Cefic-LRI ECO51 – *SWiFT: Strengthening weight of evidence for FET data to replace acute fish toxicity*

WP3: Development and evaluation of the BN model for replacing AFT

Presentation for ECHA 01.03.2022

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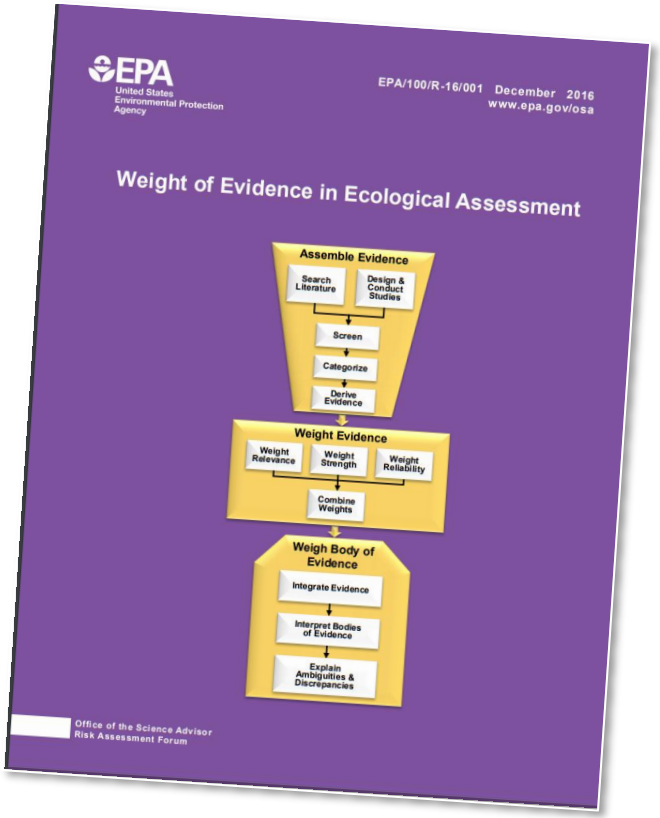
Outline

1. Weight of Evidence - our approach
2. Data sources
3. BN model
4. Model calibration and evaluation
5. Demonstration of web user interface

