Regulating a SWiFT Transition

A Bayesian Network as Weight-of-Evidence Approach to Replace the AFT With the FET

Raoul Wolf, Scott Belanger, Thomas Braunbeck, Kristin Connors, Michelle Embry, Anders Madsen, Jannicke Moe, Kristin Schirmer, Stefan Scholz, Adam Lillicrap

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Acknowledgements

Strengthening **W**eight of ev**i**dence for FET data to replace acute **F**ish **T**oxicity (SWiFT)

Researcher Team: Adam Lillicrap (PI), Jannicke Moe, Raoul Wolf, Thomas Braunbeck, Kristin Schirmer, Michelle Embry, Scott Belanger, Kristin Connors, Anders Madsen, Stefan Scholz

More Details @ 4.01.08

Weight of Evidence by Conditional Probabilities

A Bayesian Network Model for Predicting Fish Acute Toxicity Based on Fish Embryo Testing

Jannicke Moe, Anders Madsen, Scott Belanger, Thomas Braunbeck, Kristin Connors, Michelle Embry, Wayne Landis, Kristin Schirmer, Stefan Scholz, Raoul Wolf, Adam Lillicrap

Background

The 3 R's
(Russell & Burch 1959)

Reduction

Refinement

Replacement

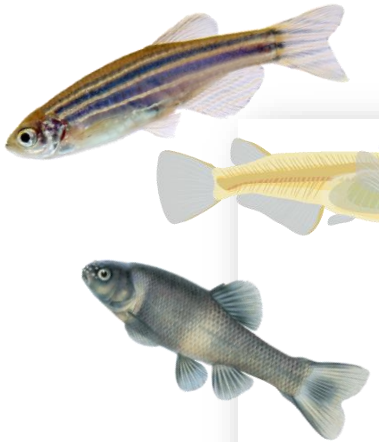
The additional 3 R's
(Lillicrap *et al.* 2016)

Reproducibility

Relevance

Regulatory applicability

Background



DRAFT GUIDELINE
May 30, 2006 (1st Version)

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

DRAFT PROPOSAL FOR A NEW GUIDELINE

Fish Embryo Toxicity (FET) Test

INTRODUCTION

1. This Test Guideline describes a Fish Embryo Toxicity (FET) test mainly developed for use with the zebrafish (*Danio rerio*) but the test method can also be adapted to fathead minnow (*Pimephales promelas*), Japanese medaka (*Oryzias latipes*) and other relevant species of interest (1). This Guideline intends to define lethal effects of chemicals on embryonic stages of fish and constitute an alternative test method to the acute toxicity tests with juvenile and adult fish, *i.e.*, the OECD Test Guideline 203 (2), thus providing a reduction in fish usage. The FET-test is mainly developed from studies and validation activities performed on zebrafish (1)(3)(4)(5)(6)(7)(8)(9)(10)(11)(12)(13)(14)(15)(16)(17)(18), but also from studies on fathead minnow (1)(19)(20)(21)(22) and Japanese medaka (1)(23)(24)(25)(26)(27)(28)(29).

Background

OECD/OCDE **236**

Adopted:
26 July 2013

OECD GUIDELINES FOR THE TESTING OF CHEMICALS

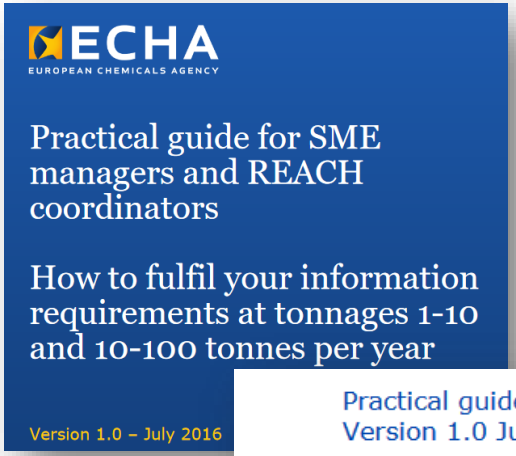
Fish Embryo Acute Toxicity (FET) Test

?

INTRODUCTION

1. This Test Guideline (TG) 236 describes a Fish Embryo Acute Toxicity (FET) test with the zebrafish (*Danio rerio*). This test is designed to determine acute toxicity of chemicals on embryonic stages of fish. The FET-test is based on studies and validation activities performed on zebrafish (1)(2)(3)(4)(5)(6)(7)(8)(9)(10)(11)(12)(13)(14). The FET-test has been successfully applied to a wide range of substances exhibiting diverse modes of action, solubilities, volatilities, and hydrophobicities (reviewed in 15 and 16).

Background



Additional tips

Short-term toxicity tests with freshwater species are preferred but if a substance is released mainly directly into seawater, tests with marine species are more relevant.

Aquatic toxicity is 'unlikely to occur' when the substance is highly insoluble in water or when the substance is likely not to cross biological membranes.

Remember that to reduce the number of tests on animals, animal testing is the last option and you have to consider the possibilities to use alternative methods. The OECD TG 236 Fish Embryo Acute Toxicity (FET) Test is an alternative to the standard test and could be used within a weight-of-evidence approach together with other supporting information justifying the reliability and adequacy of the test.

