The European Partnership for Alternative Approaches to Animal Testing

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# Overcoming barriers to validation of non-animal partial replacement methods - Integrated Testing Strategies

### A valuable approach…

As part of the overall attempt to reduce and replace the use of animals in testing, some industry sectors are already using approaches called "integrated testing strategies". Integrated testing strategies combine data and information generated from several single tests or groups of tests, and are intended to offer scope for replacing some tests for which animals are customarily used. But despite their potential, many questions remain about how integrated testing strategies should be designed, and when they should be deployed. Experts from industry and the European Commission focused on these questions in a workshop* in November - and came up with at least some answers.

### …in need of greater clarity…

The experts agreed on a working definition of what an integrated testing strategy is - or should be - in the context of safety assessment. According to the consensus they reached, it is a methodology that integrates information from more than one source for toxicological evaluation in a way that allows decisions to be made. Additionally, "this should be achieved taking into consideration the principle of the 3Rs (reduction, refinement, replacement)".

The workshop participants also agreed that, in some cases and for some forms of testing - for screening, for risk assessment and for hazard classification and labelling - integrated testing strategies could be used without prior formal validation. But they should always be of demonstrable scientific robustness, and assessment of this robustness would require a case-by-case expert judgement.

However, an integrated testing strategy would have to be formally validated before it could replace any in vivo test currently used for regulatory purposes. And this is where the questions start.

### …the questions needing an answer…

Unresolved issues include what components can or should figure in an integrated testing strategy, how to assess the predictive value of strategies (and/or their separate components), and to what extent they should be validated for regulatory purposes.

### …the pharmaceuticals perspective…

In the pharmaceutical industry, integrated testing strategies are used as support to the standard regulatory tests and are intended to bring insights into specific mechanisms in order to improve the prediction of unexpected adverse effects. They usually combine information from *in vitro*, *in silico* and *in vivo* methods – in other words, test tubes and computers, in addition to animal studies - and the majority of these methods are validated in-house by the companies that use them.

### …the chemicals perspective…

In the chemical sector, the goal is risk management. The EU chemicals legislation (known as REACH) allows industry to use a wide range of inputs to establish whether a substance has a particular dangerous property. These inputs include historical data from non-standard tests and from humans, quantitative structure-activity relationships derived from computer models, *in vitro* methods, and extrapolation from other studies. Integrating the data from these inputs into testing strategies is highly complex, and assessing the validity of the information is predominantly expert-led.

### …the cosmetics perspective…

In the cosmetics industry, the goal is risk assessment and integrated testing strategies offer the possibility of achieving full replacement of the current animal test where this is not possible with any individual in vitro or in silico test. COLIPA, the cosmetics industry trade association, presented two case studies (for eye irritation and skin sensitisation) where a partial-replacement validation rationale has been applied to candidate test methods following discussion with ECVAM.

### …the validation perspective…

From the perspective of the European Commission's European Centre for the Validation of Alternative Methods, the main objective is to reduce and replace current regulatory animal tests. Here, testing strategies composed of a number of single tests or groups of tests are envisaged for the most complex endpoints (such as systemic toxicity or skin sensitisation). Initial thinking is that individual components of integrated testing strategies should be assessed for their reliability before assessing the relevance of the entire strategy. The testing strategies should be validated retrospectively, primarily on the basis of existing information.

### …work underway…

Work is underway in many areas potentially relevant for integrated testing strategies. For example, several EU-funded projects aim to develop novel tests and frameworks for integrated testing strategies that will allow regulatory decision-making based on data generated without animals.

### …next steps

Among the priorities now for EPAA is to intensify the dialogue between academia (test developers), industry (test appliers), ECVAM (test validation) and regulators (users of test data), making sure that all the relevant stakeholders are involved in the development the integrated testing strategies.

* *"Overcoming barriers to validation of non-animal partial replacement methods/integrated testing strategies", EPAA-ECVAM, 19-20 November 2008.* A fuller report on the meeting will be made available shortly on the EPAA website.