

USE OF HUMAN DATA COLLECTED IN ACUBASE (ACUTETOX PROJECT) FOR ANALYSES OF ANIMAL AND IN VITRO DATA

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The main goal of the EU integrated “AcuteTox” project is to replace the animal testing for acute systemic toxicity by *in vitro* and *in silico* alternatives. As a part of the project, a database, “AcuBase”, was created as a central database for consistent management of all information relevant to this project, aiming to optimise and pre-validate an *in vitro* testing strategy for predicting acute human toxicity of chemicals.

In vitro and *in vivo* data for 97 reference chemicals, including drugs, industrial chemicals, pesticides and other, are collecting by several research groups within the AcuteTox project.

The database comprises two principal parts, for archiving *in vitro* and *in vivo* data respectively. The *in vitro* part of AcuBase includes the methodology for various *in vitro* tests (standard operating procedures, SOPs), as well as experimental data for the reference chemicals, obtained in several laboratories. The *in vivo* part includes animal acute toxicity data (LD50), and human acute poisoning cases (blood concentration, time from poisoning to sampling, symptoms and signs, time to death/recovery etc.), available from clinical/forensic medical reports published in the literature, or collected from several poison information centres.

A principal basis for evaluation of the *in vitro* cytotoxicity tests will be statistical correlation with animal LD50 data and with human peak blood concentration data (LC50 values).

Preliminary analyses of the *in vivo* data indicated that:

Log (LD50) values in rat show a low correlation ($R^2=0.45$, $n=72$) to log LC50 values in humans. The LC50 values are determined from time related lethal and sub-lethal acute toxicity data extrapolated to time 0.

In vitro-in vivo modelling with linear regression as well as multivariate modelling with PLS regression reveal better correlation between *in vitro* tests (50% inhibitory concentrations, IC50 values) and LC50 values for humans ($R^2=0.70$, $n=72$), compared to correlation between IC50 values and LD50 values for rat ($R^2=0.50$, $n=88$). However, the results are not directly comparable since the numbers of observations are different. From the correlations deviating chemicals were identified for further efforts to find correction factors.

Reference: Clemedson, C., Kolman, A. and Forsby, A. (2007) The integrated Acute Systemic Toxicity Project (ACuteTox) for the optimization and validation of alternative *in vitro* tests. ATLA 35, 33-38.