Alternative methods to safety studies in experimental animals

Alternative methods to safety studies in experimental animals: role in the risk assessment of chemicals under the new European Chemicals Legislation (REACH)

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Abstract

During the last two decades, substantial eVorts have been made towards the development and internationalacceptance of alternative methods to safety studies usinglaboratory animals. In the EU, challenging timelines for phasing out of many standard tests using laboratory animalswere established in the seventh Amending Directive 2003/15/EC to Cosmetics Directive 76/768/EEC. In continuationof this policy, the new European Chemicals Legislation(REACH) favours alternative methods to conventional invivo testing, if validated and appropriate. Even alternativemethods in the status of prevalidation or validation, butwithout scientiWc or regulatory acceptance may be usedunder certain conditions. Considerable progress in theestablishment of alternative methods has been made insome Welds, in particular with respect to methods predictinglocal toxic eVects and genotoxicity. In more complex important Welds of safety and risk assessment such assystemic single and repeated dose toxicity, toxicokinetics,sensitisation, reproductive toxicity and carcinogenicity, it isexpected that the development and validation of in silicomethods, testing batteries (in vitro and in silico) and tieredtesting systems will have to overcome many scientiWc andregulatory obstacles which makes it extremely diYcult topredict the outcome and the time needed. The main reasonsare the complexity and limited knowledge of the biologicalprocesses involved on one hand and the long time frameuntil validation and regulatory acceptance of an alternative method on the other. New approaches in safety testing andevaluation using “Integrated Testing Strategies” (ITS)(including combinations of existing data, the use of chemicalcategories/grouping, in vitro tests and QSAR) that have not been validated or not gained wide acceptance in the scientiWc community and by regulatory authorities willneed a thorough justiWcation of their appropriateness for agiven purpose. This requires the availability of knowledgeand experience of experts in toxicology. The challengingdeadlines for phasing out of in vivo tests in the CosmeticsAmending Directive 2003/15/EC appear unrealistic. Likewise,we expect that the application of validated alternativemethods will only have a small or moderate impact on thereduction of in vivo tests under the regimen of REACH,provided that at least the same level of protection of human health as in the past is envisaged. As a consequence, undersafety aspects, it appears wise to consider established invivo tests to be indispensable as basic tools for hazard and risk assessment with respect to systemic single andrepeated dose toxicity, sensitisation, carcinogenicity andreproductive toxicity, especially regarding quantitativeaspects of risk assessment such as NOAELs, LOAELs andhealth-related limit values derived from them. Based on theoverall evaluation in this review, the authors are of theopinion that in the short- and mid-term,

the strategy of thedevelopment of alternative methods should be moredirected towards the reWnement or reduction of in vivo tests. The lessons learnt during these eVorts will provide asubstantial contribution towards the replacement initiativesin the long-term.

Keywords Risk assessment · Chemicals · REACH · Alternative method · In vitro · In vivo · In silico ·Validation · Integrated testing strategy