Weight of Evidence - our approach

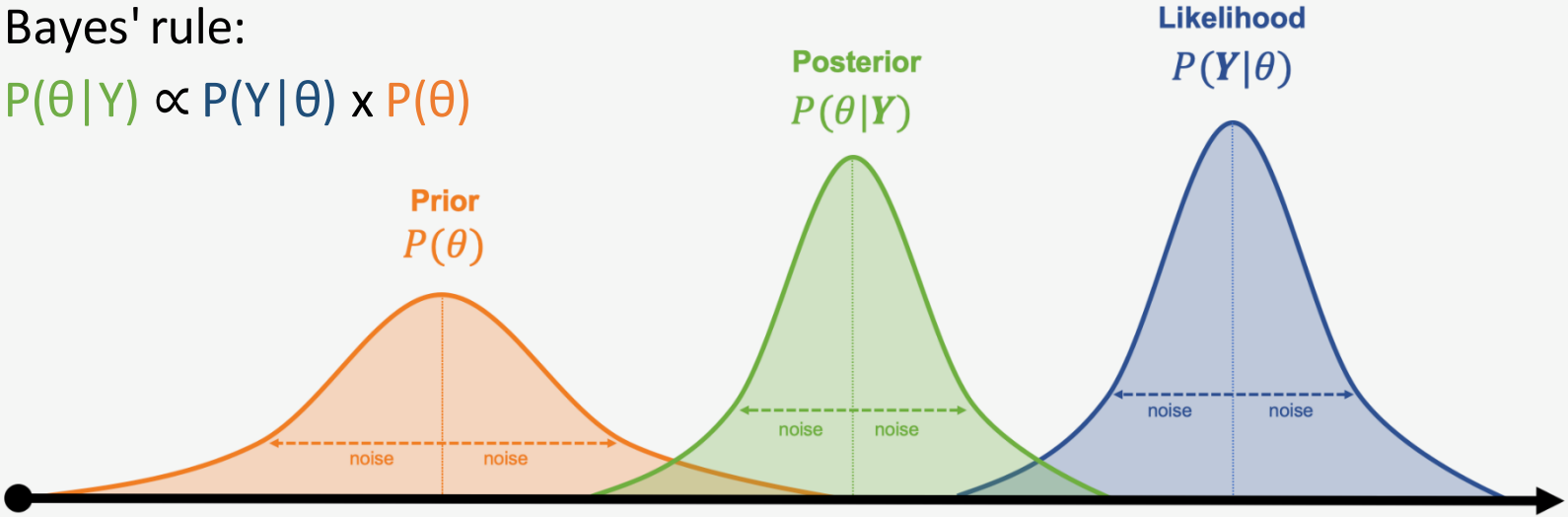
Weight of evidence frameworks



Bayesian inference

Bayes' rule:

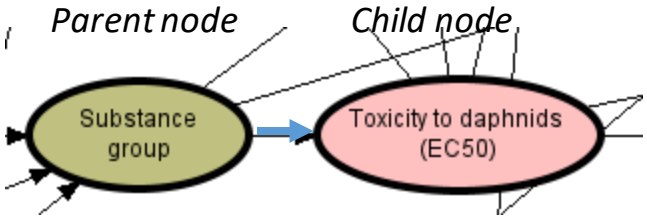
$P(\theta|Y) \propto P(Y|\theta) \times P(\theta)$

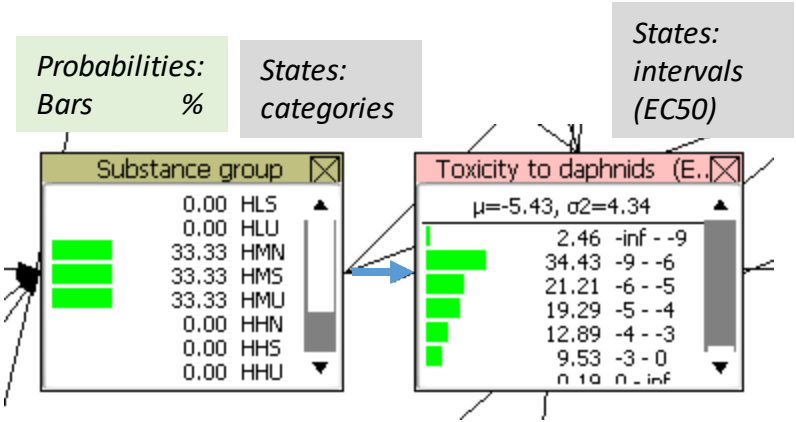


The **posterior probability** is proportional to the product of the **likelihood function** and the **prior probability**

Your **prediction** is a compromise between your **new evidence** and your **assumptions**

Bayesian networks - basics





The model uses Bayes rule to combine **new evidence** (e.g. EC50 values) with **prior probabilities** (from the conditional probability table) to predict **posterior probabilities**

Conditional probability table (CPT)

Toxicity to daphnids (EC50)

