Agency, Research Triangle Park, USA

Abstract

The US-EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) is a web-based application providing access to various types of data associated with ~880,000 chemical substances. These data include *in vivo* hazard and *in vitro* bioactivity data, experimental physicochemical and fate and transport data. Stringent curation processes have been applied for the assembly of the data to deliver high-quality datasets to support the development of QSAR models. The models include: logP, water solubility, bioaccumulation factor, bioconcentration factor, and biodegradation and fish biotransformation half-lives delivered via (T.E.S.T) Toxicity Estimation Software Tools and OPERA predictions. The dashboard also provides access to a Generalized Read-Across (GenRA) module. For chemicals of interest that are not already registered in the dashboard real-time predictions based on structural inputs are available. This presentation will provide an overview of the dashboard discussing our ongoing efforts to assemble curated data, including data from the literature and online databases and the development and delivery of prediction models. Recent efforts include the prediction of mass spectrometry spectral fragmentation patterns for over 750,000 chemical structures to support chemical identification. ***This abstract does not necessarily represent the views or policies of the U.S. Environmental Protection Agency.***

272
Application of grouping and read-across approaches in the context of REACH - good practices

Andrea-N Richarz, Andrea Gissi

European Chemicals Agency, Helsinki, Finland

Abstract

The European Chemicals Agency (ECHA)'s 2020 report on "The use of alternatives to testing on animals for the REACH Regulation" confirmed that read-across is the most prominently used adaptation of the standard testing regime in dossier submissions under the Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

There is a wealth of guidance on how to perform read-across, information on the use of available tools, as well as general considerations on chemical grouping and similarity available in the public literature. More specifically for regulatory REACH dossier submissions, ECHA's bespoke Read-Across Assessment Framework (RAAF) gives a systematic overview of the assessment criteria used by ECHA, and the OECD QSAR Toolbox provides a valuable tool to support read-across. However, for reasons which range from technical deficiencies and insufficient documentation to scientific limitations, not all submitted read-across justifications are acceptable in the regulatory context. This might also be owed to shortcomings in the understanding of the regulatory and legal needs.

The presentation will give an overview of the state and practice of the use of read-across and grouping approaches in the context of REACH. It will emphasise important issues to be considered for building a read-across argumentation, as well as for the provision and nature of adequate supporting information, including the use of the OECD QSAR Toolbox.

Non Targeted Screening, Characterising Uncertainty and Informatics

302
In silico toxicology protocols - successes and challenges

Candice Johnson[1], Dave Bower[1], Kevin Cross[1], Kevin Crofton[2], Catrin Hasselgren[3], Raymond Tice[4], Craig Zwick[5], Glenn Myatt[1]

[1]Leadscope, Inc.(an Instem Company), Columbus, OH, USA. [2]R3Fellows LLC, Durham, NC, USA. [3]Genentech, Inc., South San Francisco, CA, USA. [4]RTice Consulting, Hillsborough, NC, USA. [5]Transendix LLC, Indianapolis, IN, USA

Abstract

The implementation of the ICH M7 guideline for the assessment of DNA-reactive mutagenic impurities represented a major step forward in the acceptance of *in silico* toxicology. While the value of *in silico* toxicology is now more widely appreciated today than 20 years ago, there remain some hurdles to the implementation of *in silico* methods for the assessment of non-genotoxic endpoints for regulatory submissions. It is often unclear which methods are appropriate, what constitutes a reliable prediction and how to combine the totality of information into an overall assessment with an associated confidence level. To this end, the definition of *in silico* protocols for major toxicological endpoints is needed. While the protocols for the acute toxicity endpoints are comparatively more straightforward; albeit not simple, there remain challenges to the definition of more complex protocols such as carcinogenicity and neurotoxicity. In this presentation, an overview of the *in silico* protocols for genetic toxicity, skin sensitization, acute lethality, corrosion and irritation will be presented along with a discussion on approaches to implement such protocols. The benefits of a clearly defined adverse outcome pathway (AOP) and defined approaches are highlighted. There are unique challenges for the *in silico* assessment of toxicological endpoints where current knowledge of AOPs may be limited and/-or the quantity of experimental data on which models can be developed are inadequate. For such endpoints, we highlight areas where more fundamental research is needed and set current expectations for the contribution of *in silico* methods to an overall assessment.

227
MUST, a Modular Uncertainty Scoring Tool that Integrates Mixed Toxicity Data Streams to Aid in (Q)SAR Model Development

Jakub Kostal[1], Will Raderman[1], Hans Plugge[2]

[1]The George Washington University, Washington, USA. [2]Verisk 3E, Bethesda, USA

Abstract

In developing (quantitative) structure-activity models, one must first collect and curate available toxicological data to build high-quality training and test sets. Nowadays, this often means combining multiple pieces of evidence from many different sources (*in vivo*, *in vitro* and *in silico*). To that end, modelers are often faced with the challenge of having to reconcile conflicting toxicological data into reliable subsets. In such decision-making process, it is critical to define and quantify uncertainty that invariably accompanies every qualitative or quantitative metric, whether measured, calculated or derived from an expert judgment. Sadly, controversies and uncertainties are often undervalued in toxicological assessments; they lack methodological transparency; or they poorly integrate qualitative and quantitative sources of information. Similarly, data curation in model development is rarely done with sufficient rigor, particularly when applying big-data statistics. To systematize and alleviate hurdles of a decision process that requires synthesis of mixed data streams, we have developed MUST, a Modular Uncertainty Scoring Tool. MUST quantifies data uncertainty based on quality-weighted distribution of observables deemed equivalent by the end-user. Furthermore, the tool allows the user to incorporate his or her expert judgement, and can be trained to reproduce different decision-making paradigms. While designed to aid with predictive model development and toxicological assessments, MUST's applicability extends to any decision-making process that calls for synthesis of incongruent data into a single outcome or a reliable subset. Here we demonstrate previously unpublished utility of MUST in QSAR-model development using several prototypical datasets and toxic endpoints.

248
Determining the Predictive Limit of QSAR Models

Scott Kolmar, Christopher Grulke

US Environmental Protection Agency, Center for Computational Toxicology and Exposure, Durham, NC, USA

Abstract

Quantitatively evaluating QSAR models is becoming more important and more challenging as the number of predictive models grows. The impact of experimental uncertainty on model evaluation has been recognized in the field, but a frequently held assumption is repeated throughout the literature: that a QSAR model can not predict more accurately than the data it is trained on. This study questions this assumption by observing how the addition of simulated random error affects the prediction error for 5 common algorithms and for 7 diverse endpoints. First, an algorithm is trained on a dataset with added noise. Then, the RMSE of the predicted quantities versus the “noisy” experimental quantities are compared to the RMSE of the predicted quantities versus the original “true” data (RMSEtrue). This comparison reports on if the algorithm can predict the true values better than the noisy values. The results show that RMSE is always worse than RMSEtrue for the datasets and algorithms studied. The main conclusion is that QSAR models can make predictions which are actually *more accurate* than the noisy data on which they were trained; however, quantitatively assessing that accuracy using equally noisy validation sets obscures that truth. This conclusion has implications for many QSAR adjacent fields in which datasets have high levels of uncertainty, such as toxicology, and suggests that model predictions may be more accurate than previously thought. The views expressed in this abstract are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.

306
QSAR model applicability domain assessment – consensus of structure, descriptor and response domain information.

Sulev Sild, Uko Maran

University of Tartu, Tartu, Estonia

Abstract

A reliable prediction from a QSAR model presumes that the target chemical is within the applicability domain (AD) of the model. The evaluation of AD is a challenge, because there are no universal measures for estimating the AD or even worse the information about AD may be missing. In practice, a wide variety of AD approaches are used, either individually or in combination, based on analysis of chemical structure space, model response variables and the mechanisms of actions.

This presentation gives an overview of different AD evaluation approaches and describes a new consensus-based approach for AD evaluation. This approach combines several AD methods in a model-specific manner, where thresholds for AD estimation are adjusted on the training set data of each individual model. This approach is designed for the use in the QsarDB repository and uses the raw model data (e.g. analogues in the training set, descriptors, prediction errors) that is stored in the repository. The AD implementation has been tested and is automatically applicable to new (Q)SAR models as soon as they are uploaded in the QsarDB repository and made available to the public.

257
Semi-Quantitative Non-Targeted Analysis as a Rapid Risk Prioritization Tool: A Proof of Concept Using Activated Carbon Drinking Water Filters

Louis Groff, Hannah Liberatore, Seth Newton, Jon Sobus

US EPA, Durham, USA

Abstract

For decades, targeted gas chromatography-mass spectrometry (GC-MS) methods have been used to acquire measurement data in support of risk-based assessments of volatile and semi-volatile chemicals. While targeted measurements of known chemicals have supported most exposure studies, discoveries of new chemicals in diverse media samples have driven shifts toward broader-scope non-targeted analysis (NTA) methods. Typical NTA methods have largely

produced qualitative chemical screening results with minimal quantitative interpretation. For NTA results to be most useful in risk-based contexts, multi-step methods must be developed to estimate chemical concentrations in prepared sample extracts, and ultimately in the original sampled media. Furthermore, needs exist for statistically defensible error-bounding methods if NTA data are to be considered in risk-based decisions. Here, we illustrate a proof-of-concept risk-based prioritization using a mixture of 66 volatile/semi-volatile chemicals commonly found in drinking water, extracted from spiked activated carbon filters, and analyzed using GC high-resolution mass spectrometry. Semi-quantitative concentration estimates of all 66 chemicals were determined using regression-based modeling and surrogate response factors. Statistically defensible error bounds taken from a normalized response factor distribution were applied to prepared solution concentration estimates. Media concentrations were derived from solution estimates using percent recovery data from carbon filter extracts, and compared to existing regulatory levels for preliminary prioritization. This research serves as a model to focus larger NTA datasets on priority chemical lists for further targeted analysis and risk assessment. The views expressed are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.

Keynote – Dr. Elizabeth Mannshardt

369
Data Science: Tools for Scientists in a Data-Centric World

Elizabeth Mannshardt

US EPA, Washington DC, USA. North Carolina State University, Raleigh, USA

Poster Sessions Track 7

346
Eco-CosmePharm: Identifying eco-toxic pharmaceuticals and cosmetics products (marketed) using multi-tasking computational models

PRAVIN AMBURE, Stephen Barigye, Rafael Gozalbes

ProtoQSAR SL, Valencia, Spain

Abstract

Pharmaceutical and cosmetic products are released in the environment during manufacturing, usage, and disposal. Most of these products being water-soluble are transported to water compartments in the environment, where the toxic effects are still not completely predictable. In this scenario, the quantitative structure-toxicity relationship (QSTR) technique plays an important role to enable cost-effectively means of predicting the aquatic toxicity of chemicals. In the present work, we have developed generalized (*multi-tasking*) QSTR models using Box-Jenkins moving average approach for predicting biodegradation relevant properties (i.e., BOD and BCF), as well as, acute and chronic aquatic toxicity of pharmaceutical and cosmetics products. The employed scheme allowed us to develop multi-tasking classification-based QSAR models that can predict the responses of interest while taking into account the diverse experimental conditions such as different test organisms (*Daphnia magna*, *Pimephales promelas*, *Danio rerio, etc.*), endpoint types (LC_{50}, EC_{50}, *NOEC,* etc.), media types, exposure types, duration, etc. The final models were developed using linear discriminant analysis and random forest machine learning techniques. The computed internal and external validation metrics showed that the developed models have high discriminatory power and are robust. The multi-tasking models were then utilized to screen about 8272 marketed pharmaceuticals and cosmetic ingredients. The screening results showed that numerous marketed drugs and cosmetic ingredients can be potentially toxic to aquatic life. In the next step, we will confirm the in-silico results with the experimental assays. Undoubtedly the QSTR models surely assist us to comprehend the impact of such products on environmental health.