OECD developed a fish testing strategy to avoid (reduce) testing (OECD Short Guidance on the Threshold Approach for Acute Fish Toxicity (No. 126, 2010) and OECD Guidance on Fish Toxicity Testing Framework (No. 171, 2012)).

Bayesian Networks

What are Bayesian Networks (BNs)?

Weight-of-Evidence

- **Network of nodes** linking cause and effect
- **Conditional probability tables** (CPTs)
- Multiple **lines of evidence** (*i.e.*, data)
- Incorporation of **domain knowledge**
- **Logical sequence** from evidence to endpoint

Moe *et al.* 2020

Preliminary FET-BN

Physico-chemical properties

Chemical category

Toxicity to other taxa

FET

Preliminary FET-BN

Publications

Integrated Environmental Assessment and Management — Volume 16, Number 4—pp. 452–460
452
Received: 5 September 2019 | Returned for Revision: 21 November 2019 | Accepted: 20 February 2020

Decision Analysis

Evaluation of a Bayesian Network for Strengthening the Weight of Evidence to Predict Acute Fish Toxicity from Fish Embryo Toxicity Data

Adam Lillicrap,† S Jannicke Moe,† Raoul Wolf,† Kristin A Connors,‡ Jane M Rawlings,‡ Wayne G Landis,§ Anders Madsen,||# and Scott E Belanger‡*

Environmental Modelling and Software 126 (2020) 104655

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journal homepage: http://www.elsevier.com/locate/envsoft

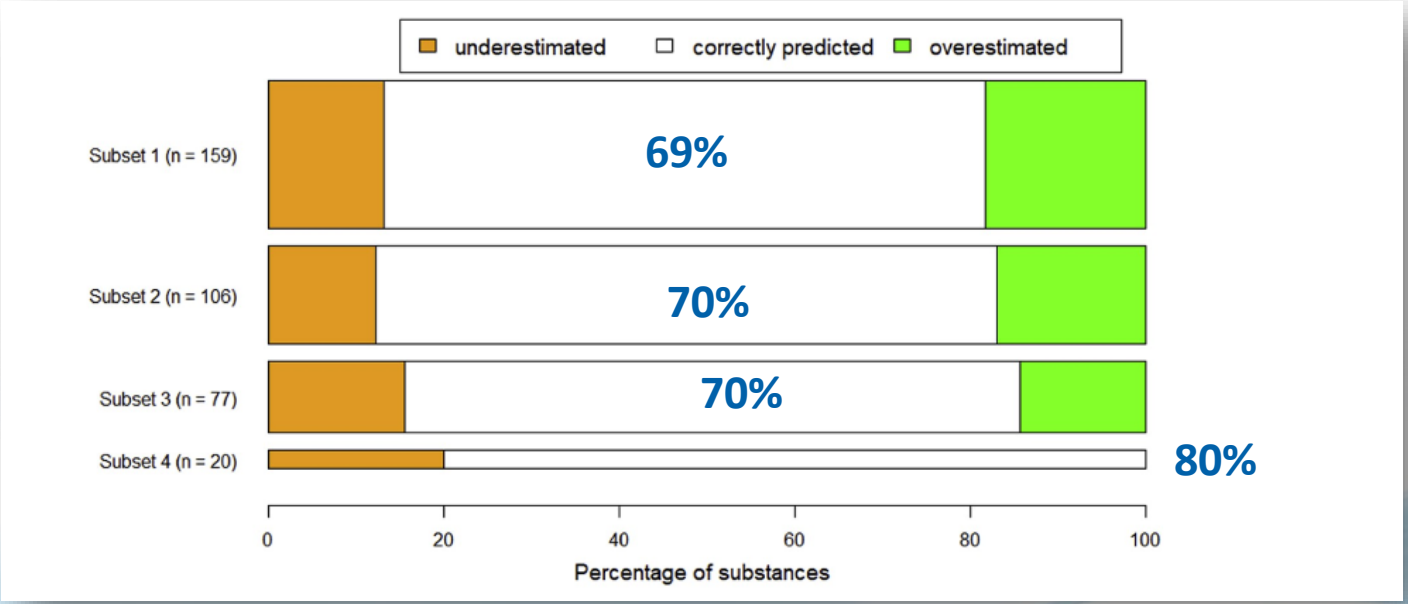
Development of a hybrid Bayesian network model for predicting acute fish toxicity using multiple lines of evidence

S. Jannicke Moe [a,*], Anders L. Madsen [b,c], Kristin A. Connors [d], Jane M. Rawlings [d], Scott E. Belanger [d], Wayne G. Landis [e], Raoul Wolf [a], Adam D. Lillicrap [a]

