# Session 6.2
# Biokinetic modelling *in silico*

## Lecture

## Lazar: An inductive database for the *in silico* prediction of carcinogenicity

*Christoph Helma*
*In silico* toxicology, c/o Machine Learning Lab, Freiburg, Germany

During the last years data mining techniques have gained much popularity for the prediction of toxic activities. This presentation starts with a review of this approach, a summary of the present state of the art in this area and a brief discussion of application areas and limitations.

The second part will describe a specific realisation of these ideas and techniques in the lazar prediction system and its application for the prediction of carcinogenicity at various levels of detail. In crossvalidation experiments lazar is capable to predict rodent carcinogenicity for the Carcinogenic Potency Database (1376i compounds) with more than 70% accuracy. This accuracy is very competitive for an endpoint, that is very hard to predict with traditional (Q)SAR techniques.

Lazar is capable of discriminating reliably between trustworthy and untrustworthy predictions. An inspection of misclassified structures reveals, that the majority of misclassified instances falls indeed beyond the prediction scope of the training data. As lazar provides the rationales for predictions in an understandable and traceable manner it can be applied for 1. The prediction of untested structures (replacement of animal experiments for predictions with high confidence), 2. The identification of information deficits and the priority setting for further testing (refinement of animal experiments), and 3. The identification of hypothesis about toxicological mechanisms.

Lecture

# Quantitative Structure-Permeability Relationships (QSPeRs) in reproductive toxicology: Crossing the placental and blood-testis barriers

*Mark Hewitt and Mark Cronin**
Liverpool John Moores University, School of Pharmacy and Chemistry, Liverpool, UK

The replacement of animal testing for endpoints such as reproductive toxicity is a long-term goal. It is probable that integrated testing strategies, combining together *in silico* and *in vitro* approaches, are likely to be the most productive. This study describes the possibilities of using simple (quantitative) Structure-Permeability Relationships ((Q)SPeRs) to predict whether a molecule may cross the placental membrane, or the blood-testis barrier. The concept is straightforward, if a molecule is not able to cross one of these barriers, then it will not be a reproductive toxicant. Such models could be placed at the start of any integrated testing strategy. To develop these models literature data were collected for the transfer of molecules across the membranes. Whilst a reasonable number of data are available for the modelling of the ability of a molecule to cross the placenta, relatively few are available for the penetration of the blood-testis barrier. This indicates a possible need for more work in this area. Modelling of the permeability data indicates that significant (quantitative) Structure-Activity relationships can be developed for the ability of molecules to cross these biological barriers.

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Poster

# Prediction of human skin permeability of chemicals in various vehicles using artificial neural network

*Hirokazu Kouzuki[1], Fumiyoshi Yamashita[2], Hiroshi Itagaki[1] and Mitsuru Hashida[1]*

[1] Safety and Analytical Research Center, Shiseido Co., Ltd., Yokohama-shi, Japan; [2] Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

This study was carried out to develop a novel method for predicting the human skin permeability coefficient (logKp) of chemicals, where vehicle effects were considered. The data set consisting of 359 measured logKp for 151 chemicals dissolved in various vehicles, was analysed. Molecular weight (MW) and log (octanol-water partition coefficient) (logP) of chemicals, and logP of vehicles were calculated by Pallas (CompuDrug International Inc., South San Francisco, CA) as molecular descriptors for prediction. The relation between these descriptors and logKp was examined using feed-forward back-propagation neural network. The neural network model with a configuration of 3-5-1 for input, hidden and output layers was much superior to the multiple linear regression model in terms of root mean square (RMS) errors (0.675 vs 0.887). A leave-some-out cross-validation demonstrated that the neural network model predicted Kp with a reasonable accuracy (predicted RMS error of 0.723).

In addition, we also developed a novel method for predicting the human skin apparent diffusion coefficient (D) of chemicals. The data set consisting of 107 measured logD for 61 chemicals was analysed. MW and logP of chemicals are used as descriptors to predict logD of chemicals. The RMS error of neural network model with a configuration of 2-5-1 was 0.553 and a leave-some-out cross-validation revealed that the neural network model predicted D with a reasonable accuracy (predicted RMS error of 0.606).

Lecture

# *In vitro* prediction of human dermal and oral absorption for Physiologically-Based Pharmacokinetic (PBPK) modelling

*David Lockley, Carl Westmoreland and Julia Fentem*
Unilever – Safety and Environmental Assurance Centre, Colworth Laboratory, Bedfordshire, UK

Traditional toxicokinetic (TK) studies provide data on the absorption, distribution, metabolism, and excretion (ADME) of a chemical to support interpretation of repeat dose toxicity tests i.e. relevance of adverse effects observed at high doses to human health. The introduction of the 7th Amendment to the EU Cosmetics Directive (76/768/EEC) will result in the ban of repeat dose toxicity and TK studies of chemicals used as cosmetic ingredients in animals by 2013. Therefore, there is a need to develop *in vitro* alternatives to these traditional *in vivo* studies.

PBPK models enable the study of chemical concentration time profiles in individual organs, tissues and plasma and can form the basis of human health risk assessment. These models are populated by *in vitro* data, including those derived from simple absorption models. We have investigated the Parallel Artificial Membrane Permeation Assay (PAMPA), Immobilised Artificial Membrane (IAM) chromatography and Caco-2 cell lines, to provide an early indication of whether these systems can adequately model oral and dermal absorption of chemicals. The hypothesis is that the data generated from these models can then be integrated into PBPK models as an alternative to data derived from TK studies in laboratory animals. In the future, the linkage of absorption simulation and PBPK models, coupled together with Pharmacodynamic (PD) modelling, will bring us closer to a full simulation of chemical disposition and effect, one that ideally could be based on only a few properties readily measured *in vitro* and/or computed.

Lecture

# Integration of PBPK and reaction network modelling: Predictive xenobiotic metabolomics

*Raymond Yang, Arthur Mayeno and Brad Reisfeld*
Colorado State University, Environmental and Radiological Health Sciences, Fort Collins, USA

The recent emphasis on the application of "systems biology" to biomedical research invariably traces its origin to "cybernetics", as advanced by Norbert Wiener in the mid 20th century. In those early days, the integration of "computing machines" and biology was advocated by a handful of visionaries. Our research group, in the past 15 years, has attempted such a systems biology approach towards the advancement of chemical mixture toxicology. Specifically, we aim to integrate computational modelling with *in vitro* and *in vivo* experimentation to address the question "How does one deal with the potentially astronomical number of combination of chemicals and other possible stressors in the context of cumulative risk assessment?" Our answer is to first focus on the fundamental biological and toxicological processes occurring in the normal system. The idea is that once we have sufficient understanding of normal biological processes, all stimuli and insults from external stressors can be treated as perturbations to these processes. The next step is to capture the essence of these processes into modelling frameworks by integrating recent advances in computational technology and modern biology. In the case of complex chemical mixtures and their interactions, the computer-assisted approach of Biochemical Reaction Network Modelling offers a ray of hope. The possible linkage between this novel computational methodology and Physiologically-Based Pharmacokinetic (PBPK) modelling could result in a multi-scale computer simulation platform capable of predicting complex pathway interactions and metabolite concentrations at the molecular level up to tissue and organ concentrations and exposures at the organism level.