284
Improvement of QSARs for Toxicity Prediction by Identifying, Characterising and Reducing Uncertainties

Samuel Belfield[1], James Firman[1], Steven Enoch[1], Judith Madden[1], Terry Schultz[2], Mark Cronin[1]

[1]Liverpool John Moores University, Liverpool, United Kingdom. [2]University of Tennessee, Knoxville, USA

Abstract

QSARs are used to predict the toxicity, fate and properties of chemicals and have found great utility for regulatory applications. The key to the practical application of predictions is their acceptability for regulatory purposes, this has historically been guided by the OECD Principles for the Validation of QSARs as well as copious guidance, for example from OECD and ECHA. To improve this process, uncertainties, variability and areas of bias have been defined for QSARs with 49 assessment criteria (https://doi.org/10.1016/j.comtox.2018.10.003). The aim of the present study was to utilise these uncertainty schemes for QSARs for a variety of toxicological endpoints to demonstrate their applicability (both of the schemes and QSARs), review their use and attempt initial quantification. The schemes to assess the uncertainty, variability and areas of bias of QSARs were summarised into “Hallmarks” for QSAR models. They were then applied to twelve recently published QSARs. Each QSAR was evaluated according to the questions defined by the schemes. The evaluation of the QSAR models found that they were generally well described and presented although for some models provenance of the data was uncertain. Areas where QSARs could be improved included the mechanistic evaluation and justification of the models and the definition of the compound / data set collection. The assessment criteria were found to be easy to apply and gave confidence to predictions from the QSAR models. This type of assessment will assist in understanding what is meant by a model being fit for purpose, especially for regulatory use.

341
EAS-E Suite: a platform to integrate curated databases and QSARs for chemical hazard, exposure and risk assessment

Alessandro Sangion[1,2], Li Li[3], Trevor Brown[2], James Armitage[4], Liisa Toose[2], Jon Arnot[2,1,5]

[1]Department of Physical and Environmental Sciences, University of Toronto Scarborough, Toronto, Canada. [2]ARC, Arnot Research and Consulting Inc., Toronto, Canada. [3]School of Community Health Sciences, University of Nevada Reno, Reno, USA. [4]AES, Armitage Environmental Sciences, Inc., Ottawa, Canada. [5]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada

Abstract

Multimedia mass balance fate, toxicokinetic, and exposure models can be used to estimate exposure and risk. However, a lot of input data are required to run these mechanistic models. Unfortunately, for thousands of chemicals needing evaluation, these data are limited, not standardized and documented across multiple sources. Validated QSARs are tools that can be used to address measurement data gaps.

The Exposure And Safety Estimation (EAS-E) Suite platform has been developed to facilitate the application of databases, tools and models to bridge the gap between evolving scientific research and assessment challenges. EAS-E Suite is comprised of chemical information databases and QSARs to automatically parameterize models and tools (e.g., RAIDAR, RAIDAR-ICE, CiP-CAFÉ and PROTEX-HT) to simulate chemical fate and exposure of ecological and human receptors. EAS-E Suite allows automatic querying of the internal curated databases and QSARs from only chemical structure to obtain the input parameters for the fate, bioaccumulation, and exposure model simulations. Three main QSAR packages are available in EAS-E suite: i) the Iterative Fragment Selection (IFS) QSAR method, ii) the QSARINS statistical models based on PaDEL descriptors and iii) OPERA models developed by EPA. Each prediction is provided with an estimate of the Applicability Domain to aid users to evaluate the reliability and consistency of the predictions. This includes estimates of potential

errors in the QSAR predictions which can be used in uncertainty analyses of model outputs fostering confidence in the application of these data for applications within EAS-E Suite or for external applications.

357
Integrating mechanistic computational modeling and QSXR techniques in support of high-throughput screening of ecological and human exposure to synthetic chemicals

Li Li[1,2], Alessandro Sangion[2,3], Frank Wania[2], Jon Arnot[3,2]

[1]University of Nevada, Reno, Reno, USA. [2]University of Toronto Scarborough, Toronto, Canada. [3]ARC Arnot Research & Consulting, Toronto, Canada

Abstract

High-throughput screening of chemicals is challenging if the ambition is to holistically account for how key determinants interactively govern a chemical's fate and risks during its journey from production to exposure. The challenge is compounded for new or premarket substances with limited or no information. In this presentation, we will introduce an input-parsimonious modeling framework, called PROTEX-HT, which supports mechanistic high-throughput screening and prioritization of synthetic chemicals based on ecological or human exposure and resulting risks. PROTEX-HT fuses mechanistic computational modules describing chemical behavior and fate in the human socioeconomic system (the "technosphere"), environment, food webs, and the human body. Integration with state-of-the-art quantitative structure-X relationships (QSXRs; X = property, activity, and use) and built-in datasets enables input-parsimonious, computationally efficient predictions based solely on molecular structure and chemical tonnage. We will also demonstrate how PROTEX-HT successfully predicts exposure and risks for 95 organic chemicals in the U.S. By being able to predict emission rates, concentrations in environmental and exposure media, exposure rates, and body concentrations, PROTEX-HT can support chemical screening and prioritization efforts in a range of academic and regulatory contexts. By mechanistically describing chemical behavior and processes, PROTEX-HT aids chemical-specific decision-making while considering the complex interplay between chemical properties, use patterns, exposure routes, and toxicities. PROTEX-HT also identifies the most relevant emission sources, receiving environmental media, and exposure routes, facilitating cost-effective measures for reducing ecological and human exposures. Interested users can access PROTEX-HT via a user-friendly online platform "Exposure And Safety Estimation (EAS-E Suite)" (www.eas-e-suite.com).

190
ANN-QSPR MODELING OF THE SOLUBILITY OF DRUG-LIKE COMPOUNDS IN SUPERCRITICAL CARBON DIOXIDE

Imane Euldji[1], Cherif Si Moussa[1,2], Mabrouk Hamadache[1,2]

[1]Biomaterials and Transport Phenomena Laboratory (LBMPT), University Yahia Fares, Medea, Algeria. [2]Department of Process and Environmental Engineering Institute of Technology, University Yahia Fares, Medea, Algeria

Abstract

The low-aqueous solubility of drugs, known as the number one influence thermodynamic property, is usually overcome with the enhancement process of the supercritical carbon dioxide (SC-CO2). This study aims to surpass the defects of traditional thermodynamic dissolution forecasting methods, and limit the use of tedious and expensive experiments by proposing a machine learning model able to predict the molar solubility fraction of drug-like compounds in SC-CO2 based on their molecule structures, and based on two independent intensive state variables, the temperature, and the pressure. A QSPR model was first applied to select the best-fit combination able to represent the target property by collecting 133 drug-like compounds, convert them to the SMILES notation, and then calculate their molecular descriptors using the software Padel. The obtained 1544 molecular descriptors were reduced to 11 significant descriptors: AATS3v, MATS2e, GATS4c, GATS3v, GATS4e, GATS3s, nBondsM, AVP-0, SHBd, MLogP, and MLFER_S. By adding the temperature and the

pressures, those 13 features were used as input variables forming the final dataset of 3590 experimental data points that have been used to build and select the best representative MLP-ANN model their predictive/correlative capacity and feasibility were examined. The results show that the model meets all of the OECD principles for QSAR validation with a global AARD of 1.06%. As well, this model is a fit candidate for predicting future data and can be used to predict the solubility of drug-like compounds, particularly for those that have not been tested as well as new compounds.

186
Exploring the Use of Interspecies Correlation Estimation Models for Regulatory Purposes: A Case Study with Alcohol Ethoxylates

Adriana C Bejarano[1], James R Wheeler[2]

[1]Shell Oil Company, Shell Health – Americas, Houston, USA. [2]Shell International, Shell Health, The Hague, Netherlands

Abstract

The need for non-animal alternatives to toxicity testing has led to directives worldwide encouraging innovation for toxicity evaluation, including the development and evaluation of New Approach Methodologies (NAMs). Interspecies Correlation Estimation (ICE) models, a possible NAMs, have gained scientific acceptance but to date have not been used extensively for regulatory purposes. ICE models leverage existing data and describe mathematical relationships between pairs of species responses that can be used to predict toxicity from surrogates to untested species. Model outputs could be used to improve assessments by developing Species Sensitivity Distributions (SSDs) from a relatively small sample of empirical data. In this work, ICE models were developed for alcohol ethoxylates (AEs), a group of chemically related nonionic surfactants with a shared mode of toxicity. Aquatic toxicity data for 32 Shell AE products (Klimisch score 1 and 2) were used. Twelve AE-ICE models were statistically significant (slope>1) and met established criteria for model reliability. Model predictions were generally within a 3-fold difference of observed values not used in model development. Prediction were also closer to the observed values than predictions from related models (i.e., broad narcosis or specific nonpolar ICE models). Results showed that Hazardous Concentrations (HC5s) from SSDs enhanced with AE-ICE predictions cover a narrow range of values (0.13 to 2.88 mg/L). Preliminary findings suggest that ICE models for structurally similar products could be used as an additional tool to fulfill information requirements for regulatory purposes, while reducing the need for animal testing.

187
In silico assessment of acute oral toxicity for mixtures

Yaroslav Chushak[1], Jeffery Gearhart[1], Darrin Ott[2]

[1]Henry M Jackson Foundation for the Advancement of Military Medicine, Dayton, USA. [2]Airman Biosciences Division, 711 Human Performance Wing, Wright-Patterson AFB, USA

Abstract

While exposure of humans to environmental hazards often occurs with complex chemical mixtures, the majority of existing toxicity data are for single compounds. The Globally Harmonized System of chemical classification (GHS) uses the additivity formula for acute oral toxicity classification of mixtures, which is based on the acute toxicity estimate of individual ingredients. We evaluated the prediction of GHS category classifications for mixtures using toxicological data collected in the Integrated Chemical Environment (ICE) developed by the National Toxicology Program. The ICE database contains *in vivo* acute oral toxicity data for ~10,000 chemicals and for 582 mixtures with one or multiple active ingredients. By using the available experimental data for individual ingredients, we were able to calculate a GHS category for only half of the mixtures. To expand a set of components with acute oral toxicity data we used the Collaborative Acute Toxicity Modeling Suite (CATMoS) implemented in the Open Structure-Activity/Property Relationship App (OPERA) to make predictions for active ingredients without available experimental data. As a result, we were able to make predictions for

504 mixtures/formulations with 72% of accuracy for the GHS classification. For 186 mixtures with two or more active ingredients the accuracy rate was 76%. The structure-based analysis of the misclassified mixtures did not reveal any specific structural features associated with the mispredictions. Our results demonstrate that CATMoS together with additivity formula can be used to predict GHS category for chemical mixtures.

197
LIFE CONCERT REACH - a new network of *in silico* models

Rodolfo Gonella Diaza[1], Antje Gerloff-Elias[1], Eva Bay Wedebye[2], Alberto Manganaro[3], Paolo Manes[4], Igor Tetko[5], Emilio Benfenati[6]

[1]knoell Germany GmbH, Mannheim, Germany. [2]Technical University of Denmark, Kongens Lyngby, Denmark. [3]Kode s.r.l., Pisa, Italy. [4]SC Sviluppo chimica S.p.A., Milan, Italy. [5]BIGCHEM GmbH, Unterschleissheim, Germany. [6]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Abstract

LIFE CONCERT REACH is an EU funded four-year project started in 2018 involving research institutes and consultancy companies. The project aims to establish a new, freely accessible, network of in silico models, including both (Q)SAR and automated read-across tools.

