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Review

Report from the EPAA workshop: *In vitro* ADME in safety testing used by EPAA industry sectors

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Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ADI, Acceptable Daily Intake; Colipa, the European Cosmetic Toiletry and Perfumery Association; CYPs, cytochrome P450s; DNEL, Derived No Effect Level; DG, Directorate General; ECHA, EU Chemicals Agency; ECVAM, European Centre for the Validation of Alternative Methods; EFSA, European Food Safety Authority; EU, European Union; FP6, 6th Framework Programme; FP7, 7th Framework Programme; GSTs, glutathione S-transferases; GLP, Good Laboratory Practice; GCCP, Good Cell Culture Practice; IMI, Innovative Medicines Initiative; ICH, International Conference on Harmonisation; IND, Investigational New Drug; ITS, Integrated Testing Strategies; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JMPR, Joint FAO/WHO Expert on Pesticide Residues; JTIs, Joint Technology Initiatives; MoS, Margin of Safety; NRC, National Research Council; NIH, National Institutes of Health; NOAEL, No Observed Adverse Effect Level; OECD TG, Organisation for Economic Co-operation and Development Technical Guideline; OSIRIS, Optimised Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information; PBBK, physiologically-based biokinetic; PBPK, physiologically-based pharmacokinetic; PBTK, physiologically-based toxicokinetic; PPPs, plant protection products; PPR, Plant Protection Products and their Residues; QPS, Qualified Presumption of Safety; QSAR, Quantitative Structure Activity Relationship; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; SCCNFP, Scientific Committee on Cosmetics and Non-Food Products intended for consumers; SCCS, Scientific Committee on Consumer Safety; SCCP, Scientific Committee on Consumer Products; SULTs, sulfotransferases; TTC, Threshold of Toxicological Concern; TK, toxicokinetics; UGTs, UDPGA-glucuronosyltransferases; FDA, US Food and Drug Administration; WHO, World Health Organization.

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ABSTRACT

There are now numerous *in vitro* and *in silico* ADME alternatives to *in vivo* assays but how do different industries incorporate them into their decision tree approaches for risk assessment, bearing in mind that the chemicals tested are intended for widely varying purposes? The extent of the use of animal tests is mainly driven by regulations or by the lack of a suitable *in vitro* model. Therefore, what considerations are needed for alternative models and how can they be improved so that they can be used as part of the risk assessment process? To address these issues, the European Partnership for Alternative Approaches to Animal Testing (EPAA) working group on prioritisation, promotion and implementation of the 3Rs research held a workshop in November, 2008 in Duesseldorf, Germany. Participants included different industry sectors such as pharmaceuticals, cosmetics, industrial- and agro-chemicals. This report describes the outcome of the discussions and recommendations (a) to reduce the number of animals used for determining the ADME properties of chemicals and (b) for considerations and actions regarding *in vitro* and *in silico* assays. These included: standardisation and promotion of *in vitro* assays so that they may become accepted by regulators; increased availability of industry *in vivo* kinetic data for a central database to increase the power of *in silico* predictions; expansion of the applicability domains of *in vitro* and *in silico* tools (which are not necessarily more applicable or even exclusive to one particular sector) and continued collaborations between regulators, academia and industry. A recommended immediate course of action was to establish an expert panel of users, developers and regulators to define the testing scope of models for different chemical classes. It was agreed by all participants that improvement and harmonization of alternative approaches is needed for all sectors and this will most effectively be achieved by stakeholders from different sectors sharing data.

Contents