Substance gr...	LHS	LHU	MLN	MLS	MLU	MMN	MMS	MMU	MHN	MHS	MHU	HLN	HLS	HLU	HM
-inf - -9	0.0114	0.009	0.0059	0.009	0.0082	0.0024	0.0034	0.0055	0.0048	0.0067	0.0096	0.0326	0.0392	0.0463	0.02
-9 - -6	0.2518	0.2628	0.2048	0.2356	0.2476	0.1547	0.1823	0.1839	0.1923	0.218	0.229	0.3792	0.4259	0.4268	0.32
-6 - -5	0.2109	0.2141	0.194	0.2124	0.2055	0.1771	0.1792	0.1909	0.1934	0.2043	0.2091	0.2119	0.2134	0.2135	0.20
-5 - -4	0.2206	0.219	0.2281	0.2242	0.223	0.2189	0.2274	0.2293	0.225	0.2224	0.2182	0.1852	0.1652	0.1669	0.19
-4 - -3	0.1624	0.1569	0.1904	0.1699	0.1683	0.2079	0.2008	0.1931	0.1861	0.1835	0.176	0.1116	0.0945	0.0908	0.13
-3 - 0	0.1405	0.1358	0.1725	0.1465	0.1443	0.2306	0.2008	0.1913	0.1931	0.1615	0.1548	0.0777	0.0609	0.0551	0.10
0 - inf	0.0024	0.0024	0.0043	0.0024	0.0031	0.0084	0.0061	0.006	0.0053	0.0036	0.0033	0.0018	0.0009	0.0006	0.00

How can our Bayesian Network be used in a WoE approach?

EFSA JOURNAL

Scientific Opinion | Open Access

Guidance on the use of the weight of evidence approach in scientific assessments

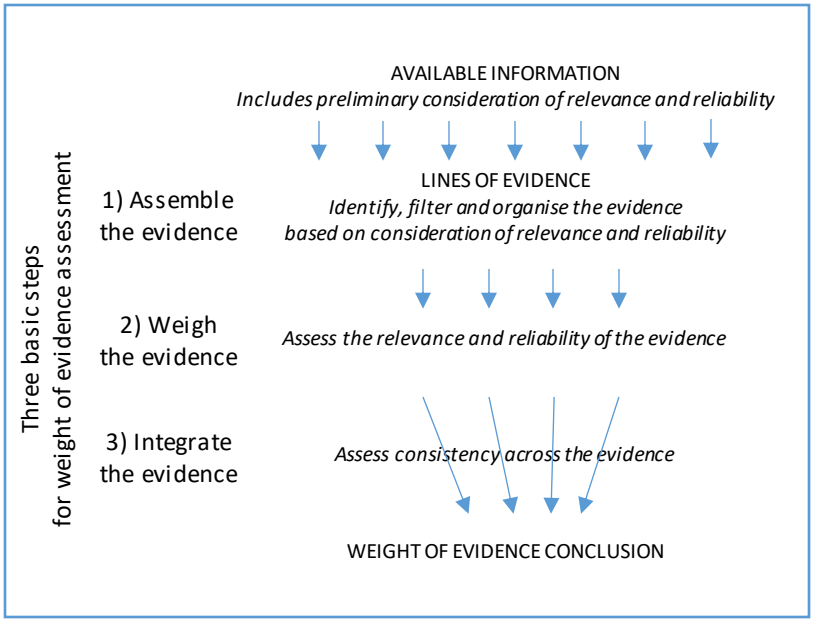
EFSA Scientific Committee, Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn ... See all authors

First published:03 August 2017 | https://doi.org/10.2903/j.efsa.2017.4971 | Citations: 47

