Regulating a SWiFT transition: a Bayesian network as weight-of-evidence approach to replace the AFT with the FET

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1. Introduction

In 2006, the fish embryo toxicity (FET) test was submitted as a new proposed OECD test guideline. The draft proposal explicitly stated that the FET constitutes an alternative to acute fish toxicity (AFT) testing. The FET was adopted as OECD guideline 236 in 2013, after a long period of careful development and extensive laboratory ring trials; but the test was not unanimously accepted before the term “alternative approach” had been removed from the guideline. Regulatory agencies, such as the European Chemicals Agency (ECHA), have declared to be open to the use of FET data within a weight-of-evidence (WoE) approach. However, industry and other stakeholders have been challenged to develop a methodology that would be needed for such a WoE implementation.

Bayesian networks are a probabilistic modelling technique that can incorporate multiple lines of evidence, which can be interpreted as a WoE approach. Large amounts of data and other information, such as expert knowledge, can be integrated by using discrete probability distributions. A BN can then be used to make predictions of specified states (categories) of a variable of interest, for example toxicity intervals of LC_{50} values from the AFT.

As a response to the challenge posed by ECHA, a preliminary BN was developed to predict AFT toxicity intervals from a combination of FET data with other lines of evidence. These additional lines of evidence included physico-chemical properties, chemical category, and toxicity to other taxa, represented by algae (264 EC_{50} values, OECD 201) and daphnids (1164 EC_{50} values, OECD 202). This preliminary BN has been successfully implemented and evaluated for a limited amount of chemicals in a proof-of-concept WoE approach.

2. Preliminary FET BN results

The preliminary BN has been created based on the threshold database provided by P&G. This database covered 237 chemicals and included effect data for algae (264 EC_{50} values, OECD 201), daphnids (1164 EC_{50} values, OECD 202), AFT (1459 LC_{50} values, OECD 203), and FET (541 LC_{50} values, OECD 236). The technical development and a regulatory evaluation have been published form the basis of our future work. A graphical depiction of the preliminary BN can be seen in *Figure 1*.

The preliminary BN already shows a promising predictive power, which is dependent on the characteristics of the input data. Overall, for 70% of the chemicals the AFT toxicity intervals are correctly predicted. When looking at a subset of high-quality data, i.e., at least three values for AFT and FET per chemical, the correctly predicted fraction increased to 80%.

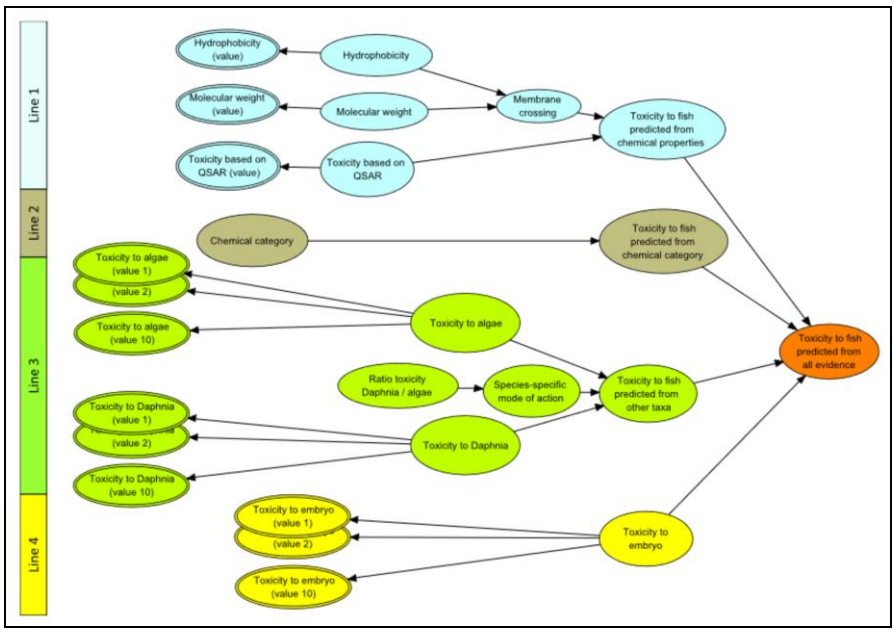

Figure 1: The main structure of the preliminary BN model, highlighting the four lines of evidence: (1) physico-chemical properties, (2) chemical category, (3) toxicity to other taxa, and (4) toxicity to embryo (FET).

3. SWiFT outlook

All lines of evidence of the preliminary BN represent regulatory accepted methods, but the model lacks details on metabolism, mode of action, and uncertainty of the toxicity nodes. The preliminary BN therefore needs to be expanded to increase its predictive power by including more information. Additional lines of evidence can include, amongst others, information on biotransformation, neurotoxicity, and chemical grouping approaches. In addition, the fish gill (RTgill-W1) cell-line assay, which is now an accepted international ISO standard (21115) and is undergoing validation by OECD, can provide complementary evidence of toxic potency of chemicals.

The SWiFT (Strengthening Weight of evidence for FET data to replace acute Fish Toxicity) project aims to provide a supportive framework for regulatory acceptance of FET data to fulfil the requirements for acute fish testing. The project will deliver an advanced and restructured BN model to predict the probability distribution of AFT for any structurally defined chemical. Additionally, an interactive web interface will provide public access. This advanced BN will represent a quantitative WoE approach with increased predictive power compared to traditional qualitative WoE approaches.

4. References

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