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

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

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FURTHER development and evaluation

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

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Decision Analysis

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

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Objective of the project: develop a WoE approach

CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number
Integrating the FET into the Weight of Evidence to Inform Acute Fish Toxicity – **LRI-ECO51**

Scope

Weight of evidence has received a large amount of attention in both regulatory frameworks (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/weight-of-evidence; SCHEER 2018; USEPA 2016) and scientific literature (Hope and Clarkson 2014; Hall et al. 2018). Flexibility is present in the myriad of approaches, so the scope here will be rather broad. Physical-chemistry, domain of

The project's objectives are to:

1. Develop an approach that provides improved WoE on acute fish toxicity beyond direct assessment of fish embryo tests as predictors of acute fish toxicity. The approach may be qualitative or quantitative.

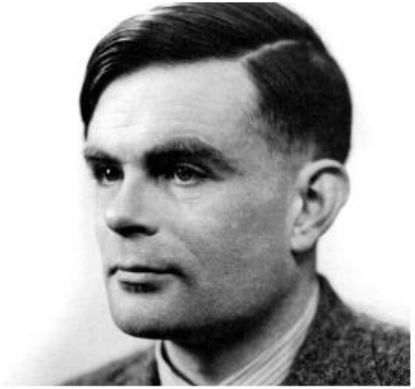
The origin of «Weight of Evidence»: Bayesian calculation

Good, I.J., 1960. Weight of evidence, corroboration, explanatory power, information and the utility of experiments. *J. Roy. Stat. Soc. B.*

$$\log \text{prior odds } \mathcal{H}_1 : \mathcal{H}_2 + \text{weight of evidence } \mathcal{H}_1 : \mathcal{H}_2 = \log \text{posterior odds } \mathcal{H}_1 : \mathcal{H}_2$$

The first practical use of the log Bayes factor to quantify the weight of evidence favouring one hypothesis over another was by Turing at Bletchley Park.

Hut 8, Bletchley Park



Alan Turing

Jack Good

The *Banburismus* procedure was based on accumulating weights of evidence for the settings of the right-hand and middle rotors of the Enigma machine. Good recounted in 1994:-

How can our BN be used in a WoE approach?


EFSA JOURNAL

Scientific Opinion | Open Access

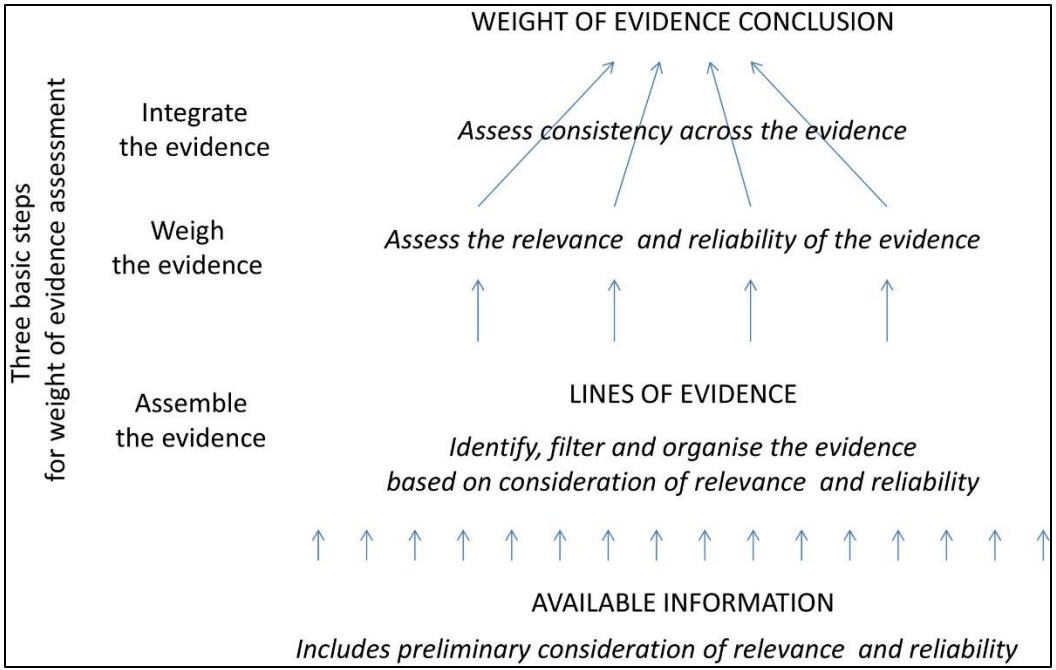
Guidance on the use of the weight of evidence approach in scientific assessments