Moe *et al.* 2020

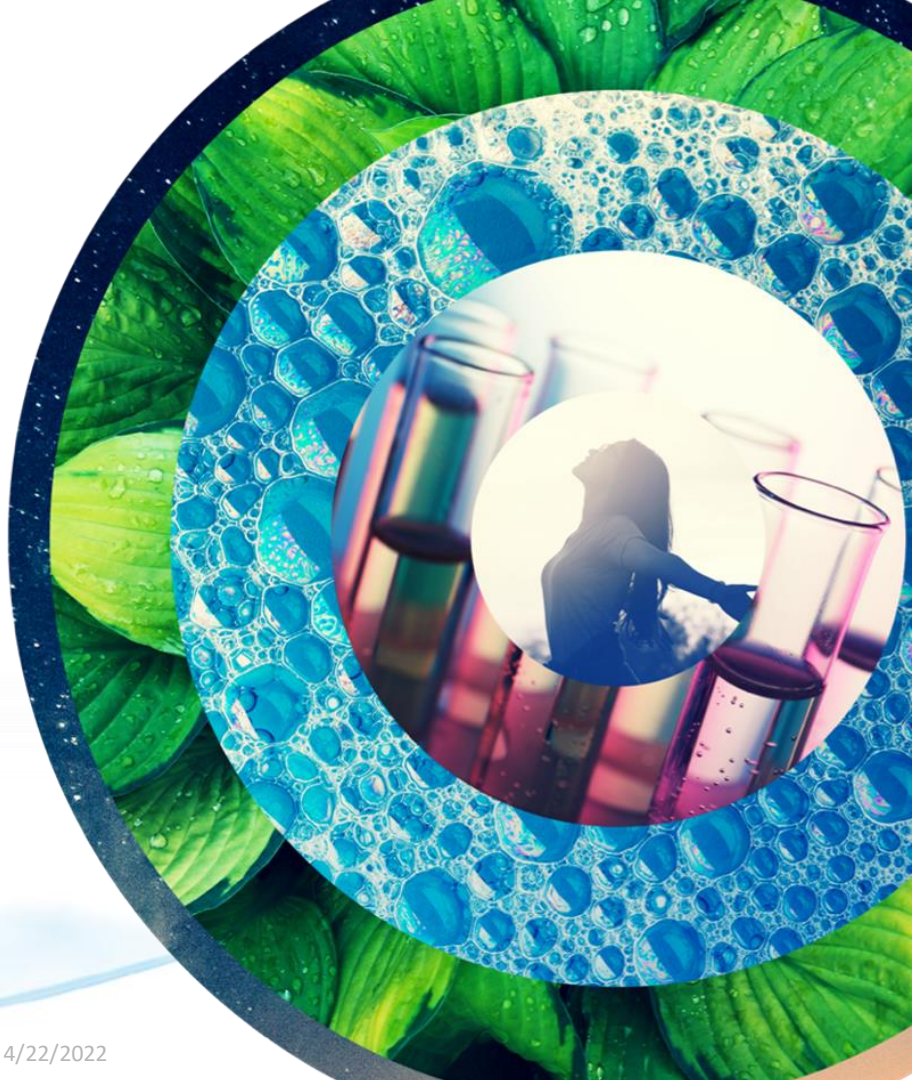
Preliminary FET-BN

Results



LRI ECO51 Integrating the FET into the Weight of Evidence to Inform Acute Fish Toxicity

Strengthening Weight of evidence for FET data to replace acute Fish Toxicity (SWiFT)



LRI Long-Range Research Initiative

cefic

NIVA

SWiFT Objectives

- Curate a **robust AFT (and FET) database**
- Investigate **additional lines of evidence**
- **Evaluate an advanced BN** in a WoE approach
- Develop a **web interface**
- Dissemination and **guidance document**

