

Implementation of *in vitro* tests for acute human toxicity assessment – the MEIC and ACuteTox projects

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In the last two decades new strategies in toxicology have been proposed in order to replace the animal lethal toxicity tests by alternative *in vitro* methods. Several studies have been conducted to develop reliable cellular assays and to evaluate their predictive value for acute human toxicity.

The most outstanding study in this field was the Multicentre Evaluation of In Vitro Cytotoxicity (MEIC) project (1989-1999), which was initiated and supervised by Dr. Björn Ekwall. The main goals of this international project were to evaluate the relevance of *in vitro* cytotoxicity tests for predicting acute human systemic toxicity and to select best combination of tests (test battery) for use in acute toxicity testing. Twenty nine laboratories in different countries around the world have tested 50 reference chemicals in 61 cytotoxicity assays. The MEIC project demonstrated a high relevance of human cell tests for the estimation of acute human toxicity *in vivo*. At the same time, the MEIC study outlined the need of organ-specific and mechanism-based *in vitro* assays, where biotransformation, toxicokinetics, and passage through biological barriers could be taken into account.

Recently, the European Commission (EC) proposed a new regulatory system called REACH (Registration, Evaluation and Authorisation of Chemicals). About 30,000 chemicals will be tested, which will cost billions of Euros, and require millions of experimental animals.

Two international projects have been granted by the EC, one of them is the ACuteTox (Acute Systemic Toxicity, with 35 partners from 13 countries), and the second one is ReProTect (Reproductive Toxicology, with 26 partners from 9 countries).

The European Centre for the Validation of Alternative Methods (ECVAM, Ispra, Italy) has elaborated a 10-year programme to support the implementation of the *in vitro* tests and their acceptance by the legislation.

The main aim of the ACuteTox project is to develop a forceful *in vitro* testing strategy for prediction of acute human systemic toxicity, and to replace the acute animal toxicity tests, used today for regulatory purposes, by *in vitro* and *in silico* alternatives. The project also includes validation of already existing and newly designed *in vitro* tests, e.g., analysis of their variability and reproducibility, analysis of outliers and comparison of human and *in vitro* data. A database with human, animal and *in vitro* acute toxicity data will be also created.