The network will be achieved by linking existing and well-known platforms (such as VEGA platform, the Danish QSAR Database, OCHEM and AMBIT), as well as developing and integrating new models, potentially covering all properties required within the framework of Regulation EC (No) 1907/2006 (REACH). The new network will include statistical and knowledge-based (Q)SARs as well as automated read-across tools. The goal of the project is to offer more than 300 freely available *in silico* models. The new integrated network will also interface with the OECD QSAR Toolbox. Both (Q)SAR models and read-across tools will be developed or updated to be compliant with current regulatory requirements under REACH (e.g. ECHA's Practical guide 5 - "How to use and report (Q)SARs" and ECHA´s "Read-across assessment framework (RAAF)"), focusing on providing all the information needed to evaluate and use the obtained results (e.g. QMRF and QPRF).

We will present here some of the new models which have been implemented in the last VEGA version and are now publicly available since 2021, and the proposed new report format from VEGA, to be much closer to the QPRF.

217
Novel Random Forest Models for Endocrine Disrupting Chemical Screening

Sean P. Collins, Tara S. Barton-Maclaren

Existing Substances Risk Assessment Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Canada

Abstract

Endocrine disrupting chemicals (EDCs) are an area of concern in toxicology and chemical risk assessment; and advances in computational toxicology can play an important role in identification and hazard characterization. In response to the need to enhance chemical screening to include the potential to be endocrine disruptors, the US EPA developed consensus models under the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP) and the Collaborative Modeling Project for Receptor Activity (CoMPARA), which aim to predict estrogen and androgen activity, respectively. Building on previous accomplishments in the field, in this work we used the evaluation sets from CERAPP and CoMPARA to train random forest (RF) models to predict estrogenicity and androgenicity, respectively. This was done as current models either have low predictive power, or limited chemical space of applicability. By utilizing simplistic descriptors and larger evaluation sets to train the models, the RF models were created to screen for EDCs. RFs were trained to over predict activity, meaning models are biased to make False Positive predictions to minimize False Negatives. Twelve unique RF

models were created; binary and multi-class models to predict binding, agonism, and antagonism for both estrogen and androgen receptors. The RF models presented in this work were found to have higher predictive capabilities than their CERAPP and CoMPARA consensus model counterparts, with some models reaching balanced accuracies of 93%. These models can be used to screen substances to support prioritization and assessment activities, flagging those which have potential to be endocrine disrupting.

226
QSAR-based prediction of the biomagnification of organic chemicals in fish

Linda Bertato[1], Olivier Taboureau[2], Ester Papa[1]

[1]University of Insubria, Varese, Italy. [2]University of Paris, Paris, France

Abstract

The potential of a substance to accumulate in biota through the diet (i.e. Biomagnification) is an important property necessary to assess Bioaccumulation. Dietary biomagnification factor (dietary BMF) in fish gained recent regulatory acceptance and a major use due to its inclusion in the OECD 305 guideline.

In silico models, based on Quantitative Structure Activity Relationships (QSAR), can be created to predict the dietary BMF for existing and new chemicals, starting from already available dietary BMF data.

In this study, a dataset of fish laboratory-based dietary BMF values composed of 736 data measured for 320 heterogeneous compounds was collected from litterature and used to develop QSARs models. After data curation, multiple data available for a single compounds were averaged and log transformed, covering a wide range of log BMF from -5.70 to 1.26.

QSAR models were developed, after calculation and selection of diverse theoretical molecular descriptors, by applying different linear and non-linear regression and classification techniques. These QSARs, perform well in terms of fitting and predictivity (R^2tr=0.79, RMSEtr=0.54, RMSEext=0.56). In addition they comply with OECD requirements for the regulatory use of QSARs, i.e. model transparency, statistical validity, defined domain of applicability as well as interpretation of the molecular descriptors found to be relevant in the models.

In conclusion, the here proposed QSARs, which are based on a large diversity of chemical's structure, can be used to generate reliable predictions of fish dietary BMFs. These models and their predictions are useful to support chemical assessment procedures.

301
Applicability of (Q)SAR tools on the PBT assessment of active substances and related metabolites

Gustavo Dias, Ana Domingues, Bruno Calçada, Sara Coelho, Sofia Sousa

Ascenza, Lisbon, Portugal

Abstract

Quantitative Structure Activity-Relationships (QSARs) are computational models that use the chemical structure of compounds to analyse and predict their physicochemical properties and bioactivity. In silico methodologies represent an alternative to animal testing in terms of their reduction, refinement and replacement, as they have the potential of being a faster, accurate and efficient way of data generation. Their applicability in areas like (eco)toxicology and environmental fate has been increasing in the last few years, namely on the field of Plant Protection Products (PPPs) risk assessment. PPPs and their constituent active substances are highly regulated, especially after the entry into force of European Regulation (EC) 1107/2009. This regulation is intended to ultimately assure the protection of human health and environment. For that,

criteria, such as Persistency (P), Bioaccumulation (B) and Toxicity (T), are used to set the approval or non-approval of PPPs.

The main aim of this study is to assess the applicability of a (Q)SAR tool on the PBT assessment of several active substances and related metabolites. To fulfil such aim, the software OECD (Q)SAR Toolbox will be used as a screening tool of a randomly selected group of active substances (available in Ascenza Agro S.A. portfolio) and some of their most important metabolites. In the end, the alignment of the in silico predictions with the classifications established for these compounds will be evaluated. A good performance by the model will validate that (Q)SAR models fit the regulatory requirements and highlight their importance to industry and regulators.

308
Prediction of Nanomaterial Genotoxicity through QSAR Approaches

Mohammad Zein Aghaji, Djordje Vladissavljevic, Mark Lewis

Health Canada, Ottawa, Canada

Abstract

Health Canada is responsible for the human health risk assessment of nanomaterials (NMs) found in Canadian commerce (i.e., NMs listed on Canada's Domestic Substances List). Risk assessment of NMs requires information on their physical-chemical properties and toxicological endpoints, which are often not available, and therefore, QSAR approaches are being explored to fill such data gaps. Employing these approaches requires a great deal of information on physical and chemical properties and toxicological endpoints of NMs. As such, a Nanomaterial Hazard Database is being developed through extensive review of the peer-reviewed scientific literature for NMs under 53 CAS RN. The database is implemented in Excel and currently contains 4000 unique particle/assay experiments published between 2010-2017. The database provides information on substance identity (i.e. Chemical Abstracts Services Registry Numbers), physical-chemical properties, experimental conditions, and hazard-related information and toxicological endpoints of NMs. Using this database in combination with machine-learning algorithms including logistic regression and support vector machines, relationships between physical-chemical properties and genotoxicity of NMs were examined, and the most relevant physical-chemical properties to genotoxicity were identified. In addition, QSAR models were built to predict the genotoxicity of NMs. With a QSAR model, general genotoxicity could be positively predicted with >80% precision and >80% sensitivity. The improvement of the QSAR models is underway by incorporating tree-based approaches and adding to the database new data published in the literature since 2017.

362
Structural Alerts For Predicting Skin Sensitization – In silico Model Derived From a Data Set of 1982 Organic Compounds

Gerrit Schüürmann[1,2], Marcus Hillebrand[3], Ralph Kühne[1], Ralf-Uwe Ebert[1]

[1]UFZ Department of Ecological Chemistry, Helmholtz Centre for Environmental Research, Leipzig, Germany. [2]Institute of Organic Chemistry, Technical University Bergakademie Freiberg, Freiberg, Germany. [3]Umweltbundesamt Dessau-Roßlau, Fachgebiet IV 1.3-1 Ökotoxikologie und Umweltrisiken Pflanzenschutzmittel, Dessau-Roßlau, Germany

Abstract

Around 15-20% of the population are allergic to one or more chemical substances.[1] Organic skin sensitizers are often electrophiles or pro-electrophiles, and occur in industrial chemicals, care products and cosmetics. In Europe, REACH requires assessing the skin sensitization potential of industrial compounds at or above 1 t/a year market volumes, with the murine local lymph node assay (LLNA) serving as method of choice. At the same time, the 3R principle has fostered research into respective in vitro, in chemico and in silico approaches.[2-7] For deriving new structural alerts, a set of 1982 organic compounds with 1090 LLNA data and 974 GPT (guinea pig maximization or Buehler test) data was collected. The

resultant in silico models outperform existing structural alert schemes regarding both concordance (85%) and chemical application domain. The fully computerized version allows the user to inspect for each compound of interest potentially available structural alerts used for respective activity predictions.

[1] Karlberg A-T, Bergström MA, Börje A, Luthmann K, Nilsson JLG 2008. *Chem. Res. Toxicol.* 21: 53-69.

[2] Enoch SJ, Madden JC, Cronin MTD 2008. *SAR QSAR* 19: 555-578.

[3] Rorije E, Aldenberg T, Buist H, Kroese D, Schüürmann G 2013. *Regulat. Toxicol. Pharmacol.* 67: 146-156.

[4] Patlewicz G et al. 2016. *Regulat. Toxicol. Chem.* 82: 147-155.

[5] Braga RC et al. 2017. *J. Chem. Inf. Model.* 57: 1013-1017.

[6] Alves VM et al. 2018. *ACS Sustainable Chem. Eng.* 6: 2845-2859.

[7] Tung C-W, Wang C-C, Wang S-S 2018. *Regulat. Toxicol. Pharmacol.* 94: 276-282.

365
Comparison of Case Ultra Skin and Eye Irritation and Models for 497 SMILES of Diesel Fuel to In Vivo Data

Jessica Ryman-Rasmussen[1], Denise Roesh[2], Chad Thompson[3], Gianna Cioffi[4], Suman Chakravarti[4]

[1]American Petroleum Institute (API), Washington, DC, USA. [2]Chevron USA, Inc., Houston, TX, USA. [3]ToxStrategies, Katy, TX, USA. [4]MultiCASE, Inc., Beachwood, OH, USA

Abstract

Diesel fuel is classified in the EU (via GHS/CLP) as a Category 2 skin irritant but is not classified as an eye irritant based on *in vivo* skin and eye irritation studies conducted via the Draize method. Diesel fuel is a UVCB substance and so cannot be represented by a unique structure and molecular formula. A library of constituents in SMILES format was therefore generated and 497 SMILES were selected and analyzed using skin and eye irritation models in CASE Ultra versions 1.8.0.0 and 1.7.0.5. Both versions showed relatively low (<2.0%) positive calls for eye irritation but high (80%) negative calls and similar levels of out-of-domain (5.8%) and inconclusive (12%) calls. Coverage for both versions was 82%. This is consistent with no classification for eye irritation for *in vivo* data and indicates a relatively low level of false positives and false negatives in both versions. For skin irritation, version 1.8.0.0 provided a 25-fold increase in positive calls (67% versus 2.6%), a 4.8-fold reduction in negative calls (16% vs. 78%), a 2.2-fold reduction in out-of-domain calls (2.2% vs. 4.8%), with slightly improved coverage (83% vs. 81%) and similar inconclusive calls (14%). These results suggest that QSAR models are promising alternatives to animal testing.