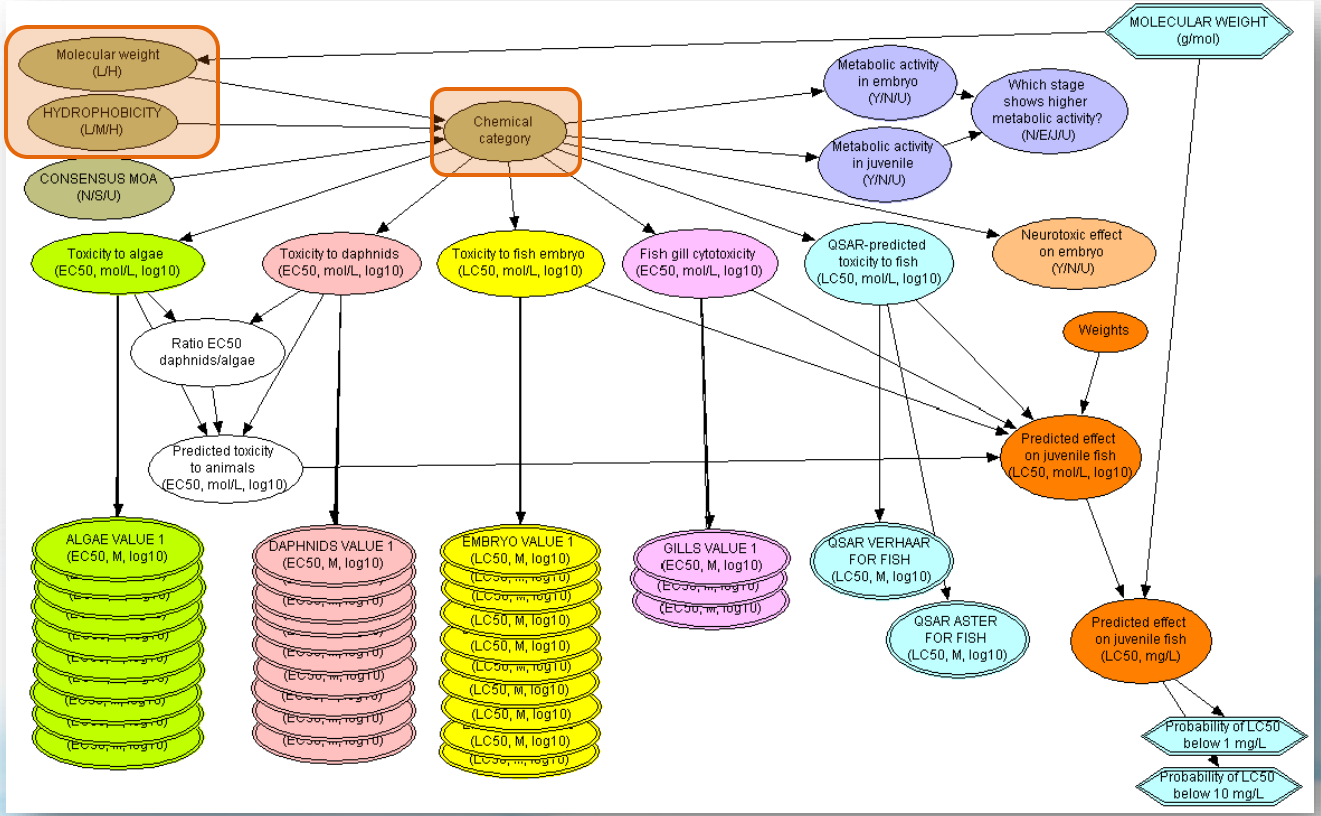
SWiFT FET-BN *status quo*

- **Advanced FET-BN** structure
- **Chemical categories**
- Data for FET-BN **priors**

- **Data requested** from users
- **Expected results** for users

Advanced FET-BN structure

Membrane-Crossing Potential



Chemical Categories

- Existing schemes (e.g., ECOSAR, Verhaar) **unsuitable**
- Structure-agnostic scheme to **categorise chemicals** in the context of **acute fish toxicity**
- 3 parameters: **molecular weight** (MW), **log K_{ow}** and **mode of action** (MoA)

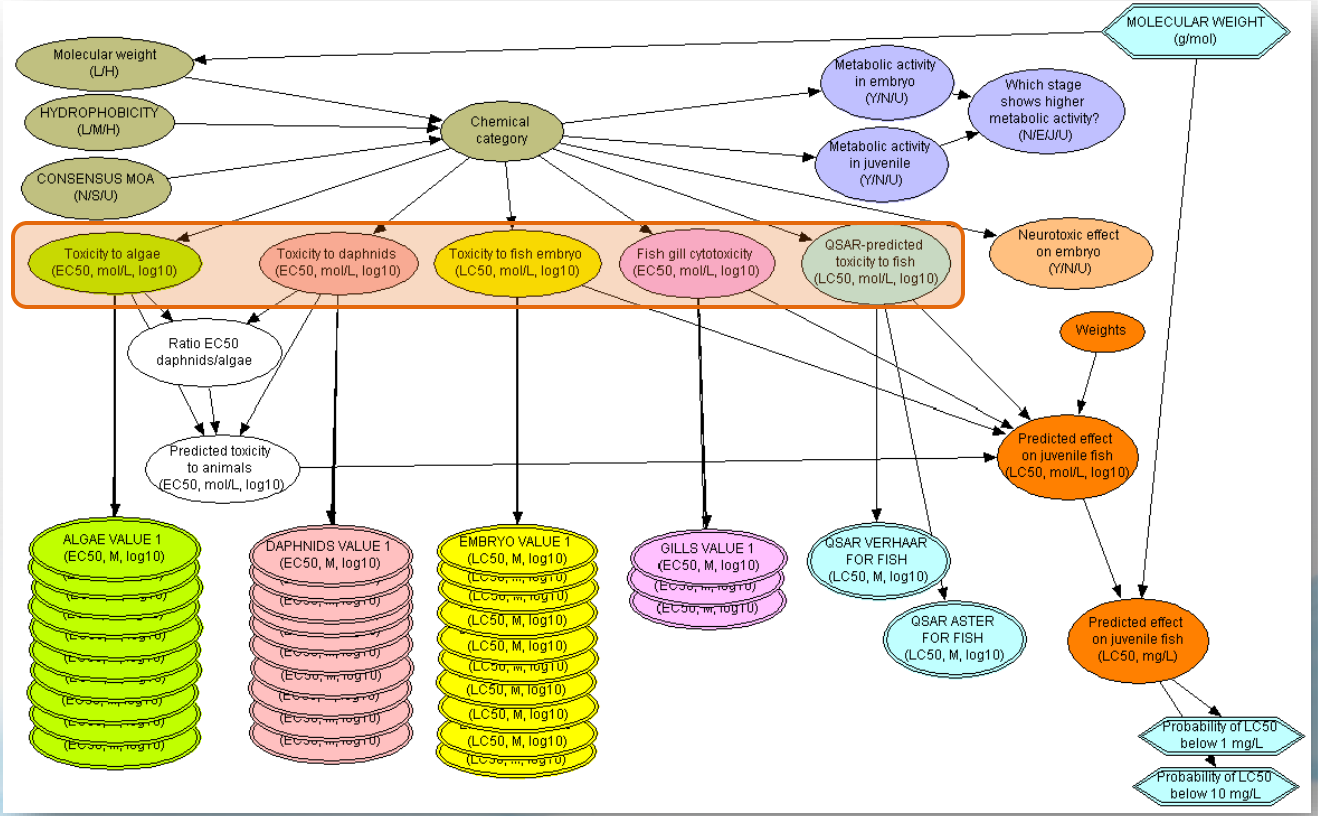
- **MW** (2): Low (<600 Da), High (>600 Da)
- **log K_{ow}** (3): Low (<4), Medium (4–5.5), High (>5.5)
- **MoA** (3): Unclassified, Narcotic, Specific