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

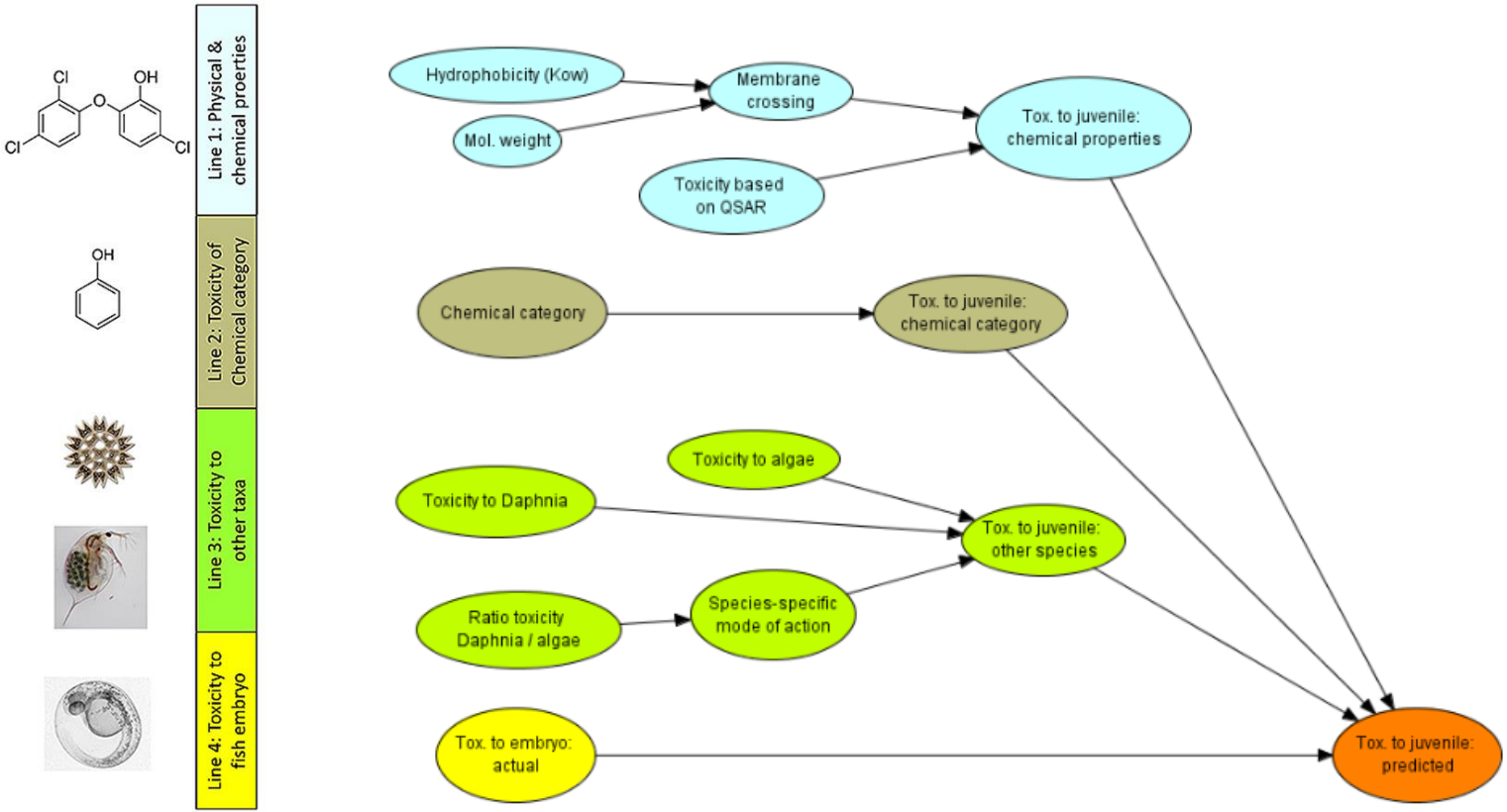
First published:03 August 2017 | https://doi.org/10.2903/j.efsa.2017.4971 | Citations: 47