367
Linking LRI AMBIT3 chemoinformatic system with the IUCLID6 substance database to support read-across of substance endpoint data and category formation

Bruno Hubesch[1], Nina Jeliazkova[2], Q Li[3]

[1]CEFIC, Brussels, Belgium. [2]Ideaconsult Ltd, Sofia, Bulgaria. [3]Clariant Produkte, Sulzbach, Germany

Abstract

Read-across and category formation are indispensable techniques in safety assessments of chemicals. The AMBIT software, funded initially within the CEFIC LRI programme, provides a web service and user friendly web interface to a chemical database, various chemical structure search facilities and toxicity prediction models. The AMBIT data model supports substances with complex compositions and substances experimental data which allows importing data from the International Uniform Chemical Information Database (IUCLID6) as well as other sources. The chemical structures already

contained in AMBIT are automatically linked to constituents/impurities/additives of the imported substances. The flexible data storage and visualization allows for user friendly presentation of study data (physicochemical properties, environmental fate, ecotoxicological and toxicological information) and composition. Comprehensive assessment workflows are developed for read-across and category formation based on all the data available in AMBIT. The assessment workflow facilitates the search for target and source structures through multiple similarity methods, generating data matrices, gap filling and generating assessment reports with predefined formats automatically. The enhanced AMBIT facilitates drafting and improves quality for read-across and category formation and will be a useful tool for experts responsible for substance assessments.

The current landscape of chemical databases is in order of many thousands, distributed under different licenses, and are being continuously updated and may be of interest in different use cases. In addition to REACH study results https://iuclid6.echa.europa.eu/reach-study-results and OpenFoodToxv2, AMBIT3 will follow stakeholder's recommendation and integrate additional sources as e.g. ECHA's REACH 2018 dataset, US EPA CompTox Chemicals Dashboard, EFSA's OpenFoodTox 2 dataset and the RepDose database.

Poster Sessions Track 8

267
Advanced QSAR for use in biokinetic models with special focus on neurodevelopmental disorders.

Ioannis Petridis[1], Spyros Karakitsios[1,2,3], Krystalia Papadaki[4], Dimosthenis. A. Sarigiannis[1,2,5,3]

[1]Aristotle University of Thessaloniki, Department of Chemical Engineering, Environmental Engineering Laboratory, Thessaloniki, Greece. [2]HERACLES Research Center – KEDEK, Aristotle University of Thessaloniki, Thessaloniki, Greece. [3]Enve-X Solutions Single Member P.C., Thessaloniki, Greece. [4]Hellenic Petroleum S.A., Thessaloniki, Greece. [5]Environmental Health Engineering, Institute of Advanced Study, Pavia, Italy

Abstract

The purpose of the study is to develop quantitative structure-activity relationships (QSAR) using artificial intelligence techniques, such as neural networks (ANN) and multiple linear regression (MLR) in order to optimize the parameterization of the physiologically based-biokinetic models (PBBK) aiming to improve accuracy on exposure estimation for "data-poor" compounds, mainly related to neurodevelopmental disorders. In this study, QSARs were developed using Abraham's solvation equation combined with LFER and PaDEL molecular descriptors in order to model certain tissue:blood partition coefficients, elimination half-life and Michalis-Menten kinetic properties of environmental chemicals. For the statistical analysis of the modeling, genetic algorithm multiple linear regression and ANN of one hidden layer were used and compared. The statistical coefficient of determination (R squared), the cross-validation coefficient of determination based on Leave-Many-Out and Leave-One-Out cross-validations (Q squared) and the mean squared error (MSE) were used as validation parameters in selecting the most efficient statistical analysis technique. Those metrics indicated that the use of PaDEL descriptors and the ANN outperform all other methods resulting in more accurate predictions. Specifically, PaDEL descriptors outweigh LFER descriptors in terms of goodness of fit, robustness and predictive ability of the models, while ANNs outweigh MLR in terms of performance. To conclude, QSAR models can be successfully used to fill the data gaps of the "poor data" chemicals and therefore positively contribute in determining health and safety risks of known and newly designed compounds by minimizing time and uncertainties of the design process as well as testing, societal and industrial costs.

297

EPA's DSSTox Chemical List Curation Protocol: Enabling list-data integration in the CompTox Chemicals Dashboard

Christopher Grulke[1], Inthirany Thillainadarajah[2], Antony Williams[1], Ann Richard[1]

[1]US EPA - Center for Computational Toxicology and Exposure, Durham, NC, USA. [2]US EPA - Senior Environmental Employment Program, Durham, NC, USA

Abstract

Computational toxicology research within EPA integrates advances in biology, chemistry, and computer science to prioritize chemicals for further research based on potential health and exposure risks. This integration is enabled by the mapping of chemical identifiers from source lists to DSSTox substances using our chemical list curation protocol (CLCP). Source-substance identifiers typically consist of chemical names, CAS-RN, and/or structures (e.g., SMILES), but rarely are all three types of IDs provided. DSSTox's CLCP employs automated algorithms to map source IDs to existing DSSTox content, identifying all possible DSSTox ID matches (including through synonym tables). Strict enforcement of uniqueness rules requiring 1:1 substance (name, CAS RN) to structure mappings is used to identify conflicts in source identifier mappings (e.g., Source name maps to one DTXSID, CAS RN maps to another), which must be resolved by expert manual curation prior to completing list registration. High rates of identifier conflicts and errors are encountered in processing of most source lists. The CLCP has resulted in the mapping of more than 400 source lists to DSSTox substances (225 available in the public Dashboard with the remainder partially mapped or internal to EPA). Three applications of the CLCP will be described, mapping substances in: (1) EPA's Toxic Substances Control Act (TSCA) "actives" list, (2) EPA's Toxicity Value database, and (3) EPA's Consumer Product Database. The CLCP has been integral to the expansion to DSSTox and data integration efforts, while ensuring quality substance-structure-data associations. A*bstract does not reflect EPA policy.*

239

In silico MS/MS fragmentation spectra for identifying chemical unknowns: applications and performance validation

Antony Williams[1], Andrew McEachran[2], Alex Chao[1], Tom Transue[3], Tommy Cathey[3], Jon Sobus[1]

[1]US Environmental Protection Agency, Research Triangle Park, USA. [2]Agilent Technologies, Santa Clara, USA. [3]General Dynamics Information Technology, Inc, Research Triangle Park, USA

Abstract

High resolution mass spectrometry (HRMS) and non-targeted analysis (NTA) are advancing the identification of emerging contaminants in environmental matrices, improving the means by which exposure analyses can be conducted. Structure identification requires integration of complementary data types such as reference databases, fragmentation prediction tools, and retention time prediction models. *In silico* fragmentation spectra predicted via Competitive Fragmentation Modeling-ID (CFM-ID) algorithms were generated for 765,000 compounds within the U.S. Environmental Protection Agency's (EPA) database (underpinning the CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard)). A prototype web-based tool for searching an experimental spectrum against the CFM-ID database has been developed where users visualize both the candidate results returned for the spectrum as well as visualizations of the predicted vs. experimental spectrum. We have reported performance validation using *in silico* fragmentation coupled with candidate ranking using various forms of meta data for structure identification. This poster will report on a number of evaluation studies that indicate that the use of *in silico* fragmentation prediction is highly beneficial in a non-targeted analysis mass spectrometry workflow. *This abstract does not necessarily represent the views or policies of the U.S. Environmental Protection Agency*

246
Predicting Chromatography-tandem Mass Spectrometry Amenability to Improve Non-targeted Analysis

Charles Lowe[1], Kristin Isaacs[1], Chris Grulke[1], Jon Sobus[1], Elin Ulrich[1], Andrew McEachran[2], Antony Williams[1]

[1]US Environmental Protection Agency, RTP, USA. [2]Agilent Technologies, Inc., Santa Clara, USA

Abstract

With the increasing availability of high-resolution mass spectrometers, suspect screening and non-targeted analysis are becoming popular compound-identification tools for environmental researchers. Samples of interest often contain a large (unknown) number of chemicals spanning the detectable mass range of the instrument. In an effort to separate these chemicals prior to injection into the mass spectrometer, a chromatography method is often utilized. There are numerous types of gas and liquid chromatographs that can be coupled to commercially available mass spectrometers. Depending on the instrument used, the researcher is likely to observe different compounds based on the amenability of those chemicals. It would be advantageous if this subset of chemicals could be predicted prior to conducting the experiment, to minimize potential false positive identifications. In this work, we combine experimental data associated with the US EPA's ToxCast library, along with mass spectrometry data from the MassBank of North America (MoNA) database, to predict the amenability of unique compounds with liquid chromatography mass spectrometry (LC-MS). The assembled dataset totals 5,517 unique chemicals either explicitly detected or not detected with LC-MS. The resulting detected/not-detected matrix has been combined with PaDEL molecular descriptors to model which chemicals are amenable to LC-MS. We have constructed random forest models for both positive and negative modes of the electrospray ionization source. The outcome of this work should help inform future suspect screening and non-targeted analyses of potential chemical compound identities. *This abstract does not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

251
Comparing performance of in silico metabolism tools using data derived from literature and non-targeted analysis

Matthew Boyce[1,2], Brian Meyer[2], Chris Grulke[2], Grace Patlewicz[2]

[1]Oak Ridge Associated University, Oak Ridge, USA. [2]Center for Computational Toxicology and Exposure, US Environmental Protection Agency, Research Triangle Park, USA

Abstract

Understanding the metabolic fate of a chemical substance is important for evaluating its toxicity. Changes in the regulatory landscape of chemical safety assessment provide opportunities to use *in silico* tools for metabolism prediction. In this study, a set of 37 structurally diverse chemicals were compiled from the EPA ExpoCast inventory to compare and contrast a selection of *in silico* tools, in terms of their coverage and performance. The tools were Systematic Generation of Metabolites (SyGMa), Meteor Nexus, BioTransformer, Tissue Metabolism Simulator (TIMES), OECD Toolbox, and Chemical Transformation Simulator (CTS). Performance as characterized by sensitivity and precision were determined by comparing predictions against metabolites reported in literature. Reported metabolites (438 in total) were extracted from 49 papers. Coverage was calculated to provide a relative comparison between tools. Meteor, TIMES, Toolbox, and CTS predictions were run in batches, using default settings. SyGMa and BioTransfomer were run with user-defined settings, (two passes of phase I and one pass of phase II). Hierarchical clustering revealed high similarity between TIMES and Toolbox. SyGMa had the highest coverage, matching an average of 41.2% of predictions generated by the other tools. SyGMa was also prone to significant overpredicting, generating a total of 5,125 predictions or 67% of total predictions. Precision and sensitivity values ranged from 4.7-23.7% and 15-27.5% respectively. TIMES had the highest performance overall. Current efforts are

focused on evaluating the concordance of *in vitro* data, newly generated, relative to the literature data and *in silico* predictions. *This abstract does not reflect EPA policy.*

278
Definition of a SMARTS-based harmonized classification of the toxicological MoA of PPP active substances towards honey bees

Domenico Gadaleta[1], Edoardo Carnesecchi[2], Alessandra Roncaglioni[1], Jean-Lue Dorne[3], Emilio Benfenati[1]

[1]Laboratory of Environmental Chemistry and Toxicology, Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy. [2]Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, Netherlands. [3]Scientific Committee and Emerging Risks Unit, European Food Safety Authority (EFSA), Parma, Italy

Abstract

Honey bees (*Apis mellifera*) have a key role in the ecosystem as pollinators and are relevant in food production. In the EU, the risk assessment of Plant Protection Product (PPP) active substances should evaluate the environmental impact associated with the potential combined exposure to these chemicals towards honey bees. The current study explores the development of harmonised Mode of Action (MoA) classification schemes to relate the structure of PPP active substances to their potential target site for toxicity towards honey bees. Qualitative information on the MoAs of a set of 113 substances was retrieved from publicly available sources, i.e. the Pesticides Properties DataBase (PPDB), the classification proposed by the IRAC, FRAC, HRAC and the scientific literature. Based on this information, PPP were classified according to their i) function (insecticide, fungicide, acaricides, herbicides, etc.), ii) chemical class and iii) MoA (site of action). Finally, chemicals were grouped according to the harmonised MoA into 33 categories. Based on this harmonised classification and on information from literature, a series of 41 SMARTS was manually defined to classify PPP based on their chemical category and their toxicological MoA. The classification scheme has been implemented in the freely available VEGA platform (www.vegahub.eu). The use of MoA information for honey bees toxicity can provide a sound mechanistic understanding of the molecular initiating event and key events leading to adverse effects at individual and colony level. It can be useful to address the toxicity of PPP active substance mixtures through clustering compounds sharing the same MoA.

