

Lecture: 7th cosmetics amendment – can all goals be achieved in time?

## Use of computer-assisted models for the prediction of toxic effects of chemical substances

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For the evaluation of existing and new chemicals as well as for the development of pharmaceutical and agrochemical compounds toxicological data are required. For animal welfare reasons and to save time and costs, computer assisted prediction models are more and more often used to gain knowledge about the toxicity of a compound. The currently mostly used models in chemical and pharmaceutical industry are combinations of different commercial software packages and in conjunction with in house developments.

The use of *in silico* tools in pharmaceutical development is more advanced than their use in the evaluation of chemicals. *In silico* tools have become standard in the selection of pharmaceutical lead candidates as well as for identification of critical metabolites and potentially toxic impurities.

Before *in silico* models can be used with confidence the applicability domain and validity of the predictions have to be assessed with in house experimental data and their limitations have to be identified. Several validation studies published in literature show that models suitable for certain pharmaceutical classes may not be appropriate for other classes or industrial chemicals.

In addition, the quality of the models is very much dependent on the size and quality of the underlying database. The larger the training set, which was used for the model development, the larger is the chemical domain of the model. The more specific information on the mechanisms of action is available for model development, the better will the resulting model perform. Toxicological model development is hindered for certain endpoints due to lack of sufficient experimental data for modelling and lack of information on the mechanism of action. Therefore, for the more complex endpoints, like reproduction toxicity, chronic toxicity, carcinogenicity involving ADME, species specificities, etc. model performance is still not sufficient for general use. However, useful information may nevertheless be gained from these models.

The level of uncertainty of the prediction is decisive for their use. For screening and prioritization purposes, a higher level of uncertainty may be acceptable than for their use in a regulatory setting. For a regulatory use, the prediction models need to be validated in order to meet acceptance by regulatory authorities and to replace current *in vitro* and *in vivo* test systems.

### References

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