Our BN-WoE should be

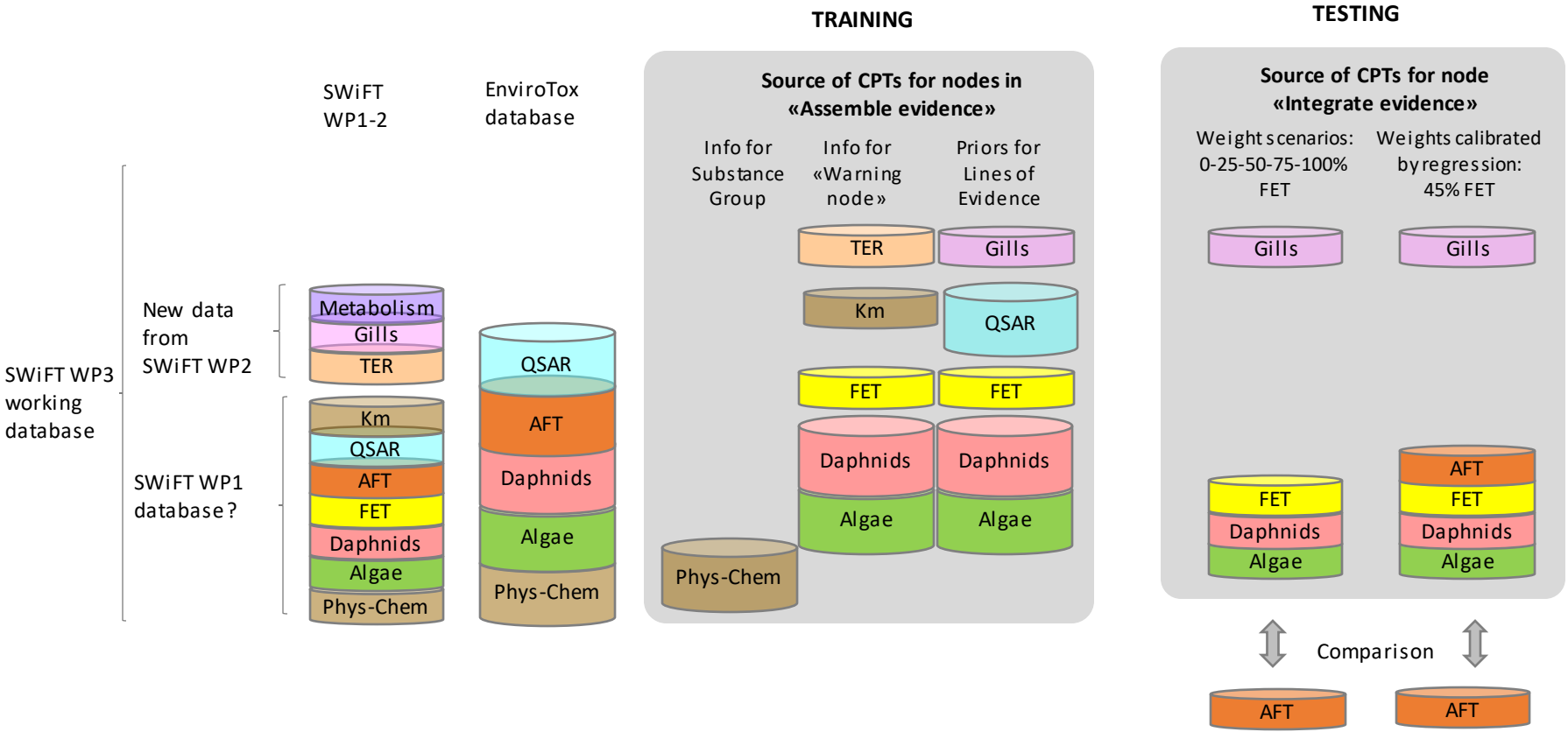
- **consistent** with WoE approaches recommended for regulatory frameworks (EFSA, ECHA, US EPA, OECD)
- **quantitative**
- **intuitive**
- **flexible**

Main steps for WoE assessment (EFSA):



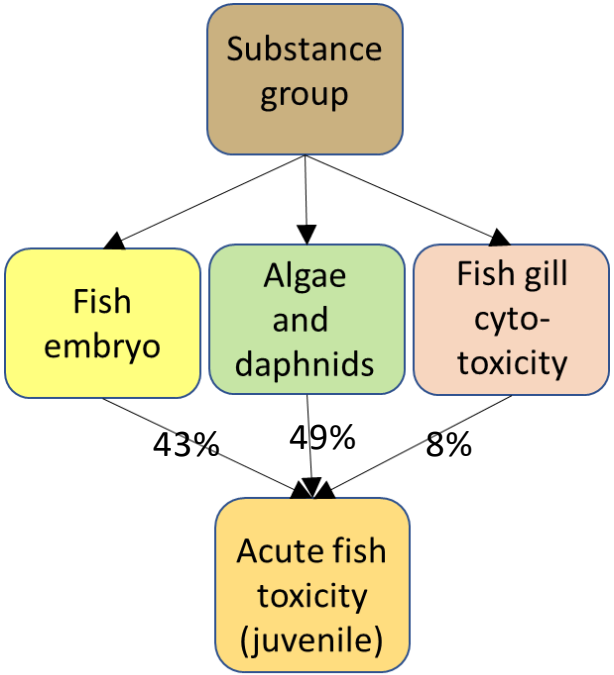
Data sources for BN development and evaluation