348
A new database and preliminary QSARs for environmentally relevant biodegradation half-lives

Trevor Brown[1], Alessandro Sangion[2], Jon Arnot[2,3]

[1]ARC Arnot Research and Consulting, Halifax, Canada. [2]ARC Arnot Research and Consulting, Toronto, Canada. [3]University of Toronto, Toronto, Canada

Abstract

Environmental biodegradation half-lives are important parameters for performing chemical hazard and risk assessment, but there is a paucity of such data for thousands of chemicals that require evaluation. While databases and Quantitative Structure Activity Relationships (QSARs) for environmental biodegradation half-lives of hydrocarbons have been developed, QSARs do not exist for other chemical classes. The objective of this study is to develop a new database of environmental biodegradation half-lives, focusing on primary aerobic biodegradation in water (HL_{pawb}), and new QSARs for this parameter. An initial dataset of 2326 HL_{pawb} values for 1114 organic chemicals was developed from publicly available datasets. The HL_{pawb} values in the dataset span a range of nearly five orders of magnitude, with good separation of labile and highly persistent chemicals. QSARs for environmental biodegradation are being developed using the new database as a training set. The IFS-based QSARs were developed and evaluated following OECD QSAR guidance, using the algorithm described in previous publications. The QSARs include a fully defined applicability domain (AD). In an external validation dataset, chemicals which are within the model AD show adequate predictions, with a q^2 of 0.65 (correlation of predicted

values regressed vs. expected values for the external validation set). Predictions for chemicals further outside the AD are less reliable. The relatively narrow AD of the model suggests that the QSAR is limited by current data availability, even with the large training dataset (n=743). The new QSAR can be used to prioritize experimental testing to address uncertainty in chemical assessments.

349
Addressing uncertainty in bioaccumulation assessment using the Bioaccumulation Assessment Tool (BAT)

Liisa Toose[1], James Armitage[2], Alessandro Sangion[1], Joshua Wyatt[1], Michelle Embry[3], Jon Arnot[1,4]

[1]ARC Arnot Research and Consulting, Toronto, Canada. [2]AES Armitage Environmental Sciences, Ottawa, Canada. [3]HESI, Washington, USA. [4]University of Toronto, Toronto, Canada

Abstract

Lines of evidence (LOE) used for bioaccumulation (B) assessment include in vivo and in vitro measurements and in silico predictions for B-metrics such as the bioconcentration factor (BCF), bioaccumulation factor (BAF), biomagnification factor (BMF) and trophic magnification factor (TMF). Quantitative Structure Activity Relationships (QSARs) play an important role in addressing data gaps. The Bioaccumulation Assessment Tool (BAT) was developed to guide the collection, generation, evaluation, and integration of various LOE for B assessment of neutral and ionizable organic chemicals in both aquatic and air-breathing organisms. The BAT includes in vitro-in vivo extrapolation (IVIVE) and mass balance toxicokinetic (TK) models for both types of organisms and food webs as well as simulated laboratory models (invertebrates, fish and rodent) to calculate B-metrics (e.g., BCF, BMFs, half-lives). Each experimental, field and QSAR B-metric included in the BAT is critically evaluated and scored for reliability using Data Evaluation Templates (DETs). The BAT DETs have been derived primarily from OECD technical guidance documents. When multiple LOE are available for biotransformation half-lives, an uncertainty factor is calculated and propagated in the BAT TK model B-metric calculations. When parameterized with multiple biotransformation half-life QSARs and/or in vitro biotransformation rate data, the BAT TK models calculate the uncertainty for each BAT model predicted B-metric. The objective is to demonstrate the application of the BAT with a focus on estimating the uncertainty associated with biotransformation half-life estimates. The BAT TK model BCF, BAF and BMF predictions for aquatic and mammalian organisms are compared to field and laboratory data.

313
Machine learning model comparisons for endocrine disruption prediction

Kimberley Zorn[1], Daniel Foil[1], Thomas Lane[1], Wendy Hillwalker[2], David Feifarek[2], Frank Jones[2], William Klaren[2], Ashley Brinkman[2], Sean Ekins[2]

[1]Collaborations Pharmaceuticals Inc., Raleigh, USA. [2]Global Product Safety, SC Johnson and Son, Inc., Racine, USA

Abstract

Endocrine disruption is a major focus of toxicology research, therefore human estrogen and androgen receptors are key targets of interest. Downstream effects of receptor activation are difficult to anticipate without *in vitro* and *in vivo* testing, so the Environmental Protection Agency (EPA) has prioritized alternative approaches to evaluate endocrine bioactivity, including mathematical and computational methods. The EPA has used high-throughput ToxCast/Tox21 screening data of relevant targets and bioprocesses to calculate area-under-the-curve scores and predict the likelihood of chemicals to mediate endocrine activity. However, these ToxCast pathway models required a suite of *in vitro* assay data to generate a prediction. In contrast, machine learning (ML) methods are capable of prospective prediction from molecular structure alone and we have published on the broad applicability of ML to drug discovery and toxicology research. The current study describes the application of several ML algorithms (including deep learning, Bayesian, and regression algorithms) to similar *in vitro* ToxCast/Tox21 data to generate suites of models to anticipate endocrine disruption. Model performance

was evaluated by internal five-fold cross-validation metrics as well as external predictions with androgenic and estrogenic reference chemicals; these predictions were compared to results reported by the EPA's published studies. Furthermore, we have similarly modelled aromatase inhibition data, another component of in endocrine disruption. This study builds upon our previous work with Bayesian models that demonstrated a similar level of accuracy seen in previous EPA publications and expands techniques employed. Results continue to demonstrate the utility of ML for endocrine activity prediction to fill data gaps.

182
In silico screening for "drug of abuse"-like compounds: Identification of physico-chemically similar compounds to facilitate technological harm reduction research

Fabian Steinmetz[1,2], Heino Stöver[3,2]

[1]Delphic HSE (Europe) B.V., Schiphol, Netherlands. [2]Schildower Kreis, Frankfurt am Main, Germany. [3]Frankfurt University of Applied Sciences, Frankfurt am Main, Germany

Abstract

"Drugs of abuse" (or better: controlled substances) are widely used throughout the globe despite their legal status and associated penalties. As there are many health risks which can be mitigated by safer-use-education, regulated supply and other measures, public health policies focussing on so called "harm reduction" are getting more popular. Heroin-assisted treatment and pill-testing, both done in many European cities, are just two of those harm reduction success stories. Many harms are closely related to the route of administration, e.g. smoking, injecting and insufflation, which makes harm-reducing drug formulations and/or devices interesting options for public health policies. However, due to extremely strict narcotic regulations and high costs, research is inhibited vastly, particularly for small NGOs. With the help of in silico screening, compounds with similar properties can be identified to support low budget or early stage technological research. One example illustrated here would be a harm reduction device for crack cocaine users focussing on the reduction of typical lung injuries and overdoses. Uncontrolled substances were identified as physico-chemical substitutes for cocaine and suggested for feasibility studies and/or technological development. Further uncontrolled substances could be identified for other relevant formulations and devices to overcome teething problems within the poorly funded harm reduction sector.

189
Reverse Docking To Identify Toxin Targets

Michael McCarthy, Yaroslav Chushak, Jeffery Gearhart

Henry Jackson Foundation, Bethesda MD, assigned to the 711th Human Performance Wing, RHBBA, Dayton, USA

Abstract

We have focused on the development of *in silico* tools to identify targets for molecules with unknown toxicity. Complementary QSAR methods we have developed a reverse docking GUI and pipeline to identify potential neurological targets and predict activity with deep-learning models based on docking identified interactions. A selection of human neurologic receptors were obtained from the Protein Data Bank (PDB), then curated and prepared for docking. Multiple Python scripts were developed to automate setup and execution of docking for thousands of molecules in parallel, using Autodock4. To generate the data for TensorFlow based deep learning models for each receptor, we ran a high throughput virtual screen (HTVS) of known neurological receptor binders. The HTVS was conducted with a subset of molecules from the Binding Database which were curated by removing molecules with 2D structural information only, duplicates, and those that bind to non-neurological targets. Thus far, we have docked thousands of molecules onto multiples sites on multiple different neuroprotein structures, generating millions of docked poses and scores. With this data we have identified protein and ligand interactions and compared that to previously described laboratory results. The data was

transformed to an image representation and used to generate 2D Conv deep-learning models. To date, we have generated 17 deep-learning models, of which 15 are over 90% accurate on validation data and the remaining two are 84% and 87% accurate. As an example, we have correctly predicted a real-world molecule, toluene, as a GABA(B) agonist.

203
SpheraCosmolife: a new tool for the risk assessment of cosmetic products

Gianluca Selvestrel[1], Federica Robino[2], Alberto Manganaro[3], Diego Baderna[1], Giovanna Lavado[1], Alessandra Roncaglioni[1], Emilio Benfenati[1]

[1]Istituto di Ricerche Farmacologiche Mario Negri - IRCCS, Milan, Italy. [2]Angel Consulting s.a.s., Milan, Italy. [3]Kode s.r.l., Pisa, Italy

Abstract

The European Regulation on cosmetics represents a paradigm shift in Europe for the safety assessment of cosmetics, introducing a completely novel strategy, where the use of animal for toxicity testing is completely banned. The possibility of using *in silico* tools is particularly appealing because they can generate safety data for cosmetic ingredients without testing.

Within the LIFE project VERMEER, a new, freely available software for the risk assessment of cosmetics has been designed. The novel software system combines an expert-system approach, which reproduces the sequence of steps done by the assessors, with some machine learning and statistical models, to provide predictions. This software allows an overall toxicological evaluation of cosmetic ingredients and it applies defined exposure scenarios to derive risk for consumers. It takes regulatory thresholds into account, as defined by European authorities (other lists from Asia will be added soon) and uses either experimental values, if available, or predictions. There are models towards mutagenicity, genotoxicity, skin sensitization, NOAEL, TTC, internal and external exposure, and other endpoints will be added soon. Predictions are calculated using *in silico* models implemented within the VEGA software (www.vegahub.eu).

SpheraCosmolife is designed as a support tool for the safety assessors of cosmetic products and can be used to prioritize the cosmetic ingredients or formulations according to their potential risk for the consumers. This software is opening up fresh avenues to research on *in silico* models, moving towards the real case application and providing solutions lowering the barriers to the use of *in silico* models.

