

1

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In vitro test methods for developmental toxicity testing

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There is a growing interest in alternative assays for developmental toxicity testing, to reduce animal use, and to support mechanistic approaches. Three established assays are the Rodent Whole Embryo Culture (WEC), Embryonic Stem Cell Test (EST) and Zebrafish Developmental Assay (ZFA). WEC has the advantage of assessing complete morphogenesis, albeit in a restricted period of embryogenesis. The absence of the maternal compartment allows direct study of embryotoxicity. ZFA allows study of the entire vertebrate embryogenesis. Zebrafish genetics are well described and transgenic models facilitate mechanistic studies. Differences between fish and mammals are a challenge for extrapolation. EST allows lineage-specific analysis of effects on embryonic cell differentiation.

Transcriptomics and proteomics can be easily applied in this test. Comparison between rat and human stem cell lines facilitate interspecies extrapolation, although extrapolation of EST results to full embryogenesis is challenging. WEC has been formally validated in a ring study. Results showed a high reproducibility among participating laboratories and strong correlation between endpoints for growth and general malformations. Furthermore, the embryotoxic potency measured in the WEC generally showed good correlation with in vivo embryotoxicity, and preliminary correction for pharmacokinetic differences improved the correlation. The EST and ZFA will be validated against the WEC and in vivo data using the same set of compounds. The complementary, mechanistic information from these assays can be used for hazard identification and screening of compounds in drug development.