# International Harmonization

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International agreements to harmonize toxicity test protocols, regulatory testing requirements, and validation guidance, as well as the mutual acceptance of test data, are important components in reducing animal testing worldwide. Cooperation on these issues can immediately reduce animal use by reducing duplicative animal testing for the same substance between companies, industries, and countries. In the longer term, cooperation and harmonization efforts can reduce duplication of validation efforts and encourage wider adoption of new test methods. Harmonization efforts are also valuable to manufacturers in that they may reduce product costs and product testing requirements and, therefore, overall time to market.

The ultimate goal of *international harmonization* efforts is *international regulatory acceptance* of a new or revised test method. The anticipated future successes in international regulatory acceptance of non-animal alternative methods will have a significant impact on reducing animal use in regulatory assessments.

Three organizations involved in establishing and harmonizing international validation and regulatory acceptance criteria and processes for toxicological test methods are the focus of this article: the Organisation for Economic Cooperation and Development (OECD), the European Centre for the Validation of Alternative Methods (ECVAM), and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

Other organizations involved in international harmonization efforts of test protocols and regulatory testing requirements include the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH), the World Health Organization (WHO), and the United Nations (UN), as well as many national regulatory authorities such as the US Environmental Protection Agency (EPA) and the Japanese National Institute of Health Sciences (NIHS). The relevant activities of each of these organizations are described in detail in other sections of AltTox.org.

**International Harmonization of Validation Processes and Criteria**

The development of specific criteria for the validation of alternative toxicity test methods took place in the European Union (EU) and US, and internationally in OECD forums, in the early to mid-1990s. By 1997, ECVAM, ICCVAM, and the OECD had all adopted a similar set of validation criteria, although some of the processes and interpretations of criteria varied. However, the internationally harmonized “validation concept” was considered a success (Spielmann, 2001). ECVAM and NICEATM-ICCVAM (National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods) have continued to work to establish methods to minimize duplication of efforts, to accept each other’s peer review

of validation studies, and to develop collaborations to support other international validation efforts (Balls, 1999; ICCVAM, 2001; Schechtman, 2006; Stokes, *et al.*, 2002).

**International Harmonization of Regulatory Acceptance Criteria**

The OECD is the leading international organization in providing guidance for the international acceptance of new or revised test methods for hazard assessment. The following excerpt from the *Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment* (Series on Testing and Assessment, No. 34) summarizes the OECD position (OECD, 2005):

"Validation as described in this Guidance Document contributes strongly to the international acceptance of any proposed test method and encourages and supports worldwide Mutual Acceptance of Data (MAD). However, regulatory authorities may still have additional questions on the test method beyond its established reliability and relevance, which could affect its regulatory acceptance. Harmonisation of international regulatory acceptance of adequately validated test methods may be achieved by considering the guidance provided in this document."

OECD decisions are made by consensus rather than by majority, and once the OECD Council formally adopts a decision (a Council Decision) it is binding on all Member countries (Koëter, 2003). The Council Decision most relevant to the hazard testing of chemicals is the OECD Guidelines for the Testing of Chemicals (Test Guidelines), which include the Mutual Acceptance of Data. The OECD principle of mutual acceptance of data states that (OECD, 1981):

"…data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment."

Koëter (2002, 2003) described the processes and role of the OECD in achieving international acceptance of harmonized OECD Test Guidelines (TG). The availability of an internationally harmonized TG for an *in vitro* test method encourages and facilitates the adoption and use of that method by national regulatory authorities.

*Work sharing* agreements among countries are another OECD approach to reducing duplication of animal testing for hazard assessments. For example, the recently developed work sharing on pesticide registration reviews occurs when "two or more countries divide the work required to review a pesticide data submission" (OECD, 2007). Work share between regulatory agencies is part of OECD's 2004 "ten-year vision for the harmonisation of regulatory approaches for agricultural pesticides" (OECD, 2004a). Discussions for implementing work sharing for new chemical hazard assessments have also taken place (OECD, 2004b). These work sharing opportunities can contribute to animal welfare, as well as reduce time and costs for industry.

Several opportunities are provided for cooperative work among countries on the *investigation of existing chemicals*. Activities on chemicals by member countries carried out before 2005 are

available in the OECD EXICHEM database. The SIDS (Screening Information Data Set) database tracks all High Production Volume (HPV) chemicals through the OECD programme on the Investigation of Existing Chemicals. When data gaps for a specific chemical exist a country or industry can "sponsor" additional investigations. The results of these assessments are then made available in the SIDS database. The eChemPortal is a free Internet resource for information on chemical properties, environmental fate, toxicity, and hazard and risk assessments that was launched by the OECD in 2007. It will continue to be updated with new databases and search functionalities. The *Guidance on Grouping of Chemicals* (Series on Testing and Assessment No. 80) describes processes for grouping of chemicals into categories so that individual chemicals do not need to be tested for every endpoint in a hazard assessment. These cooperative efforts on sharing of information on existing chemicals can contribute to animal welfare, as well as reduce time and costs for industry.

ECVAM and ICCVAM work collaboratively and with other international authorities and stakeholders to promote the international adoption of validated methods (Stokes, *et al.*, 2002). ECVAM and ICCVAM worked jointly to support the development of the 2005 OECD guidance document on validation and international acceptance (Schechtman, 2006).

The NIHS in Japan has also been involved in many international cooperative efforts. "OECD-related examples of [NIHS] cooperation include projects for evaluating the safety of existing chemicals and newly developed food products, and the development and revision of toxicity testing guidelines."

Spielmann (2002) made the following observation:

"The harmonization of toxicity test guidelines initiated by the Organisation for Economic Co-operation and Development in 1982 has been the most successful measure to reduce pain and distress of laboratory animals in regulatory testing. From the animal welfare perspective, the international harmonization of test guidelines and the mutual acceptance of data are, therefore, the way forward for all areas of chemicals testing."

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