ADME JOINT WORKSHOP

flash

Ispra, 13-14 October 2011

« Potential for further integration of toxicokinetic modeling into the prediction of in vivo dose-response curves without animal experiments »

THE ISSUE

Knowledge on absorption, distribution, metabolism and excretion (ADME) of a substance is a prerequisite when assessing the safety of consumers, patients and the environment. A lot of the information can be generated at tissue/cell or sub-cellular level in in vitro and/or in silico studies and used to estimate the internal/tissue dose by means of physiologically-based toxicokinetic modeling (PBTK). Computer modeling avoids unnecessary animal experimentation and improves the predictivity of in silico (QSAR) and in vitro tests by integrating the results of all available relevant approaches.

Metabolism was originally considered to be responsible for inactivation or detoxification of foreign compounds in the human body. However, in the current regulatory requirements for chemicals and cosmetics, toxicokinetic and metabolism evaluations are not part of the main base-set of tests. Yet, it has become increasingly clear that metabolism-mediated toxicity is an important issue in regulatory toxicology.

ABSORPTION
DISTRIBUTION
METABOLISM
EXCRETION

With a view to replacing animal testing, particularly in cosmetics, in vitro/in silico methods for establishing the toxicokinetics and metabolism of unknown chemicals will provide essential information for risk assessment. They may provide the decisive part of the information used for further decision-making. Kinetic parameters will be vital for gathering the most valuable toxicity data and for designing appropriate testing strategies.

Currently, certain gaps e.g., regarding information on the reliability of tests and availability of methodological tools withhold PBTK modeling from being used for in vitro and in vivo extrapolation (IVIVE) of in vitro toxicology data. The main goal of the EPAA project is to progress physiologically based toxicokinetic modeling as an accepted part of a new integrated risk assessment paradigm.

THE WORKSHOP

This workshop was a follow-up to the first EPAA workshop on this topic, in November 2008 in Dusseldorf, which was successful in identifying the challenges and bringing together the relevant stakeholders. The results of the workshop have recently been published in "Toxicology in vitro[1]" . The main objective of this second workshop was to identify both scientific and methodological gaps and to generate recommendations on how to address them.

More than 50 invited experts attended the event, sharing their experiences and insights on the potential and the limitations of in silico (QSAR) and in vitro kinetic models used in PBTK as well as the PBTK modeling platforms themselves. Also, the experts were willing to work on the development of concrete guidance for test developers, toxicologists, safety assessors and regulators on which priorities to focus in order to further progress this new integrated risk assessment paradigm.

In their welcome , Joachim Kreysa and Sandra Coecke (In Vitro Methods Unit, ECVAM, IHCP, JRC) emphasized the importance of Integrated Testing Strategies as the way forward and invited participants to officially submit new test methods via the ECVAM website as a necessary (pre) validation step to gaining regulatory acceptance.

In his presentation "PBTK modeling for the prediction of human in vivo dose-response curves" Jos Bessems (Senior Scientist at the Dutch RIVM, the National Institute for Public Health and the Environment) described the current state of the art and discussed the reasons for the infrequent use of such models. George Loizou (Head, Computational Toxicology Team, Health and Safety Laboratory, UK) gave an overview of commercial and public PBTK tools, describing their minimal data >>

1 Schroeder K et al. (2011) Report from the EPAA workshop: In vitro ADME in safety testing used by EPAA industry sectors. Tox. in Vitro 25 (2011) 589–604 (Pubmed link) http://www.ncbi.nlm.nih.gov/pubmed/21167275

requirements, applicability domains and accessibility. Harvey Clewell (Director of the Center for Human Health Assessment at Hamner Institutes for Health Sciences, USA) focused on the concrete non-testing use of a PBTK model in vitro – in vivo extrapolation (IVIVE) and finally Kannan Krishnan (Professor of Occupational and Environmental Health at the University of Montreal, Canada) described the progress achieved to-date for SARs and QSARs (in silico tools) for predicting chemical-specific input parameters of PBTK models.

These keynotes were followed by eight flash presentations providing information on the presenter's own results and experiences in terms of alternative methods and QSAR models used to generate input parameters for PBTK models.

A first Breakout Group , chaired by Kannan Krishnan with Jos Bessems as rapporteur, focused on "Gaps in non-animal test methodology for the assessment of Absorption, Distribution, Metabolism and Excretion (ADME)". The Group produced a collection of models allocated to three stages of development. The status of all available models (listed below) was ranked according to three levels:

Status 1 – suitable for PBTK modeling and ready for some kind of evaluation (e.g. pre-validation). However, if the method has already shown enough reliability and reproducibility there might be no need for further validation.

Status 2 – suitable for PBTK models, but not yet ready, further improvement needed

Status 3 – not demonstrated with respect to input for PBTK models, but could be made applicable for PBTK

A second Breakout Group, chaired by Harvey Clewell with George Loizou as rapporteur, focused on "PBTK models as such". This group addressed the issues surrounding user-friendly software tools and free-to-use web applications were investigated in an attempt to understand the requirements for wider and increased take-up and use by regulators, risk assessors and toxicologists in general.