205
Developing QSAR models for toxicity of metal oxide based nano-mixtures to Daphnia magna

Tung X. Trinh[1,2], Myungwon Seo[1], Tae Hyun Yoon[2,3], Jongwoon Kim[1]

[1]Chemical Safety Research Center, Korea Research Institute of Chemical Technology (KRICT), Daejeon, Korea, Republic of. [2]Department of Chemistry, College of Natural Sciences, Hanyang University, Seoul, Korea, Republic of. [3]Institute of Next Generation Material Design, Hanyang University, Seoul, Korea, Republic of

Abstract

Mixtures of nanomaterials and inorganic/organic chemicals can cause combined toxicity effects (e.g., addition and synergism). Metal oxide (MeOx) based nano-mixtures are known as one of the most popular nano-mixtures used in toxicity testing1. Recent toxicity studies showed that MeOx based nano-mixtures combining either inorganic or organic compounds might cause the mixture toxicity2,3,4. Predictive toxicity models not only support screening potentially toxic chemicals and mixtures, but also to optimize the design of intensive experiments especially for determining the toxicity of various mixture compositions. Previous predictive models for toxicity of nano-mixtures limited to only TiO2 based nano-mixtures5,6,7. In this study, quantitative structure-activity relationship (QSAR) models were developed and tested for predicting the toxicity of MeOx based nano-mixtures containing either inorganic or organic compounds to *Daphnia magna* by using curated literature data, machine learning techniques and a newly proposed mixture descriptor combining

quantum chemical descriptors of MeOx NPs and their co-formulants. The study highlights: *i*) applications of theoretical nano-mixture descriptors for developing QSAR models and *ii*) potential of QSAR models, which could cover toxicity prediction for several metal oxides based nano-mixtures (i.e., TiO2, ZnO, Fe3O4, and MnO2).

References

1. Trinh and Kim. *Nanomaterials* 11.1 (2021): 124.
2. Park, *et al*. *Journal of Nanoparticle Research* 21.8 (2019): 166.
3. Lopes, *et al*. *Journal of hazardous materials* 320 (2016): 1-9.
4. Renzi and Andrea. *Ecotoxicology* 28.8 (2019): 878-889.
5. Mikolajczyk, *et al*. *Nanoscale* 11.24 (2019): 11808-11818.
6. Mikolajczyk, *et al*. *Environmental Science: Nano* 5.5 (2018): 1150-1160.
7. Trinh, *et al*. *Manuscript in preparation*.

219
NICEATM Computational Tools and Data Resources

Jaleh Abedini[1], Shannon Bell[1], Xiaoqing Chang[1], Neepa Choksi[1], Bethany Cook[1], Amber Daniel[1], David Hines[1], Agnes Karmaus[1], Kamel Mansouri[1], David Allen[1], Nicole Kleinstreuer[2]

[1]ILS, Research Triangle Park, USA. [2]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, USA

Abstract

Implementing new approach methodologies (NAMs) for chemical safety assessment requires resources that can support both development and evaluation of NAMs. The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) works with a wide range of stakeholders to advance NAMs that reduce or replace animal use while protecting human health and the environment. In partnership with stakeholders from government, industry, and academia, NICEATM has developed a set of computational tools and data resources. These resources give developers and users of NAMs direct access to curated, computationally accessible in vitro, in chemico, and in vivo data as well as chemical information. NICEATM also provides in silico tools for comparing chemical lists based on their physicochemical properties and for estimating in vivo equivalent doses based on in vitro bioactivity. This presentation describes NICEATM's approaches for data acquisition and curation, including how we facilitate these labor-intensive processes and how users can access our compiled datasets. We provide an overview of our annotation of assay data, which supports Findable, Accessible, Interoperable, and Reusable (FAIR; https://www.go-fair.org/fair-principles/) principles to achieve optimal value and enhance data reusability. We also summarize the development and application of computational tools, including quantitative structure-activity relationship models included in the Open Structure-activity/property Relationship App (OPERA) and physiologically based pharmacokinetic models that facilitate in vitro to in vivo extrapolation accessible through the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/). This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

263
New CSRML-based features to categorize and fingerprint PFAS structure lists for cheminformatics analysis and read-across

Ann M. Richard[1], Ryan Lougee[2], Grace Patlewicz[1], Christopher Grulke[1], Antony Williams[1], Chihae Yang[3], James Rathman[4], Tomasz Magdziarz[3]

[1]US EPA, Durham, NC, USA. [2]ORISE Fellow, Durham, NC, USA. [3]MN-AM, Nürnberg, Germany. [4]MN-AM, Columbus, OH, USA

Abstract

Per- and polyfluoroalkyl substances (PFAS) are of high interest due to widespread production, environmental persistence, and potential adverse ecological and health impacts. In 2019, the Organization for Economic Development (OECD) published a list of >4500 PFAS with potential environmental occurrence. EPA's CompTox Chemicals Dashboard hosts a list with over 8000 curated structures spanning several public PFAS lists, inclusive of OECD's. Studies to-date have focused on the health effects of a small number of PFAS compounds, such as PFOA and PFOS, whereas little is known about the health effects of the majority of PFAS and their byproducts. Means for profiling the PFAS chemical structure space are needed to support modeling and structure-based categorization efforts. However, publicly available molecular fingerprinting methods are ill-suited to effectively capturing PFAS-defining features and structure diversity. Similarly, PFAS chemical category terms are limited to simple categories (e.g., perfluorocarboxylic acids) and often lack clear structure definition. Building on publicly available ToxPrint (TxP) features coded in CSRML (Chemical Subgraphs and Reactions Markup Language), we developed 34 new TxP_PFAS features to serve as PFAS structural categories and more than 130 fingerprints to capture unique aspects of PFAS structures, such as perfluoro chains, polyfluoro substructures, fluorinated rings, and various perfluoro branching patterns, as well as functional groups. These CSRML PFAS categories and features can be used with the public Chemotyper, provide comprehensive coverage of available PFAS lists, and are being used to profile and describe PFAS chemical lists currently undergoing testing within EPA. Abstract does not reflect EPA policy.

Poster Sessions Track 9

209
Criteria for assessing the reliability of toxicity predictions: Ames mutagenicity

Elena Kaloyanova[1], Petko Petkov[1], Hristiana Ivanova[1], Terry Schultz[2], Ovanes Mekenyan[1]

[1]Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria. [2]The University of Tennessee, College of Veterinary Medicine, Knoxville, TN 37996-4500, Tennessee, USA

Abstract

The strain-dependent bacterial reverse mutation assay (Ames test) is typically part of regulatory batteries of methods used for *in vitro* evaluation of substances eliciting mutagenicity via short-chain-length DNA damage. Given the crucial role of the Ames test in these batteries, especially for predicting higher-tier endpoints, such as carcinogenesis and *in vivo* mutagenicity, a set of criteria for evaluating reliability of Ames *in silico* predictions is introduced in this work. The presented criteria are different from the OECD principles for acceptance of (Q)SAR models. Besides belonging to model applicability domain, the proposed criteria are evaluating alerts reliability/performance, assessing adequacy of simulated *in vitro* S9 metabolism associated with metabolic activation of chemicals, identifying the structural and mechanistic analogues having experimental data and validating reactive intermediates resulting from the metabolic activation of non-mutagenic parent compounds. The criteria introduced in the current work are with emphasis on estimating adequacy of simulating metabolism which is usually underestimated in traditional (Q)SARs. Presented criteria could be used as weights of evidence to make a final decision for reliability of the obtained Ames prediction. Although demonstrated for the Ames endpoint, the proposed criteria could be customised to other toxicity endpoints.

211
Uncertainty of experimental data in low- and high-tier endpoints:results from LLNA and RDT tests

Atanas Chapkanov, Ksenia Tankova, Hristiana Ivanova, Gergana Dimitrova, Todor Pavlov, Reni Syarova, Viktor Rusev, Ovanes Mekenyan

Laboratory of Mathematical Chemistry (LMC), As. Zlatarov University, Bourgas, Bulgaria

Abstract

During last years *in silico* alternatives to testing methods became more and more popular given the regulatory controled restrictions for testing chemicals. Read-across and QSAR predictions are used to demonstrate the hazard potential of chemicals. In this respect, understanding the uncertainty inherent to the prediction methods and underlying experimental data becomes very important. Also the uncertainty in experimental data is critical for setting regulatory thresholds and more specifically for knowing the so-called “grey zones” (areas with uncertain classification) around the thresholds, where no straightforward predictions could be done. The goal of the current project is to find estimates for uncertainty resulting from LLNA and RDT tests. By using these tests as typical representatives of low- and high-tier endpoints, respectively, we aimed to demonstrate the limitations inherent to the predictions from both endpoint groups. Using variability in repeated experiments conclusions are drawn about probability distributions of these results. We also tried to estimate the size of “grey zones” around some widely accepted regulatory thresholds. Complexity of RDT tests predetermines additional difficulties for assessing the “grey zones”. Measuring different effects at different doses adds a new factor in the equation, namely the sensitivity of the effect from the dose. Thus, we tried to show differences in “grey zones” for some of the mostly tested RDT effects.

265
Performance Evaluation of Mixture Toxicity Prediction Models: CA, IA, and QSAR-TSP models

Minju Na[1,2], Myungwon Seo[1], Tung Xuan Trinh[1], Jongwoon Kim[1]

[1]Chemical Safety Research Center, Korea Research Institute of Chemical Technology (KRICT), Daejeon, Korea, Republic of. [2]Department of Public Health Sciences, Graduate School, Korea University, Seoul, Korea, Republic of

Abstract

Under European Union Biocidal Product Regulation (BPR) and Korean Household Chemical Products and Biocides Safety Act (Chemical Product Safety Act, also known as K-BPR), the mixture toxicity which can be caused by toxicological interactions among mixture components should be evaluated appropriately. Due to the extremely large number of possible mixture combinations, predictive models are essential as alternative approaches to animal tests for estimating the toxicity of a mixture. Conventional regulatory mixture risk assessment has employed concentration addition (CA) and independent action (IA) models, which assumes that all mixture components are either similarly or dissimilarly acting chemicals, respectively. However, since such information on the toxic modes of action of mixture components is often insufficient, the CA and IA models can have limitations from the scientific aspect. To overcome such limitations, a quantitative structure–activity relationship-based two stage prediction (QSAR-TSP) model was developed to combine the CA and IA models in 2014. The QSAR-TSP clusters mixture components into mode of action groups according to their structural similarities, and conduct the CA [for each group] and IA [for all groups] calculations in two steps to estimate mixture toxicity. In this study, we tested the performance of the CA, IA, and QSAR-TSP models with different mixture toxicity data sets collected from the literature.

