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THE ACUTETOX PROJECT –DEVELOPMENT AND PRE-VALIDATION OF AN IN VITRO TESTING STRATEGY FOR ORAL ACUTE SYSTEMIC TOXICITY

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A-Cute-Tox is a large international 5-years project funded by the EU 6FP, with the aim to develop and pre-validate a simple and robust in vitro testing strategy for the prediction of human acute systemic toxicity of chemicals. It is designed to replace the animal testing for acute systemic toxicity, widely used today for regulatory purposes, by *in vitro* and *in silico* alternatives. In spite of the fact that earlier studies on acute systemic toxicity demonstrated a good correlation between *in vitro* basal cytotoxicity data (the 50% inhibitory concentration, IC50) in human cell lines and rodent LD50 values, and an even better correlation between IC50 values and human lethal blood concentrations, only very few in vitro tests have been accepted for general use. An existing problem with the in vitro to in vivo correlations to predict acute toxicity is that for a number of chemicals under- or overprediction of their toxicity was observed and these compounds are described as outliers. The approach taken in ACuteTox is to identify these outliers from a list of 97 selected chemicals tested using 6 basal cytotoxicity assays and for which human and animal data are collected from literature. The outliers of the in vitro/in vivo correlations are evaluated in order to introduce further parameters such as absorption, distribution, excretion, metabolism and specific organ toxicity, in particular haemato-, neuro-, nephro- and hepatotoxicity. A combined analysis of obtained data allows the identification of assays that could improve the in vitro/in vivo correlations. Integration of alerts and correctors derived from the selected tests into a prediction algorithm will allow the development, and pre-validation of a new in vitro testing strategy to predict acute oral toxicity. A new database, AcuBase, containing descriptions and results of *in vitro* tests and information on the tested compounds, as well as the results of animal experimentation, and human acute toxicity data, are generated within the framework of the project. The general structure of the project and the preliminary results obtained so far will be presented.