Kienzler *et al.* 2020

- **18 categories**

Advanced FET-BN structure

Prior CPT Distributions



Data for BN Priors (1/2)

Valid data from the following standardized testing guidelines/protocols

***Daphnia* sp. Acute Immobilisation Test** (OECD TG 202)

- 48 h EC_{50} & confidence interval, chemical, species, study

Freshwater Algae and Cyanobacteria Growth Inhibition Test (OECD TG 201)

- 72 h E_rC_{50} & confidence interval, chemical, species, study

Determination of Acute Toxicity of Water Samples and Chemicals to a Fish Gill Cell Line (RTgill-W1) (ISO 21115)

- 24 h EC_{50} & confidence interval, chemical, probe/indicator, replicates

Data for BN Priors (2/2)

Valid data from the following standardized testing guidelines/protocols

QSARs for acute fish toxicity (e.g., ASTER, TEST, VEGA, …)

- 96 h LC_{50} (& confidence interval), chemical, (species), QSAR, (method)

Fish Embryo Acute Toxicity Test (FET) (OECD TG 236)

- 96 h LC_{50} & confidence interval, chemical, study

Fish, Acute Toxicity Test (AFT) (OECD TG 203)

- 96 h LC_{50} & confidence interval, chemical, species, study

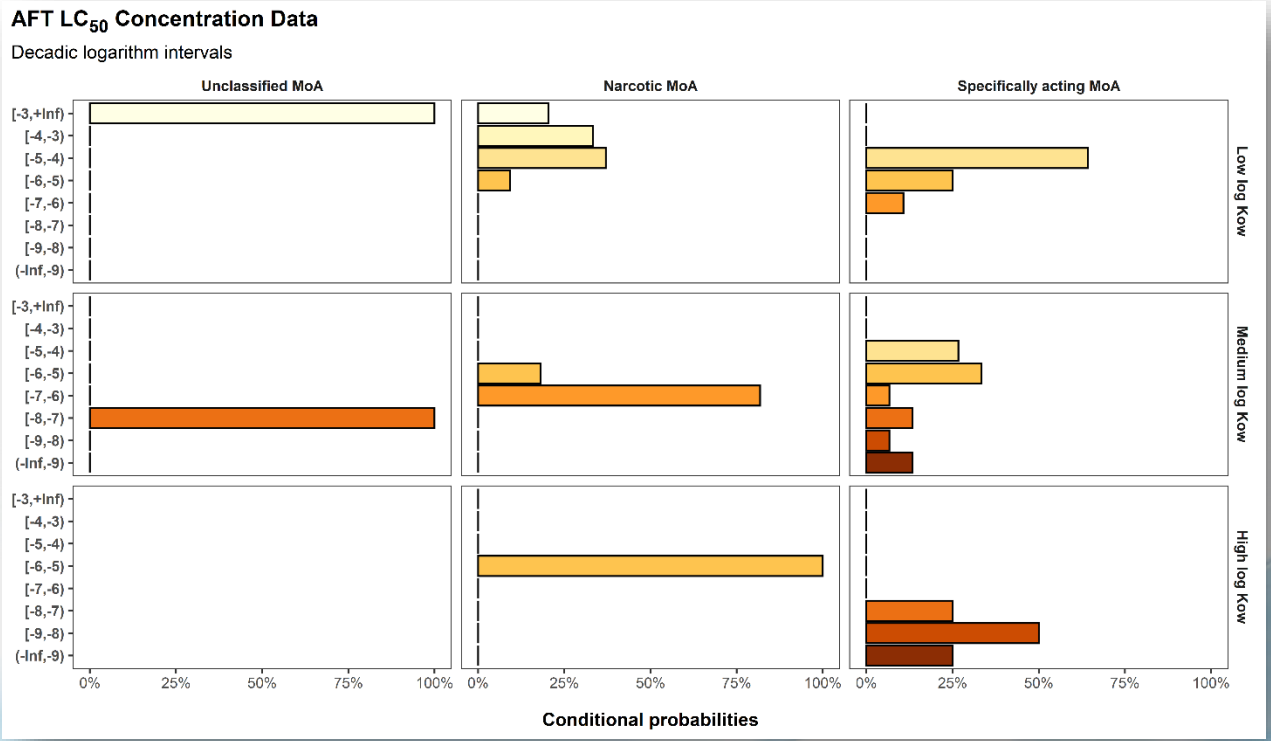
Example of BN Priors

Hierarchical Bayesian models (HBMs)

- **Generalisation** of available data
- Account for ~~all~~ *some* **sources of variation**
- Incorporate known and quantify unknown **uncertainty**
- Robust prediction of **conditional probabilities**