355
Characterizing Activity Cliffs Using Chemical Similarity Maps

Emily Golden[1], Thomas Hartung[1,2], Alexandra Maertens[1]

[1]Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University, Baltimore, USA. [2]CAAT-Europe, University of Konstanz, Konstanz, Germany

Abstract

The fundamental percept of structure-based computational models is that toxicity can be determined largely from structure, and chemicals with similar structures will have similar toxicity. Usually, this is true; however, activity cliffs complicate this assumption, as there are instances where toxicity is radically different for similar chemicals. Here, we use

chemical similarity maps to identify and characterize activity cliffs in two sensitization data sets (skin sensitization – n = 404; respiratory sensitization – n = 251). Using a relatively stringent similarity cutoff (Tanimoto distance = 0.80), several clusters in both data sets contained both sensitizers and non-sensitizers, indicating that relying on structural similarity alone will likely prohibit perfect *in silico* model accuracy. On the other hand, some clusters contained only sensitizers or non-sensitizers, indicating that for some chemical classes (e.g., acrylates, fatty acids), structural similarity alone is adequate for predicting toxicity accurately. Exploring toxicological activity cliffs can begin to shed light on the reasons behind some of the mispredictions in computational models to predict sensitization, (e.g., Toxtree, OECD QSAR Toolbox). In some cases, the activity cliffs may be due to inaccurate data, while in other cases it shows where toxicity is dependent on a feature not captured by the model (e.g., steric hindrance, metabolism). Therefore, exploring activity cliffs can potentially provide solutions that will ultimately improve *in silico* tools, further bolstering their usefulness and continuing to build the case for wider regulatory acceptance as animal alternatives.

235
Datamining Relational Databases for Regression Analysis

Paul Harten[1], Henry Helgen[2], Wilson Melendez[3]

[1]EPA, Cincinnati, OH, USA. [2]GDIT, Duluth, MN, USA. [3]GDIT, Chicago, IL, USA

Abstract

Datamining complicated MySQL relational databases and preparing this data for QSAR analysis in Python can challenge researchers. Sometimes, this entails more than a simple dump of records in CSV format with every row having all numerical descriptors and values to be predicted. Instead, many MySQL scripts and Python routines must be written and implemented to sufficiently refine data for machine learning methods. This presentation gives examples of the routines written to datamine the MySQL database EPA's NaKnowBase and organize it into a CSV format file. These routines can be straightforwardly modified for researchers' relational databases and QSAR applications.

356
On strengthening the reliability of (Q)SAR and read-across assisted data gap filling

Svava Osk Jonsdottir

insilTox ApS, DK-2800 Kgs. Lyngby, Denmark

Abstract

With increasing prioritization on replacing animal tests with animal free methods, it is of outmost importance to optimally capitalize on available historical test data, knowledge on toxicological mechanisms, and toxicokinetic and physico-chemical parameters.

The general recommendation is to use *in silico* tools to supplement data obtained by *in vitro* methods, and huges efforts are being devoted to developing new *in vitro* assays, identifying relevant biomarkers and defining adverse outcome pathways to guide this development.

However, the combination of high quality *in silico* modelling and fit-for-purpose integration of data, can in many cases provide sufficiently reliable assessments for specific adverse effects. The present efforts by different stakeholders on better evaluating uncertainties and reliabilities of read-across and (Q)SAR predictions for regulatory purposes, will strengthen the acceptance of *in silico* based assessments when these are appropriate.

This presentation is focused on exploring how to improve the overall reliability of data gap filling based on rule-based SAR, statistical QSAR and read-across analysis, through case studies for effects like skin sensitization, developmental and reproductive toxicity and chronic systemic toxicity.

In addition, a variety of (Q)SAR tools and category building strategies for read-across analysis are evaluated. This includes comparing the ability of the underlying descriptors of the QSAR models to discriminate between active and inactive compounds, and for identifying analogue compounds of adequately structural similarity.

289
Facilitating Robust QSAR and Read-Across Through the Enablement of Honest Brokers

Markus Frericks[1], Daniel Urbisch[1], Felix Kluxen[2], Katy Bridgwood[3], Ewan Booth[3], Shaila Rao[4], Anja Hueser[5]

[1]BASF SE, Limburgerhof, Germany. [2]Adama, North Rhine Westphalia, Germany. [3]Syngenta, Bracknell, United Kingdom. [4]Gowan, Yuma, USA. [5]Bayer, Monheim, Germany

Abstract

The European Union Plant Protection legislation requires a dietary risk assessment to evaluate the exposure in plant and livestock as well as the toxicological properties related to an active ingredient and all known residues. Great focus is placed on the genotoxicity (mutagenicity, clastogenicity and aneugenicity) evaluation.

The evaluation of genotoxic potential includes the active and all residues with a discernable chemical structure. Considering increasing analytical sensitivity and requirements set by the Threshold of Toxicological Concern (TTC), evaluations may be required for hundreds of residues. Grouping residues/metabolites into classes with active and other substances having experimental data is then performed. This is followed by a weight-of-evidence evaluation which considers experimental data, QSAR, Read-Across and expert judgement to derive reference values and advise on additional in vitro and in vivo testing to fill toxicological gaps and minimize unnecessary in vivo testing.

Critical needs include high-quality data, common language and level of expertise for stakeholders involved with QSAR and RA. On-going initiatives, including the development of in silico protocols and training classes exist to supplement these needs.

Globally, very little is being done to accommodate the availability of relevant high-quality data. For example, a significant portion of Plant Protection data is absent from the training sets used to derive the currently available QSAR models. To address this issue, industry proposes a consortium like eTRANSAFE to facilitate information exchange between industry, QSAR vendors, and authorities to enable the development and increase the quality of existing QSAR models and Read-Across for Plant Protection needs.

291
In silico approaches in organ toxicity hazard assessment: current status and future needs

Arianna Bassan[1], Candice Johnson[2], Kevin Cross[2], Manuela Pavan[1], Glenn Myatt[2]

[1]Innovatune srl, Padova, Italy. [2]Leadscope (an Instem company), Columbus, Ohio, USA

Abstract

New Approach Methodologies (NAM) based on *in vitro* and *in silico* approaches are being developed to predict adverse effects induced on vital organs. The present work aims at setting the pillars for the development of an *in silico* toxicology (IST) protocol that drives the use of (Q)SARs for the prediction of potential organ toxicity. This is done by proposing a draft hazard assessment decision framework useful to combine data originating from different sources (e.g., *in vivo* and NAM) for the evaluation of organ toxicity. The framework is the result of an extensive review of relevant endpoints and their relationships, (Q)SAR models and current experimental approaches. It provides the building blocks for the development of an IST protocol that should standardize the use of (Q)SARs in the context of organ toxicity. The IST protocol initiative is a large collaborative project involving several organizations and summarizes the current status of *in silico* toxicology for hazard identification and characterization. It aims at developing standardization procedures that promote acceptability of the methods and corresponding (Q)SARs predictions and that provide a means to support a more

transparent analysis of the results (Myatt et al, 2018. *In silico* toxicology protocols. Regulatory Toxicology and Pharmacology 96, 1–17).

The draft assessment framework proposed hereafter focuses on the major organ systems, namely liver, kidney, heart, and lung, and builds on the analysis of biological basis, processes and endpoints for hepatotoxicity, nephrotoxicity, pulmonary toxicity, respiratory irritation and sensitization as well as functional and structural cardiac toxicities.

229
Open-source QSAR-ready chemical structure standardization workflow

Kamel Mansouri[1], Chris Grulke[2], Richard Judson[2], Ann Richard[2], Antony Williams[2], Nicole Kleinstreuer[1]

[1]NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA. [2]CCTE/EPA, RTP, NC, USA

Abstract

The rapid increase of publicly available chemical structures and associated experimental data presents a valuable opportunity to build robust QSAR models for applications in different fields. However, a common concern is the quality of both the chemical structure information and associated experimental data. Especially when collected from multiple sources, chemical records usually contain many duplicates and molecular inconsistencies. Such issues can alter the molecular descriptor calculation procedure and, subsequently, the quality of the derived QSAR models in terms of accuracy and repeatability. Here we describe the development of an automated workflow to standardize the chemical structures according to a set of standard rules to generate "QSAR-ready" forms prior to calculating molecular descriptors. The workflow design was conducted in the KNIME data-mining environment. This workflow performs a series of operations on chemical structures including desalting, standardizing tautomers and nitro groups, correcting valence, neutralizing when possible, and removing duplicates. This workflow has been used in different international collaborative QSAR related projects as well as all models included in the OPERA application (https://github.com/NIEHS/OPERA). The workflow was also used to standardize over 750k structures available on the EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) and NTP's Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/). This standardization workflow can be downloaded and used in the KNIME environment or in command-line within a Docker container (https://github.com/NIEHS/QSAR-ready). Recently, it was also embedded in OPERA to standardize structures prior to running the models. *This abstract does not necessarily reflect NIEHS and EPA policy.*

234
Practical Implementation of New Approach Methodologies (NAMs): A Corporate Perspective for Diverse *in silico* Applications

Colin Owens, Lawrence Milchak

3M Company, Saint Paul, USA

Abstract

3M has always been firmly committed to animal use reduction and has made significant progress with utilizing *in silico* methods for evaluating human health hazard potential of raw materials and products. A particular challenge is finding methods to effectively work across a broad product portfolio, including industrial, consumer and health care products, while having cost effective utility for product development. The computational toxicology program utilizes multiple approaches in evaluations for read-across, structural alerts and (Q)SAR analysis to build a weight of evidence approach for preparing toxicity estimates. These assessments have been used for a wide variety of purposes, including FDA ICH M7 assessments for new and existing products, REACH and other global chemical registrations, GHS and other hazard classifications, and the screening of new chemistries. Customized (Q)SAR models utilizing historical test data have been built for specific endpoints of interest, such as inhalation toxicity to help develop substances with more favorable hazard profiles. A database has also been developed to store the *in silico* results that is searchable by chemical structure/similarity

and currently contains over 1000 chemicals that have been assessed. The results of these *in silico* efforts have provided valuable information for safety and risk assessment purposes for highly diverse products, particularly during product development, while allowing significant reductions in animal use. A key learning has been ensuring the tools incorporated have practical utility to the business needs, while also utilizing multiple tools and approaches to reduce reliance on any one method or software.

236
In silico tools for the prediction of *in vitro* biotransformation

Nicola Chirico, Linda Bertato, Ilaria Casartelli, Ester Papa

University of Insubria, Varese, Italy

Abstract

The assessment of toxicokinetic parameters (TK) is becoming more and more important in the general context of chemical hazard and risk assessment.

Alternative methods to animal tests are helpful to predict TK properties using *in vitro* or *in silico* strategies. *In silico* QSAR models allow to generate predictions based on the chemical structure of existing and new chemicals. In a recent project addressing the integration of *in vivo, in vitro,* and *in silico* information to assess bioaccumulation of chemicals in mammals, we have developed more than 100 models for the estimation of *in vitro* biotransformation (i.e. intrinsic hepatic clearance) in different matrices such as hepatocytes, and microsomes.

In this poster we provide an overview of the *in silico* tools (e.g. frameworks and software) that we have created to aid the application of these models. In particular, the new software "IVBP suite" (*in vitro* biotransformation prediction suite) generates predictions either as single value or as a combination of predictions from multiple models, taking into account the potential reactivity of chemicals based on putative cytochrome P450 (CYP) mediated reactions.

IVBP suite predictions can be generated in batch for multiple chemicals according to different CYP-450 mediated reactions, organisms (e.g. human or rodents), and *in vitro* assay (e.g. hepatocytes or microsomes), in a user-friendly manner. Models are also accompanied by the respective QMRF (QSAR Model Reporting Format) document, which formalizes the compliance of each QSAR with the OECD principles for the use QSAR predictions for regulatory purposes.