Our BN-WoE should be

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



The BN model shown so far is a conceptual version



The real BN model is quantitative

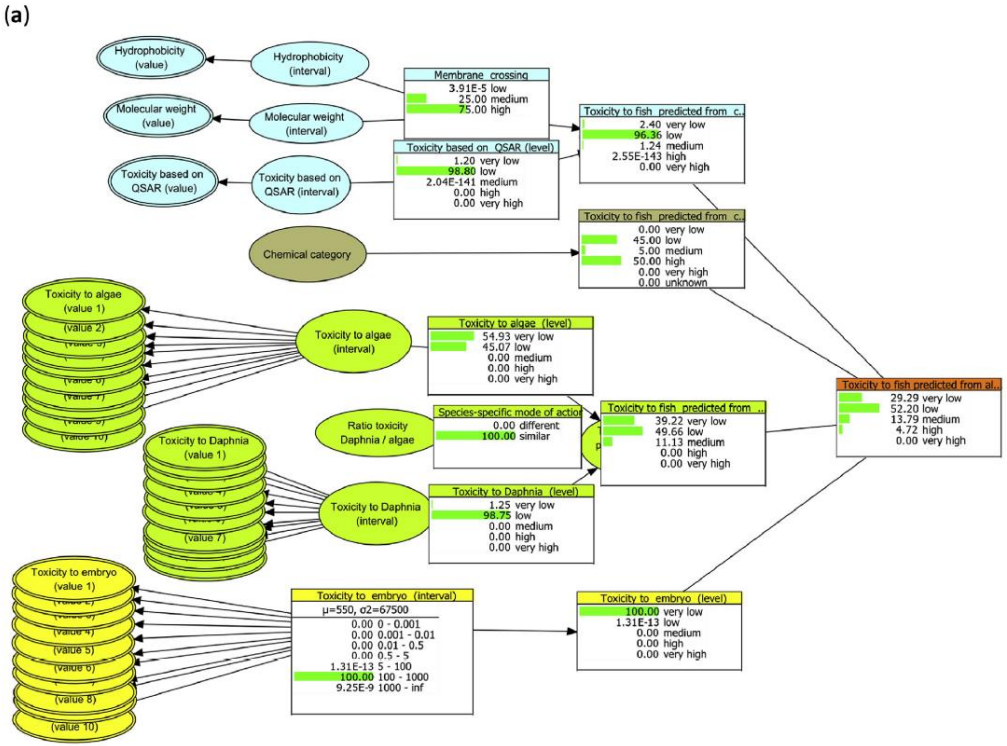


Fig. 3. Examples of BN model predictions for three selected substances: (**a**) Carbamazepine, (**b**) Tetradecyl sulfate, (**c**) Triclosan. Monitor windows with posterior probability distributions are shown for selected nodes in each line of evidence (please see Fig. 1 for complete node lables and arrows). The full set of input values and selected output values for example (a) are given in Table 4.