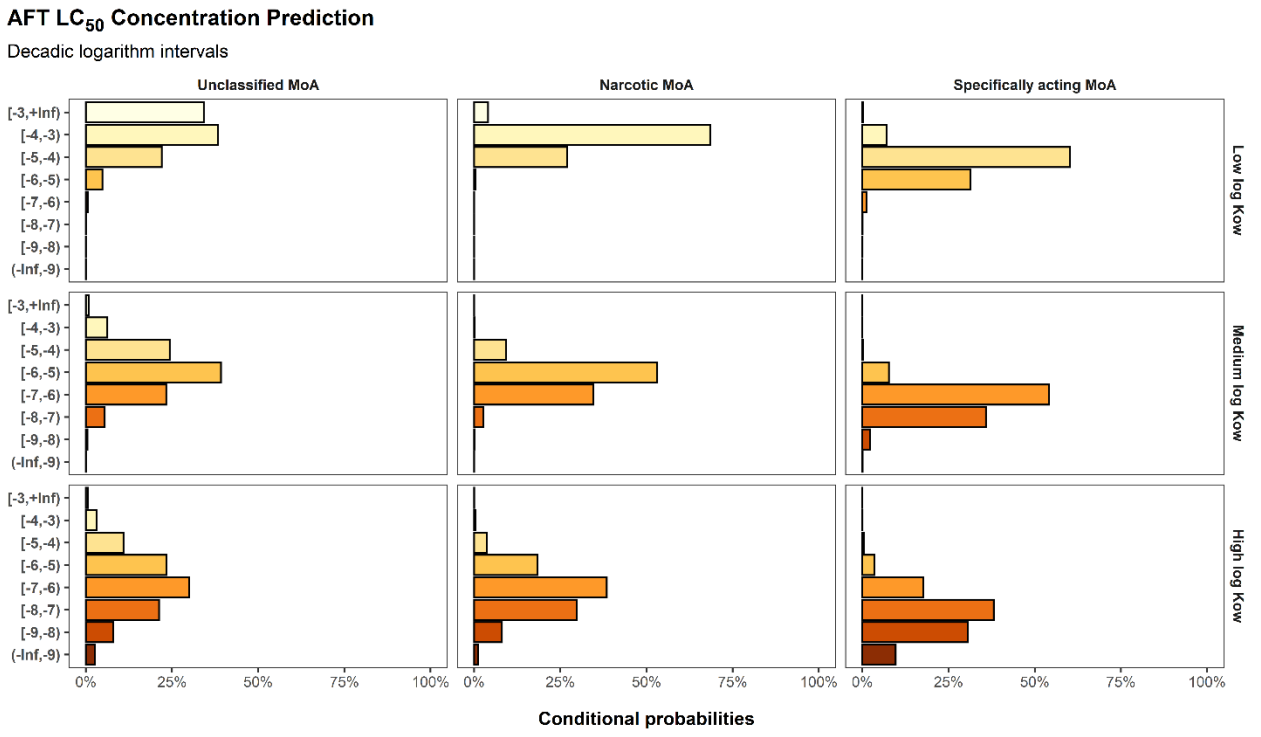
Raw Data

Example of BN Priors

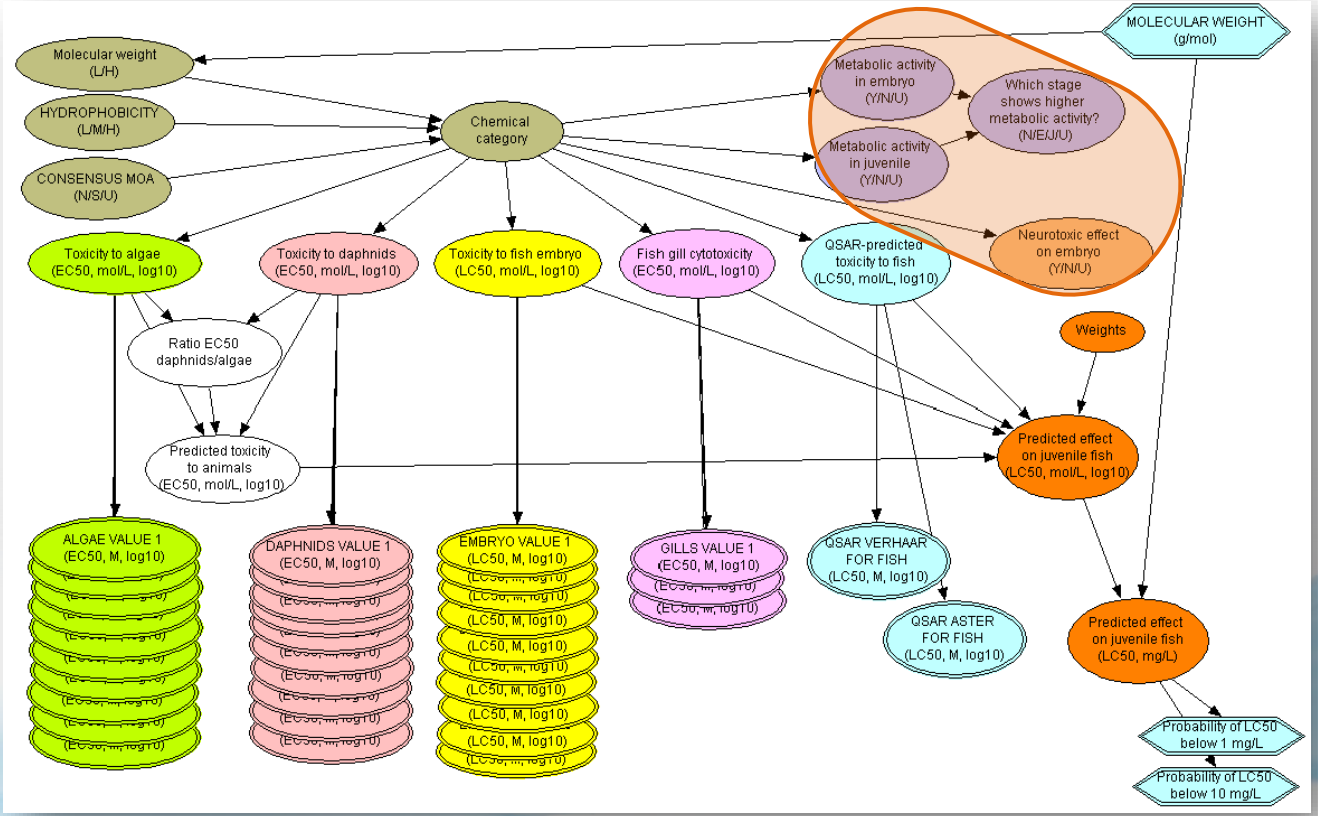


HBM
(based on the same data)

Example of BN Priors



Advanced FET-BN structure



Additional Information

Additional Information for BN Structure

