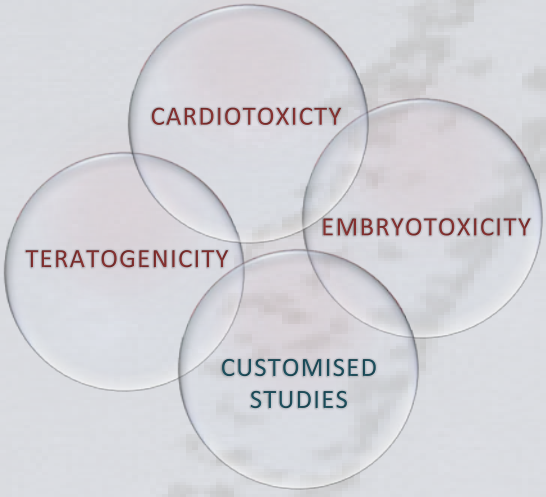
ZEBRAFISH MODEL

WHY USE THE ZEBRAFISH MODEL?

The tropical fish *Brachydanio rerio*, commonly known as Zebrafish, was identified in the 1980s as a promising genetic model of development. Currently, the Zebrafish embryo is widely used in developmental biology and molecular genetics, as well as for evaluating the toxicity of different molecules (Hill et al., 2005). The interest of using the developing Zebrafish embryo is growing due to several inherent advantages: Zebrafish are small, inexpensive to maintain, easily bred in large numbers (a single mating produces 100–200 eggs), and have a relatively short generation time (2–3 months).

Additionally, their ex utero development and optical clarity during embryogenesis permit visual analyses of early developmental processes and organ morphology. By 24 hours post fertilization (hpf), the entire body plan is established and all the precursor cells and tissues of the brain, eyes, and heart can be easily visualized using light microscopy. Embryogenesis is complete by 72 hpf, and most of the internal organs, including the cardiovascular system, gut, liver, and kidney, are fully developed by 96 hpf. This rapid development is comparable to 3 months of development in human embryos. Furthermore, many molecular pathways are evolutionarily conserved between Zebrafish and humans (Zon and Peterson, 2005).



WHAT CAN WE OFFER?

Fish embryo toxicity test with Zebrafish

(FET, draft proposal OECD, 2006)

This test is based on chemical exposure to newly fertilized Zebrafish eggs for up to 96 hours. Lethal effects are determined by comparison with controls to identify the LC50, NOEC and LOEC-values. It can be used as alternative approach to classical acute fish toxicity testing (OECD, 203).

Teratogenicity test

The teratogenic potential of a substance is characterized by exposure of newly fertilized Zebrafish eggs for up to 96 hpf. Lethal effects and several morphological effects are evaluated during exposure time. At the end of the test, LC50, EC50-values and a teratogenic index are calculated in order to establish the teratogenic potential of a substance.

Cardiotoxicity test

Compounds are tested in order to characterize their potential to alter cardiac rhythm and cause QT-prolongation. Zebrafish larvae (3 days post fertilization) are exposed to chemicals for 3 hours. Cardiac function is evaluated after chemical exposure (ventricular and auricular heart rate, cardiac output and stroke volume).

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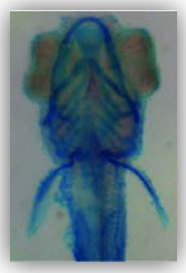
APPLICABILITY AREAS

Ecotoxicology

Fish are considered the primary aquatic vertebrate class; that's why they are an indispensable component of integrated ecotoxicity testing strategies.
Current OECD guidelines acknowledge this importance by covering acute toxicity (OECD 203 (OECD, 1992a)), early life-stage toxicity (OECD 210 (OECD, 1992b)), short term toxicity test on embryo and sac-fry stages (OECD 212 (OECD, 1998)), and juvenile growth (OECD 215 (OECD, 2000)).
The FET is a mandatory component in routine whole effluent testing in Germany since 2005 (DIN, 2001) and represents the most promising alternative approach to classical acute fish toxicity testing with live fish (OECD Nº203, 1992a).

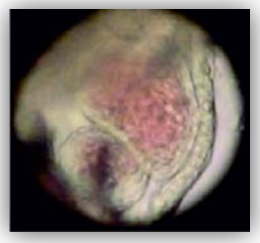


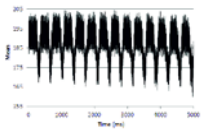
Drug safety and efficacy

Safety pharmacology is integral to the non-clinical safety assessment of new chemical entities prior to first administration to humans. The Zebrafish is an emerging vertebrate model for drug discovery that permits whole animal drug screens with excellent throughput, combined with ease of use and low cost.

Non-clinical toxicology studies

Zebrafish is a potentially valuable model for assessing side effect liabilities of compounds in the early drug discovery phases, such as lead selection or lead optimization. Developmental toxicity assays using Zebrafish have a potential to be used as an intermediate step between cell-based test and mammalian test and to reduce the number of mammals that are used in experimental toxicology.





REACH

This model is particularly ideal for studies of environmental toxicity in the context of REACH ("Registration Evaluation and Authorization for Chemicals") and can be used as tool to group and prioritize chemicals

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✓*Zon LI, Peterson RT. 2005. In vivo drug discovery in the zebrafish. Nat Rev Drug Discov 4:35–44.*