RECOMMENDATIONS, NEXT STEPS AND FUTURE PLANS OF THE ADME PROJECT TEAM

The workshop agreed on two sets of recommendations:

1. Methodological: case studies, «SAR Models as Tier 1 for qualitative assessment of metabolic clearance», analytics, in vitro assays for absorption, etc.

2. Strategic: creation of a database in the EU (possibly located at the JRC), collect human kinetic data (here EPAA could be helpful by asking pharmaceutical companies for human data, as well as agrochemical and animal health companies for their animal data from failed compounds, another proposal was to connect this with the US approaches such as ToxCast), etc.

The full report of the worskshop will be published in a peer-reviewed journal; first authors will be Jos Bessems and George Loizou.

The group will follow-up on the recommendations and discuss who could take on a "champion role" regarding certain recommendations / issues, and an assessment will be made on how these should be addressed. It is possible that small collaborative projects involving cooperation with several organizations will follow, for which - to start with - some small rapidly expedited projects with a high potential for success were proposed followed by some medium term new research projects and in the long term to cooperate with the US or other outside EU partners

"Kinetic parameters will be vital for gathering the most valuable toxicity data and for designing appropriate testing strategies."

WORKSHOP PARTICIPANTS

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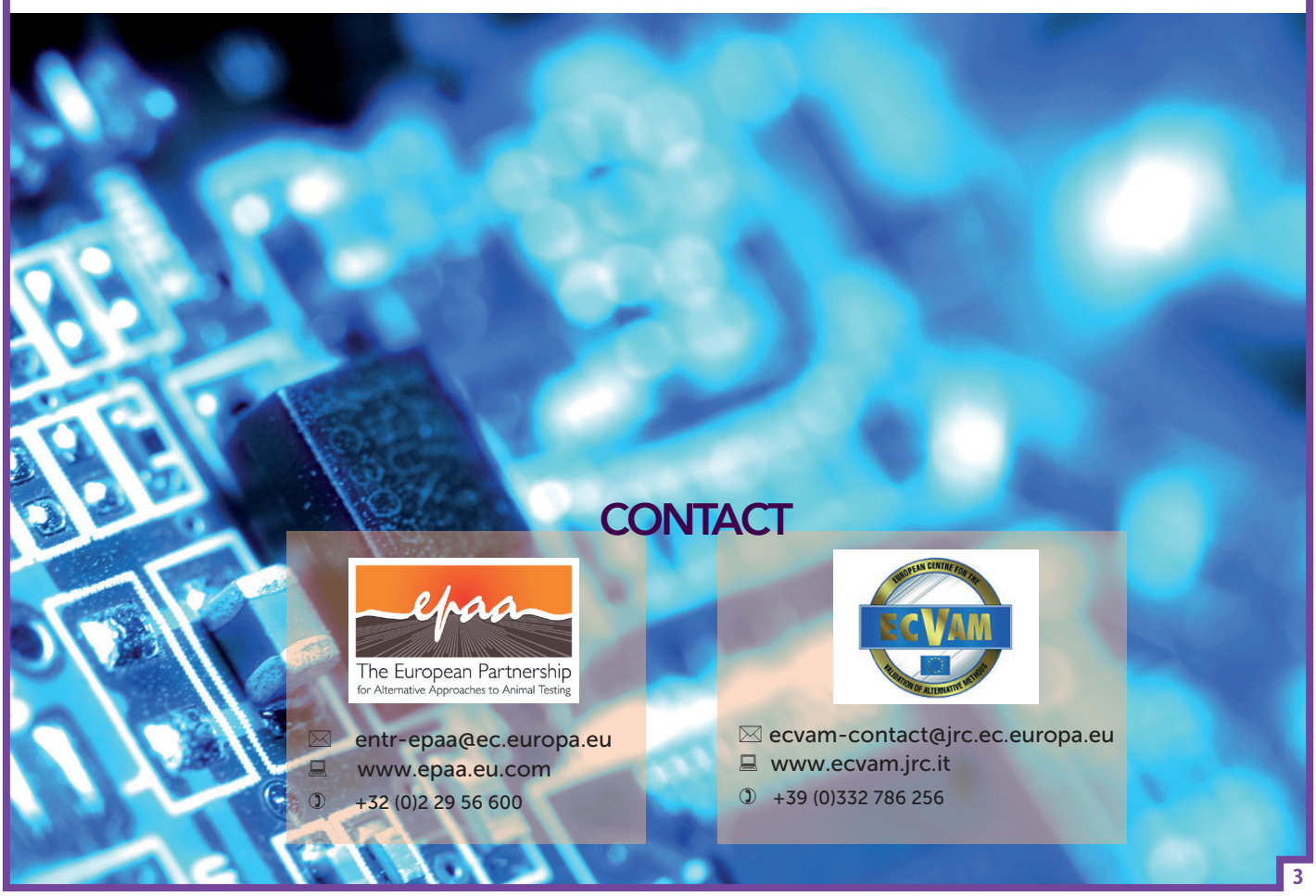

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