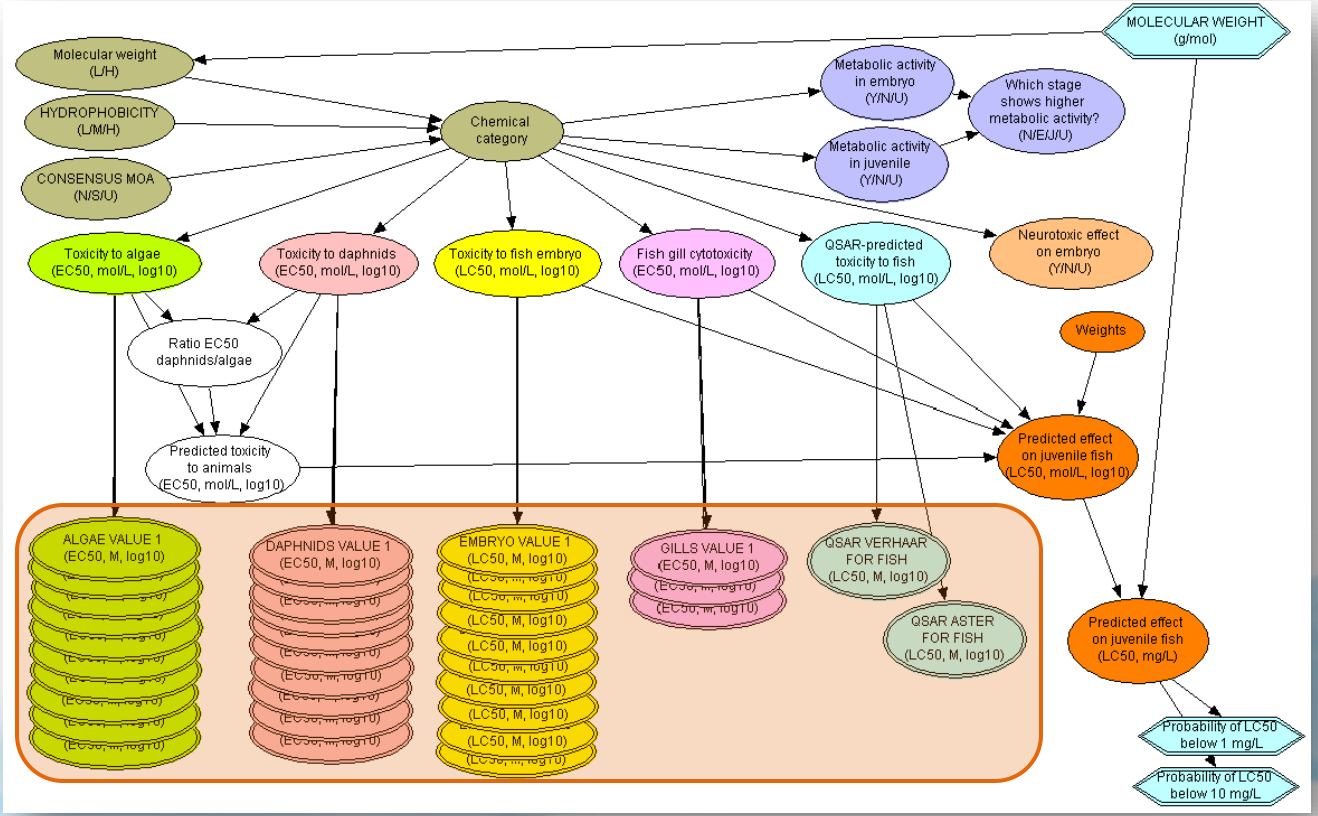
Metabolic activity

- Is the metabolic activity of embryos and juvenile fish **comparable**?
- **Systematic review** currently under review Braunbeck & Lörracher 2021
- Advanced FET-BN will **flag** known deviations

