

Proposal abstract

The European Union White Paper entitled “Strategy for a future chemical policy (COM 2001/88, final, 14.02.2001) proposes to harmonise the testing requirement for existing chemicals, by developing a new system for the “Registration, Evaluation and Authorisation of Chemicals” (REACH).

This could result in an increase in animal use estimated in a range of million.. Thus the need of reliable alternatives in vitro models becomes urgent. One of the areas in which in vivo animal models are widely used is the study of absorption and metabolism of drugs, nutrients, contaminants, following oral exposure, also in compliance with current regulations on chemicals. Although several in vitro models are available, including hepatocytes and intestinal cell cultures, they are not yet accepted into regulations, as they still require better characterisation and optimisation to reach the validation stage.

The main aim of the project is to optimise and provide established protocols and experimental in vitro models for testing intestinal and liver absorption, metabolism and toxicity of molecules of pharmacological interest. The added value of the project, with respect to the existing experimental approaches in this field, is to provide optimised sequential procedures, easily amenable to validation studies for screening and testing of new drugs, possibly by miniaturized and automated technology. The direct participation of SMEs also in the research activities will assure that those procedure will also fit with the requirements of industrial application.

The project is therefore articulated in different approaches, which will integrate at various levels. A first basic approach will be the optimisation of in vitro liver and intestinal models for their use in transport and toxicity of structurally diverse reference drugs chosen with the help of a steering committee of relevant stakeholders. A parallel approach will deal with the identification of the transport and metabolic pathways and possible cytotoxic effects of these drugs, in order to develop appropriate monitoring procedures. New advanced technologies (genomics, proteomics, metabolomics) will be used in order to develop high throughput models related to the specific area of intestine-liver absorption and biotransformation. Each approach will take care of the reliability of the protocols used and of the relevance of the whole procedure to the in vitro/in vivo extrapolation of drugs effects. To this end, a unit in charge of computer-based studies will support and pilot the project all along its course.