249
Estimation of toxicity via T.E.S.T. (v5.1) and WebTEST

Todd Martin[1], Antony Williams[2], Valery Tkachenko[3]

[1]EPA/CCTE, Cincinnati, USA. [2]EPA/CCTE, Durham, USA. [3]Science Data Experts, LLC, Rockville, USA

Abstract

T.E.S.T. was developed to estimate toxicity values (e.g. acute mammalian toxicity and Ames mutagenicity) and physical properties (e.g. melting point and water solubility). T.E.S.T. estimates toxicity using several QSAR (quantitative structure activity relationship) methodologies. In the most recent version of T.E.S.T., version 5.1, the interface has been completely redesigned, structure searching has been vastly improved, the calculation speed has been increased, and the ability to process complicated molecular structures has been improved. Recently EPA has released the Chemical Transformation Simulator (CTS), a web-based tool for predicting environmental and biological transformation pathways and physicochemical properties of organic chemicals. The CTS web-service is now utilized within T.E.S.T. to predict environmental transformation products and simultaneously estimate their toxicities. WebTEST (Web-services Toxicity Estimation Software Tool) was recently developed within the US EPA's Chemicals Dashboard to allow users to estimate toxicity values directly within their web browser. Users can make predictions for single chemicals by drawing them or by searching in the Dashboard. Users can also access WebTEST predictions via web-services (such as using a simple URL).

258
The use of (Q)SAR models for classification and labelling

Glenn Myatt[1], Arianna Bassan[2], Dave Bower[1], Kevin Cross[1], Candice Johnson[1], Scott Miller[1], Manuela Pavan[2]

[1]Leadscope (an Instem company), Columbus, USA. [2]Innovatune srl, Padova, Italy

Abstract

The Globally Harmonized System (GHS) classification of toxicity is extensively used for classification and labelling. *In silico* methods to calculate a GHS category would support the 3Rs (reduction, refinement, and replacement of animal studies). This poster describes how the use of multiple computational methodologies coupled with an expert review of supporting information can be used to predict GHS categories for different endpoints. Such an approach is fit-for-purpose since it avoids mis-classification of highly potent chemicals. In a recent cross-industry exercise using acute rat oral toxicity models, around 95% of chemicals (using an external test set of over 2,000 chemicals) were either correctly predicted or were predicted with a more conservative category and the majority of these predictions being in the correct category or one category more toxic. This poster will outline a workflow for how such models may be used to support classification and labelling.

266
A Tool to Identify the Structural Analogues of the Persistent and Highly Bioaccumulative Regulated Chemicals under Chemical Substances Control Law in Japan

Yuki Sakuratani, Natsuko Mizuike, Kensuke Takeuchi, Yuri Zaitsu, Masashi Horie, Shino Kuwa, Asako Matsumoto, Shunichi Goshima

National Institute of Technology and Evaluation, Tokyo, Japan

Abstract

Under Chemical Substances Control Law (CSCL) 74 chemicals are regulated as the chemicals having persistent and highly bioaccumulative properties (33 Class I specified chemical substances and 41 Monitoring Chemical Substances). We have developed profilers for the OECD QSAR Toolbox as a tool to identify these regulated chemicals and their structural analogues based on chemical structure.

Two profilers for identifying the structural analogues of the regulated chemicals were developed. One is based on structural similarity and the other is based on substructures. For the profiler identifying the structural analogues based on substructure the basic structure of each 74 regulated chemicals that is considered to dominate the persistent and highly bioaccumulative properties was specified by expert knowledge. By grouping the chemicals with same basic structure, total 31 categories were formed, and their structural boundaries were coded in the profiler.

As a result of validation it was found that the profiler can identify important analogs those could not be identified by simple structure similarities. The biodegradation and bioaccumulation properties of a target chemical categorized by the profiler can be estimated by read-across using the test data of structural analogues those are falling in the same category. That is, this profiler enables even non-experts on read-across to easily find appropriate structural analogs for the endpoints.

These profilers are publicly available from our website and practically used for the evaluation of the small production volume new chemicals under CSCL.

270
Mutagenicity prediction of phytotoxins

Elena Lo Piparo[1], Arianna Bassan[2], Manuela Pavan[2]

[1]Nestlè Research, Lausanne, Switzerland. [2]Innovatune srl, Padova, Italy

Abstract

Toxic plant-produced compounds, so-called phytotoxins, constitute a category of natural compounds belonging to a diversity of chemical classes. Some of them (e.g., alkaloids, terpenes, saponins) are associated with high toxic potency, while for many of others no toxicological data is available. In this study, the mutagenic potential of 1586 phytotoxins, obtained from the Toxic Plants–PhytoToxins (TPPT) database[1] was investigated applying different *in silico* approaches. (Q)SAR models (including statistical-based and rule-based systems) were used for the prediction of bacterial *in vitro* mutagenicity (Ames test) and the results from multiple tools were combined to assign consensus predicted values (positive, negative, inconclusive). These outcomes were further analysed in terms of chemical classes with special focus on those raising concern for mutagenicity. The results highlighted that about 10% of the screened compounds were predicted to have mutagenic potential and the critical classes of concern, such as alkaloids, were further investigated in terms of subclasses (e.g., indole alkaloids, isoquinoline alkaloids, …), getting a deeper insight on the possible presence of naturally occurring chemicals in plant materials intended to be used for human consumption.

[1] Günthardt, B.F., Hollender, J., Hungerbühler, K., Scheringer, M., Bucheli, T.D., 2018. Comprehensive Toxic Plants–Phytotoxins Database and Its Application in Assessing Aquatic Micropollution Potential. J. Agric. Food Chem. 66, 7577–7588. https://doi.org/10.1021/acs.jafc.8b01639 (freely available at:

https://www.agroscope.admin.ch/agroscope/en/home/publications/apps/tppt.html).

273
Addressing the global challenge of N-nitrosamine impurity assessment

David Ponting, Michael Burns, Rachael Tennant, Andrew Thresher

Lhasa Limited, Leeds, United Kingdom

Abstract

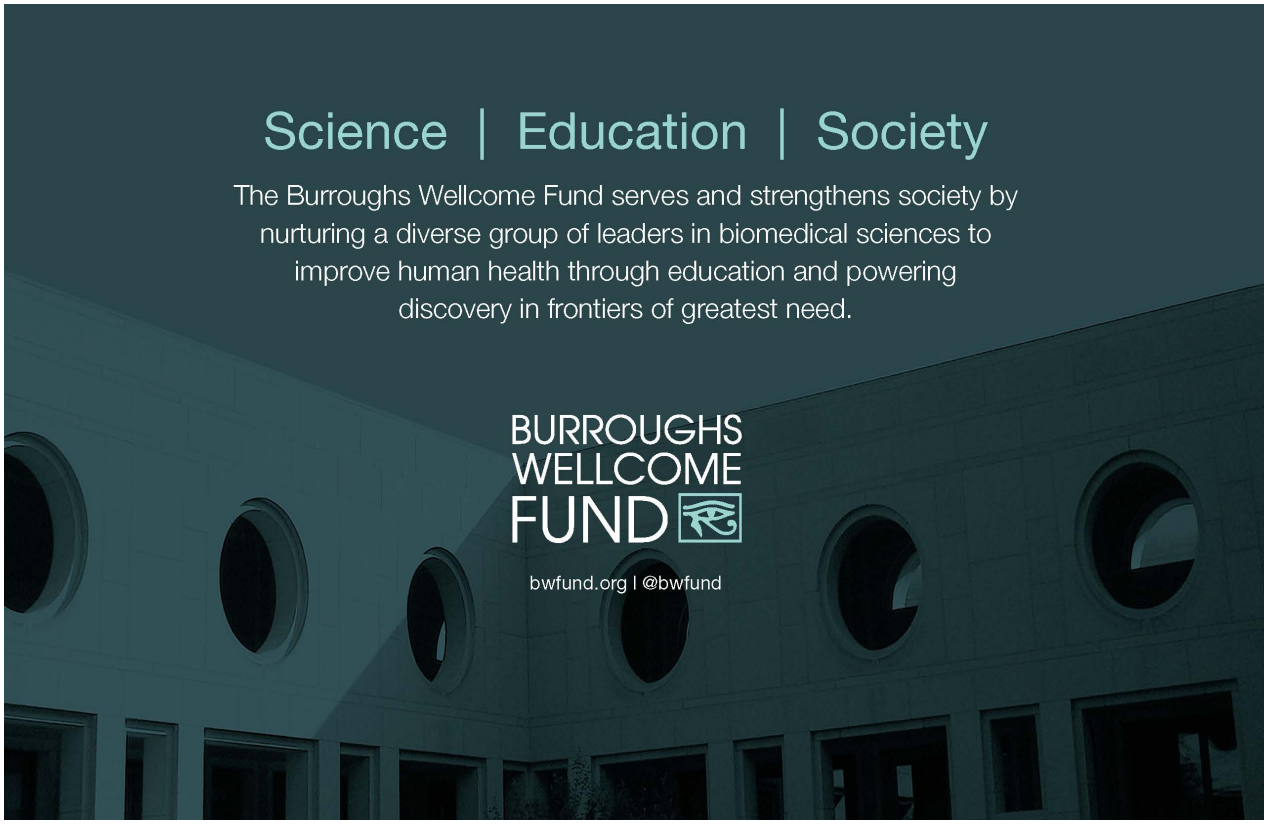
The discovery of N-nitrosamine impurities in several marketed pharmaceuticals has led to the requirement for further investigation into N-nitrosamine mutagenic and carcinogenic activity. Updated regulatory requirements mean that marketing authorisation holders for human medicines, containing chemically synthesised active substances, must review their medicines for the possible presence of N-nitrosamines and test all products at risk.

By combining expert knowledge with public and proprietary data sources, software tools have been refined as follows:

- databases have been expanded to offer comprehensive coverage of mutagenicity and carcinogenicity data for N-nitrosamines from public sources. A database of 518 N-nitrosamines, 411 with Ames test data, 234 with rodent carcinogenicity data and 184 with both Ames and rodent carcinogenicity data was collated. The freely-available Lhasa Carcinogenicity Database now contains 137 N-nitrosamines, of which 46 have both Lhasa and Carcinogenic Potency Database (CPDB) TD50 values.
- structure activity relationships (SAR) for the mutagenic and carcinogenic potential of N-nitrosamines have been refined and incorporated into an expert knowledge base for toxicity prediction. Structural features that have been observed to eliminate mutagenic and/or carcinogenic activity have been excluded from the corresponding alerts.
- a statistical system for mutagenicity prediction has been updated with new N-nitrosamine data to improve predictivity.

- the knowledge of N-nitrosamine reactivity within oxidative and reductive transformations, present in a tool to facilitate purge assessments, has been augmented to include further justification for consortium-assigned reactivity purge values. This updated knowledge base includes additional literature and mechanistic justifications for the predicted purge values to facilitate expert review.

Sponsors



PETA SCIENCE CONSORTIUM INTERNATIONAL e.V.

PETA Science Consortium International e.V. coordinates the scientific and regulatory expertise of its members to advance the development, use, and global regulatory acceptance of *in silico* and *in vitro* testing approaches that protect human health and the environment. We do this through a variety of means, including:

- Funding the development and validation of animal-free tests
- Collaborating with international companies and regulatory agencies
- Providing education and training
- Advancing international harmonization

To learn more or to apply for one of our open positions visit our website at ThePSCI.eu

WHAT WE DO

FUND Annual Open and AiR Challenge grant programs have made over $3.5 million in research grants

PROMOTE Sponsor scientific meetings that advance non-animal methods

REWARD Recognize achievements in alternatives science through the William and Eleanor Cave Award and the AiR Challenge Prize

@ALTERNATIVESRESEARCHDEVELOPMENTFOUNDATION
@ARDF_GRANTS
WWW.ARDF-ONLINE.ORG
INFO@ARDF-ONLINE.ORG