Neurotoxic potential

- Are there known **neurotoxic/behavioural effects** of chemicals?
- Several endpoints **under investigation** (e.g., TER)
- Incorporation into advanced FET-BN **pending**

Advanced FET-BN structure



Data from Users

Data Requirements for Users

Mandatory information

- **Molecular weight** (Da)
- **log K_{ow}** (L/M/H)
- **Mode of Action** (U/N/S)

Determination of chemical category

(mg/L to mol/L conversion)

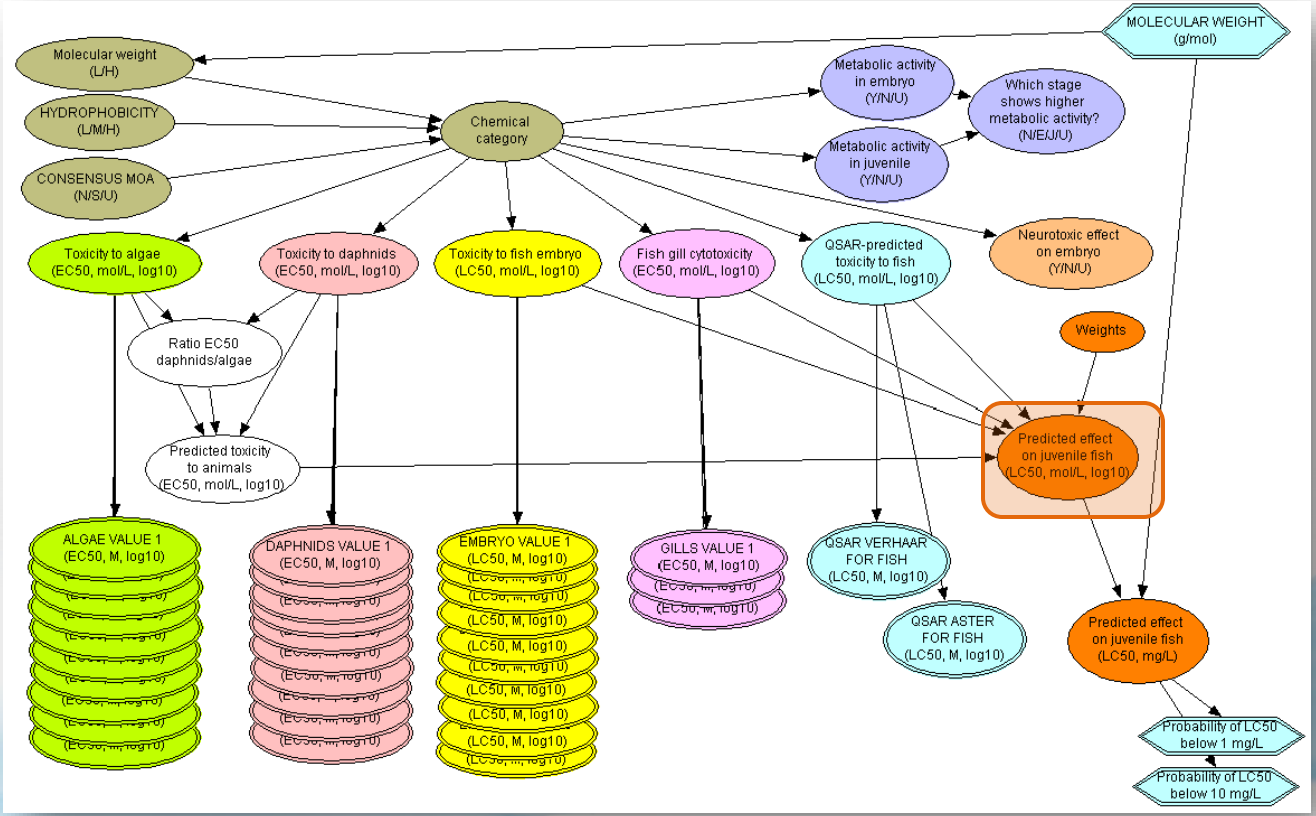
Data Requirements for Users

Optional information

- OECD TG 236: **96 h LC_{50}**
- OECD TG 202: **48 h EC_{50}**
- OECD TG 201: **72 h E_rC_{50}**
- ISO 21115: **24 h EC_{50}**
- QSAR: **96 h LC_{50}**

up to 10 values each

Advanced FET-BN structure



Results!

Advanced FET-BN Results

Hard facts

- **Predicted AFT LC_{50}** & confidence interval
- Two units: **mol/L** and **mg/L**
- **Probability** for each concentration interval

Nice things

- Automatically generated **report**
- **Summary** of results and input data
- Available through the **SWiFT website**

https://www.niva.no/swift

SWiFT Summary

- **FET data** can be used in **WoA** approaches like **BNs**
- **SWiFT** advances the published preliminary FET-BN
- Extended and robust **data sources**
- Incorporation of **additional lines of evidence**
- **Web interface** and **guidance document**

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