Data sources



BN model structure

Schematic model structure

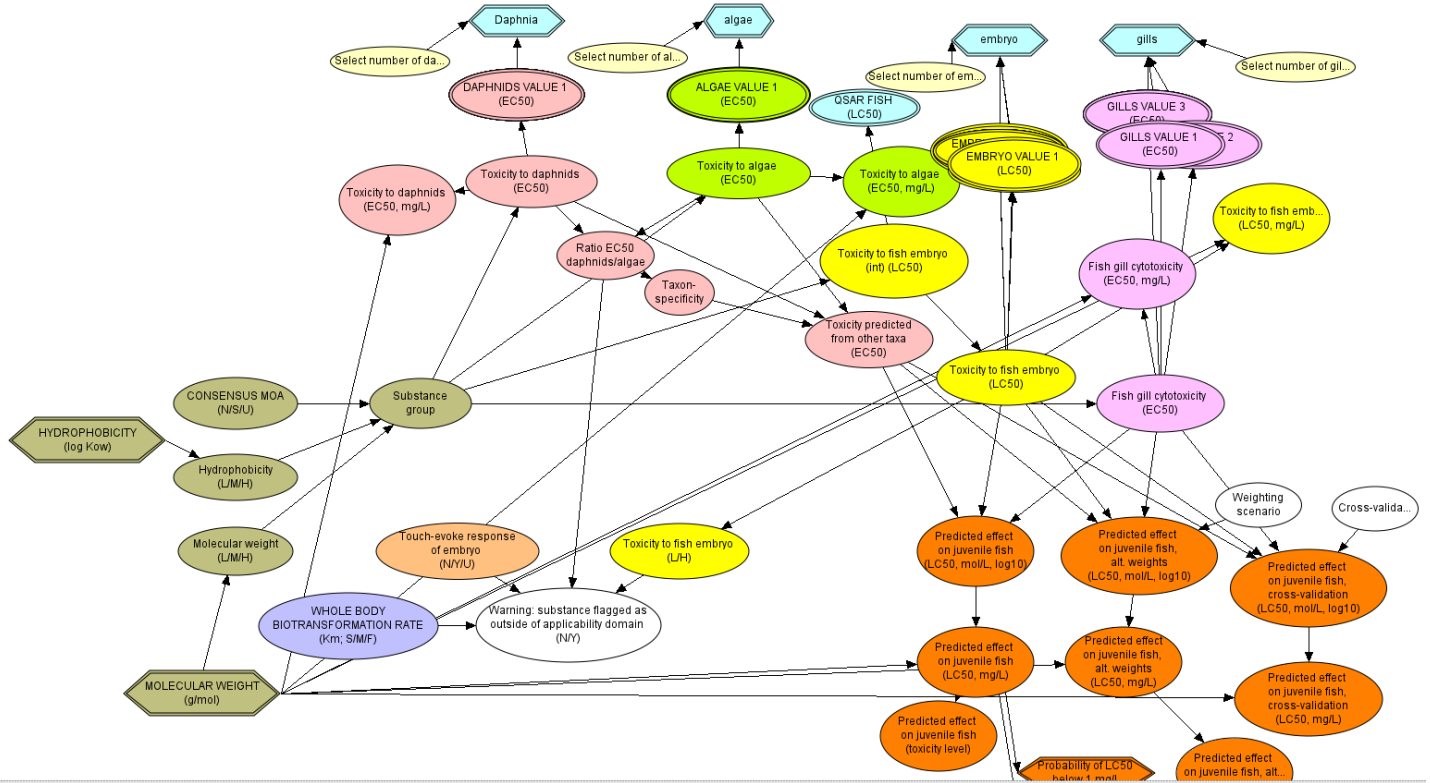


- Prior probabilities of toxicity to fish organised by substance group
- *User: Enter information on substance*

