Extended One-Generation Reproductive Toxicity

A proposal was released by the International Life Science Institute-Health and Environmental Sciences Institute (ILSI/HESI) Agricultural Chemical Safety Assessment (ACSA) Technical Committee for generating meaningful data in respect of reproductive toxicity, which covered aspects like developmental neurotoxicity, developmental immunotoxicity as well as reproductive toxicity, while tracking the endocrine hormones. Cooper et. al., were the pioneers in describing the Extended One-Generation Reproductive Toxicity (EOGRT) study design, in order to assess the reproductive toxicity of chemical substances. This test method was adopted by the Organisation for Economic Cooperation and Development (OECD) in July 2011, as Test Guideline 443, with the latest version being released on June 25, 2018.

Objectives of this study are to provide hazard characterisation data, for risk assessment, by evaluating particular life stages not covered by other types of toxicity studies, and to minimise excessive uses of experimental animals.

In brief, a single study of EOGRT assesses parental (P) fertility and reproductive function, and offspring (F_1) development, including assessment of sexual landmarks (in Cohort 1A), developmental neurotox (in Cohort 2), and developmental immunotox (in Cohort 3). Animals may be mated to produce F_2 generation, if there are signs of potential adverse effects in Cohort 1A, going on to establish further confirmatory data in Cohort 1B.

EOGRT	Two-generation study
Follows the 3R principle as mating of F_1 animals is not a part of the basic study design. The need for data of F_2-generation depends on the regulatory requirements, i.e., study results already obtained or certain specific criteria based on existing information, and equivocal effects obtained.	Mating of F_1 animals is part of basic study design. Data generated using F_2 animals in most of the cases does not change risk assessment or classification and labelling of chemicals.
Improves the sensitivity of the study by addressing more parameters while assessing large number of F_1 animals.	It provides limited information, however uses the greater number of F_1 animals.
Increases the number, extent, and duration of F_1-offspring assessments resulting in more thorough and efficient utilisation of the F_1-generation while excluding the F_2-generation of offspring unless triggered.	
At weaning, certain F_1- offspring are allotted to specific Cohorts for further investigation of the sexual maturation, reproductive organ integrity and function.	At weaning, selected F_1- offspring are assigned to, for further investigation of the sexual maturation, reproductive organ integrity, performance and function. Requires separate studies to evaluate the effect on developmental nervous and immune system.

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Inclusion of endocrine sensitive end-points – like anogenital distance, thyroid hormone analysis at different interval, and nipple retention in male pups.	No such parameters.
Cost of the study is more as it generates a lot of data.	Cost of the study is less.
Logistical bottlenecks occur at weaning of F1 litters, but can be resolved by professional detailed planning and experienced personnel.	No logistical bottlenecks.

The lab which performs two-generation studies can also perform EOGRT (only Cohort 1). However, it requires a very good experience in planning in scheduling the mating activity, excellent facilities which ensure that no extraneous environmental factors affect the endocrine function, capability to dose Juveniles, state of the art facilities for acquiring reliable and meaningful data for neuro-behavioural observations, instrumentation to capture such data electronically. None of the above are adequate without having a bunch of passionate, and experienced scientists for conducting all the Cohorts. From sponsor's point of view, CRO should select the correct dose level (by using blood kinetics or milk kinetics) and be able to report accurate NOAEL/NOEL from huge data generated during study enabling the sponsor, thereby, to assess the risk and help for classification and labelling of the chemical.

References:

- *Beekhuijzen M, Barentsen H, Marsden E, Zmarowski A, Aujoulat M, Picut C, Sloter E, (2016). Implementing the extended one generation reproductive toxicity study (EOGRTS): important points to consider, Critical Reviews in Toxicology, 46:4, 332-347.*
- *Cooper R.L, Lamb J.C, Barlow S.M, Bentley K, Brady A.M, Doerrer N.G, (2006). A tiered approach to life stages testing for agricultural chemical safety assessment, Critical Reviews in Toxicology 36 (January (1)):69–98.*
- *Cooper R.L, (2009). Current developments in reproductive toxicity testing of pesticides, Reproductive Toxicology, 28 (September (2)):180–7.*
- *Fegerta I, Billingtonb R, Bothamc P, Carneyd E, FitzGeralde R.E, Hanleyf T, Lewisc R, Martyd M.S, Schneiderg S, Sheetsh L.P, Stahli B, van Ravenzwaayg B, (2012). Feasibility of the extended one-generation reproductive toxicity study (OECD 443), Reproductive Toxicology 34 (2012) 331– 339.*
- *OECD, (2011). The Organisation for Economic Co-operation and Development (OECD) guidelines for the Testing of Chemicals, OECD 443, "Extended One-Generation Reproductive Toxicity Study", adopted by the council on July 28, 2011.*

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