

The Extended One Generation Study

Under REACH, reproductive toxicity testing will count for a large part of necessary resources needed for safety testing. The major part thereof will be expended due to the requirement for two-generation studies according to the OECD test guideline 416.

In 2006, the ILSI Health and Environmental Sciences Institute published a strategy for agricultural chemical safety assessment (ACSA) that included an adapted design for reproductive and developmental toxicity evaluation (Cooper et al, 2006.). It is important to bear in mind that the ACSA testing proposal was designed in the context of an intelligent testing strategy for the evaluation of agrochemicals, aimed at addressing the inefficient development of data much of which is not used in the final risk assessment (Carmichael et al, 2006.). It is a scientifically robust approach to reduce and refine the studies required for registration of agrochemicals. One core element of the ACSA testing proposal is –besides others- an extended one-generation reproductive toxicity study to replace the classical 2-generation study (OECD 416). However, this extended one-generation study was not designed as a stand-alone study for reproductive toxicity, and adaptation of this study design for other uses should take into account the endpoints required for sector-specific risk assessments. The extended one-generation reproductive toxicity study design is currently under consideration as an alternative to the current one- and two-generation tests, with potentially widespread applicability and impact on chemical safety assessment across many industry sectors.

The European Partnership for Alternative Methods to Animal Testing (EPAA) evaluated whether this new approach developed for agrochemicals, could also be applied to other sectors (e.g. industrial chemicals). In an ECVAM workshop held in September 2006 and an EPAA workshop held in November 2006, which was hosted by BASF and attended by more than thirty experts from industry and the regulatory community, it was discussed in detail and agreed that the extended one-generation study as developed by the ACSA project could, in principle, be applicable to safety testing under REACH. However, it was also agreed that the complex ACSA protocol could be modified in order to meet the current requirements for industrial chemical safety testing. This will deliver animal welfare benefits with regard to both refinement and a reduction in the number of animals used (more than 40% compared to the two-generation study).

Since the extended, one-generation study does by far address more endpoints than currently required for chemical risk assessment, a major modification of the ACSA test protocol for use under REACH will be to design reliable triggering and/or waiving criteria for the components of the protocol as modules. An ECETOC task force has developed these criteria (ECETOC Doc. No. 45, 2008) and a subsequent workshop, jointly convened between ECETOC and ECVAM, was held to discuss the triggering and waiving criteria and agree on their relevance and on possible validation needs. The workshop was an active event with invited participants representing industry, academia, and the regulatory community. A workshop report has just been prepared, which represents the results of the discussion and the consensus that has been achieved. The approach to discuss current developments with the relevant stakeholders, especially with regulators, was welcomed as being a constructive and cooperative way to expedite the extended one-generation reproductive toxicity study design.

Feasibility of the ACSA extended one-generation study protocol is currently being evaluated. Studies on model compounds, based on this protocol, have been initiated by industry partners (BASF, Bayer Crop Science, Dow, Syngenta) of the EPAA. It is expected that results from these feasibility studies will be available towards mid 2009.

An OECD expert group was set up end of 2007 to develop a draft guideline and evaluate the validity of the endpoints used. A draft guideline was promoted by Germany, the Netherlands

and the U.S. and most technical questions have been solved in the meantime. The draft test guideline is expected to be submitted for WNT Approval at the WNT 22 meeting, in 2010.

References:

Carmichael NG, Barton HA, Boobis AR, Cooper RL, Dellarco VL, Doerrer NG, Fenner-Crisp PA, Doe JE, Lamb JC IV, Pastoor TP. 2006. Agricultural chemical safety assessment: a multisector approach to the modernization of human safety requirements. *Crit Rev Toxicol* 36:1-7.

Cooper et al.: A Tiered Approach to Life Stages Testing for Agricultural Chemical Safety Testing. *Critical Reviews in Toxicology* 36: 69-98 (2006)

ECETOC Doc. No. 45, 2008