

## **Multivariate methods for analyses of *in vitro* data and for *in vitro-in vivo* modeling**

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At present, a multitude of different *in vitro* assays for measuring acute toxicity are described and aimed for *in vitro-in vivo* modeling. In general, the different assays with respect to information content are rather similar to each other, expressed by their high correlations to each other. Typical for these data is also missing values due to different reasons. Thus these data is well suited for multivariate analysis dealing with highly correlated variables, as well as with missing values. Here the multitude of variables is summarized in one or a few latent variables. For example, with help of principal component analysis (PCA) the similarity/dissimilarity of the variables can be studied, and non consistent behaving chemicals may be found. Similarly, partial least squares regression (PLS) can be used to develop *in vitro-in vivo* regression models based on batteries of *in vitro* variables, instead of looking at one *in vitro* variable at a time, and correlate it to the *in vivo* variable of interest.

In this presentation, the usefulness of multivariate methods will be illustrated, as well as how small sets of variables can be found with good predictive capability. The data-sets that will be used are from the Multicenter Evaluation of In Vitro Cytotoxicity (MEIC) project (1) and from the running ACuteTox project, which is an integrated project within the EU FP6. The MEIC data represents 50 chemicals and 61 *in vitro* assays, whereas the ACuteTox project includes 97 chemicals and about hundred variables.

A new approach to determine human blood LC50 values will be presented here, demonstrating their usefulness in *in vitro-in vivo* modeling (2). The LC50 values were calculated from time-related sub-lethal and lethal blood concentrations determined from human acute poisoning cases.

Both studies (1, 2) have shown that by using multivariate methods, models with a higher predictive capability will be obtained, compared to correlation of a single *in vitro* variable to an *in vivo* variable. However, the analyses from both projects also have shown that additional organ-specific and biokinetic tests or other correctors for specific chemicals are needed in order to improve the predictability of the models.

### References:

(1) Ekwall, B., Ekwall, Ba., Sjöström, M. MEIC evaluation of acute systemic toxicity. Part VIII. Multivariate partial least squares evaluation, including the selection of a battery of cell line tests with a good prediction of human acute lethal peak blood concentrations for 50 chemicals. ATLA 2000, 28, 201-234.

(2) Sjöström, M., Kolman, A., Clemedson, C., Clothier, R. Estimation of human blood LC50 values for use in modeling of *in vitro-in vivo* data of the ACuteTox project. Toxicol In Vitro. 2008 Aug;22(5):1405-11.