
Since 1997, the number of novel compounds submitted to the Food and Drug administration (FDA) of the U.S. for approval has halved. For an explanation, the FDA pointed to deficits in toxicology: “We use last century’s models for this century’s drug development”. The European Community has embarked on the REACH program that entails the testing of tens of thousands of compounds. Criticism has been raised that the EU may have “overREACHED” in their plans for chemical testing: The planned testing paradigms would require the use of more than 50 million mammals at an overall cost of 9 ½ billion Euro (Hartung and Rovida, Nature (2009), vol 460, p1080).

Since testing with mammals is expensive and time-consuming, and raises serious ethical issues, there is an urgent need to develop alternative models. The zebrafish with its small and transparent embryo is a much cheaper model for systematic testing of the toxicological and teratological effects of chemicals than mammals. Most importantly, fish embryos are widely accepted as being valid replacements for mammals in such experiments and they do not fall under the legislation for animal testing. In addition, the use of zebrafish embryos allows an alternative ‘whole organism’ approach to testing, which addresses systemic toxicity and complex mechanisms (e.g. neurobehaviour) and thus offers complementary information to current cellular alternatives under development and validation (e.g. see ECVAM website). The results from numerous small-scale pilot experiments indicate that zebrafish embryos are promising models to predict the toxicity of chemicals in mammals including humans. For example, a study addressing the cardiotoxicity of compounds suggests that the toxic effect of substances on the human heart can be predicted in zebrafish embryos with more than 80% success (Milan et al., Circulation, (2003), vol10, p1355). Similar promising results are also available for developmental, neuro-, hepato- and gastrointestinal toxicity. More recently, the long-standing mystery of the teratogenic action of thalidomide has been solved by the use of zebrafish, demonstrating its power as a model system to unravel the complex mechanisms underlying the effects of developmental toxicants (Ito et al., Science, (2010), vol 327, p1345). However, to convince regulators and industry of the virtues of the zebrafish model as a reliable predictor of toxicity in humans requires a systematic comparison of chemicals for their toxicity in humans and zebrafish.

We therefore strongly request funding bodies to support the systematic assessment of the predictive power of zebrafish embryos in toxicology. This support is an essential prerequisite for the introduction of this alternative model into the testing arena for human toxicology and drug development, next to its current use for environmental toxicity testing. We thus propose to bring toxicologists who already employ zebrafish together with human toxicologists, regulators and industries in order to demonstrate the validity of this alternative test system. A selection of 100 substances representing different chemical classes and known to have toxic effects in humans should be evaluated in a systematic manner in double-blind experiments with zebrafish embryos for their target site toxicity in relevant organs such as heart, kidney, liver, central nervous system (including developmental neurotoxicity and teratology). To achieve this task with a comprehensive contribution of excellence in all these fields, an integrated project is required.

The benefit for Europe is manifold: The results will go directly into new regulatory tests. This will have an impact on both human health and the quality of our environment, as well as improving the competitiveness of the European pharmaceutical and chemical industries.