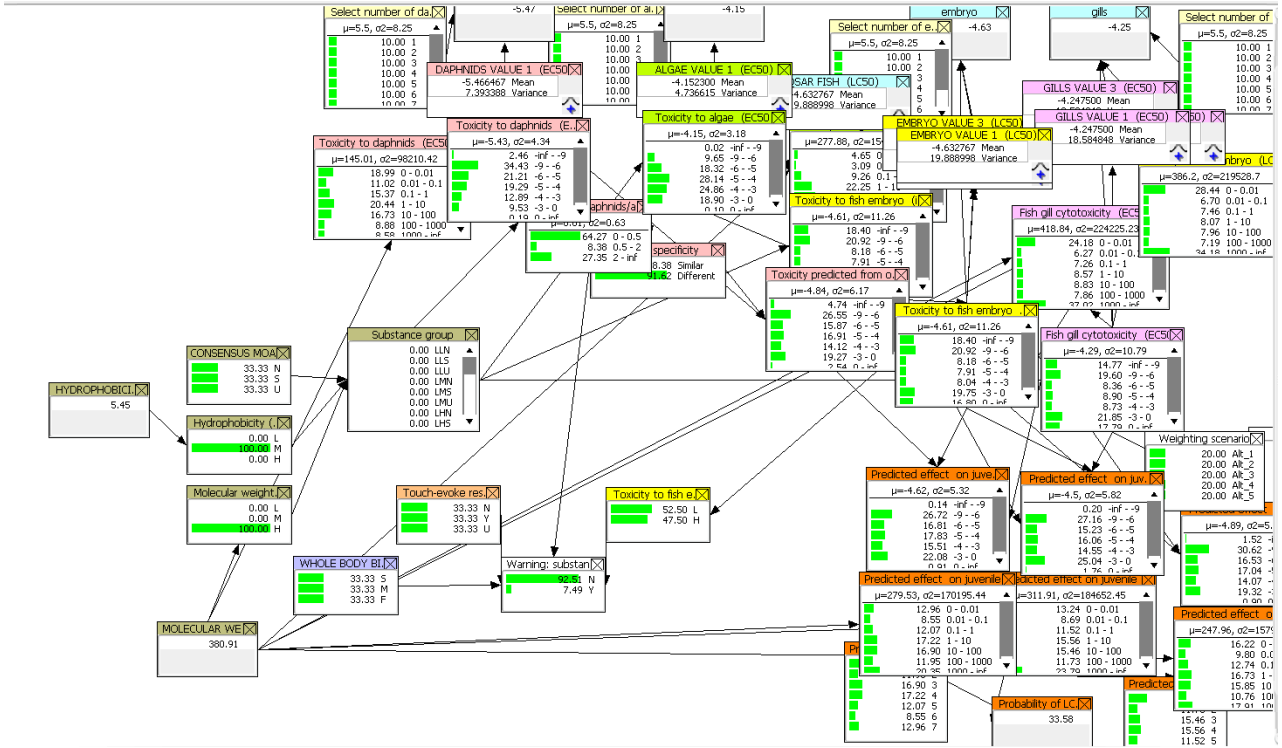
- 3 lines of evidence
- *User: Enter toxicity values*

- Posterior probability
- *User: check warning (applicability domain)*
- *User: get model prediction*

The full BN model: structure

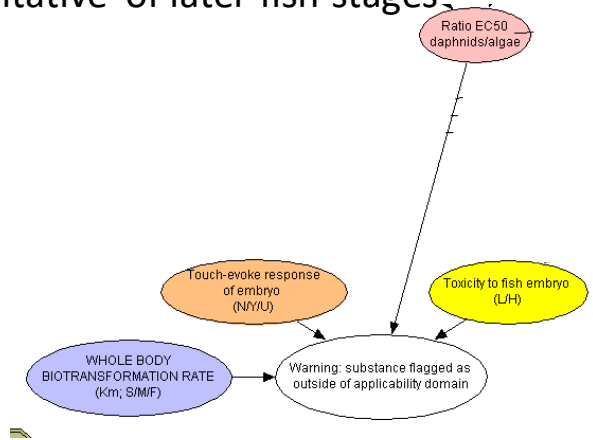


The full BN model: probability distributions



«Warning node»

- Purpose:
  identify substances for which the BN predictions may not be reliable
- Reasoning:
  response of fish embryo may not representative of later fish stages



Current criteria to trigger a warning:

- Fish embryo toxicity = Low
- Daphnia/algae toxicity ratio = High
- **Touch-evoke response** = Yes / Unmeasured
- Biotransformation rate = Fast

Ongoing work:

- Refine Embryo toxicity criterion
  (< Daphnia & Algae toxicity)
- Include **Metabolic activity**
  (embryo vs. juvenile fish)
  as alternative variable?

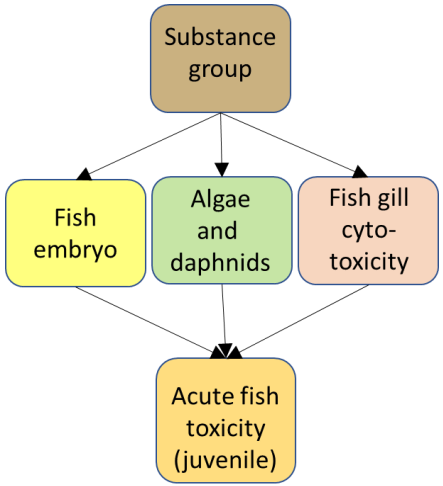
Define the applicability domain of the BN

Critieria for exclusion from the applicability domain:

1) "Warning node": substances with certain combination of toxicity values and other properties
2) Substances without QSAR values: metals
3) ... [to be continued]

- Applicability domain is a scientific decision, not a technical issue
- Criteria must be defined in the Technical user manual (task 4.2) and the Guidance document for stakeholders (task 5.3)

How can our Bayesian Network be used in a WoE approach?



Main steps for WoE assessment (EFSA):

Main steps of our BN model, run for substance X:

Three basic steps for weight of evidence assessment

AVAILABLE INFORMATION
Includes preliminary consideration of relevance and reliability

0) Prior probabilities: toxicity of substance groups, for each LoE (stored in CPTs)

1) Assemble the evidence

LINES OF EVIDENCE
Identify, filter and organise the evidence based on consideration of relevance and reliability

1) Enter evidence for substance X as measured toxcity values for each LoE

2) Weigh the evidence

Assess the relevance and reliability of the evidence

2) Weighing evidence: by uncertainty quantified in CPTs for each LoE

3) Integrate the evidence

Assess consistency across the evidence

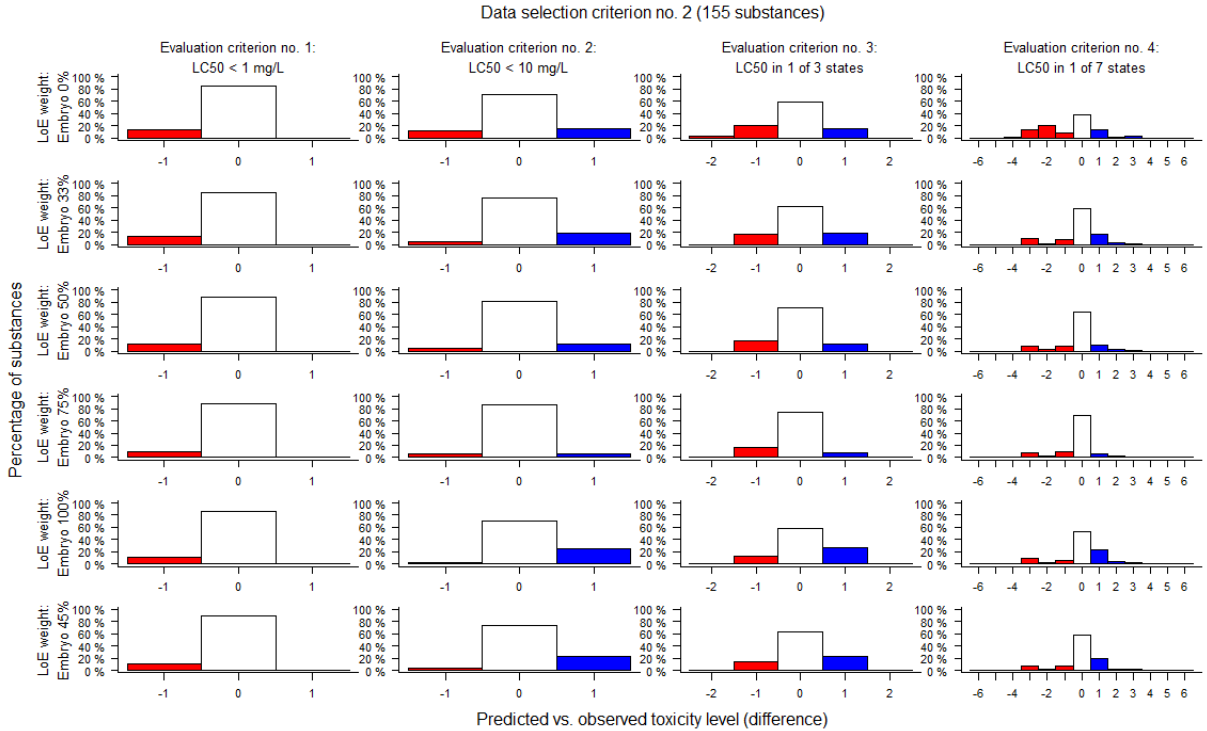
WEIGHT OF EVIDENCE CONCLUSION

3) Integration: by an equation giving weights to each LoE; accounting for consistency across LoEs

CPT = Conditional Probability Table

Model evaluation

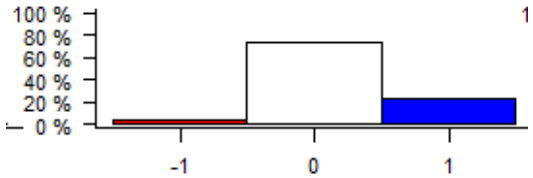
Model evaluation: 6x4x4 criteria



Model evaluation: example

Data selection criterion no. 2 (155 substances)

Evaluation criterion no. 2:
LC50 < 10 mg/L



Predicted vs. observed toxicity level (difference)

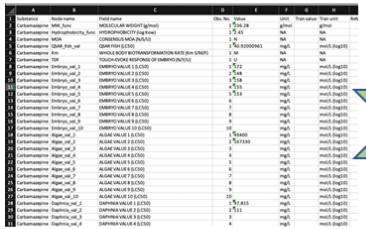
Predicted toxicity = observed toxicity
➔ accurate prediction

Predicted toxicity < observed toxicity
➔ less protective

Predicted toxicity > observed toxicity
➔ more protective

Web-based user interface (WP4, Anders Madsen - HUGIN)

Web-based user interface architecture



xlsx file

UP

Transformation

Calculation

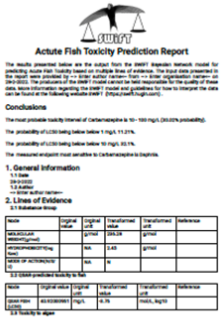
Presentation

Javascript

HUGIN WS API

HUGIN Decision Engine

DOWN



PDF file

https://swift.hugin.com/models/extended3/