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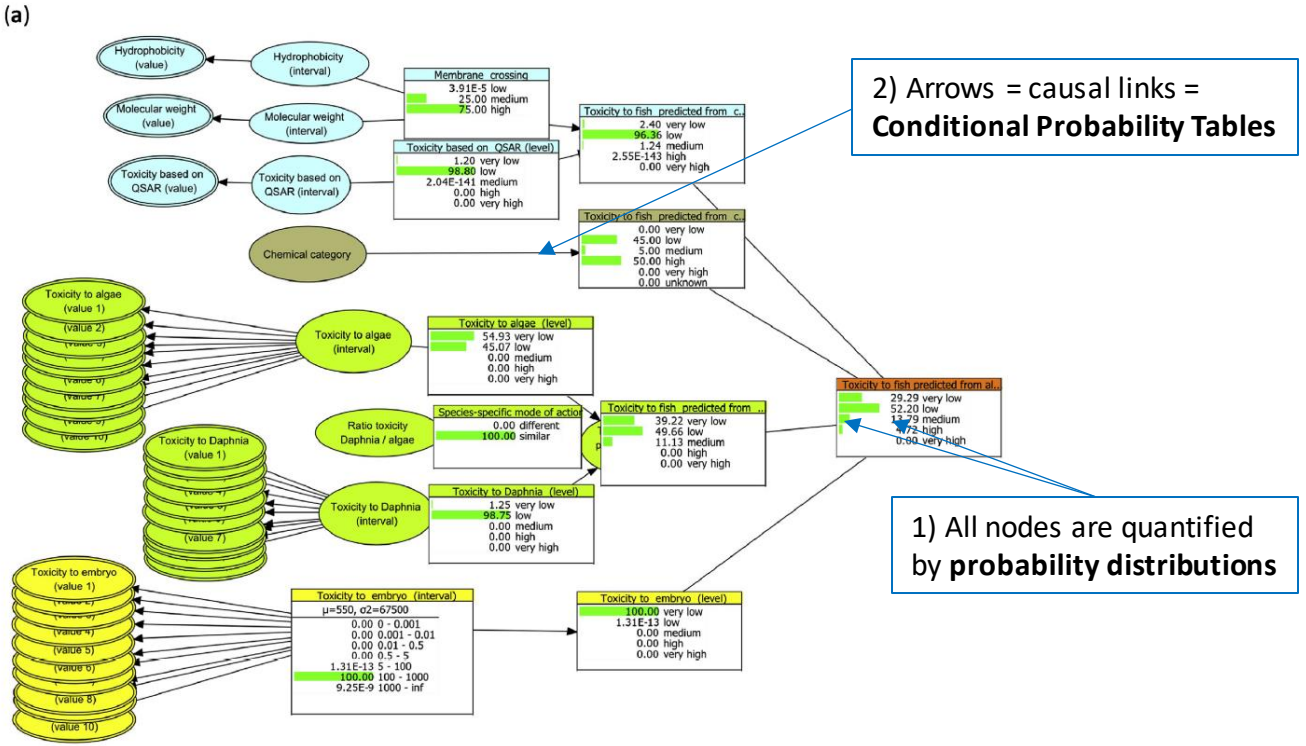
The real BN model is quantitative



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What are Conditional Probability Tables?

(a)

Toxicity to fish predicted from chemical properties															
Membrane crossing	low					medium					high				
Toxicity based on QSAR	very low	low	medium	high	very high	very low	low	medium	high	very high	very low	low	medium	high	very high
very low	0.8	0.1	0	0	0	0.9	0.05	0	0	0	1	0	0	0	0
low	0.2	0.8	0.1	0	0	0.1	0.9	0.05	0	0	0	1	0	0	0
medium	0	0.1	0.8	0.1	0	0	0.05	0.9	0.05	0	0	0	1	0	0
high	0	0	0.1	0.8	0.2	0	0	0.05	0.9	0.1	0	0	0	1	0
very high	0	0	0	0.1	0.8	0	0	0	0.05	0.9	0	0	0	0	1

(b)

Toxicity to fish predicted from chemical category										
Chemical Category	Aniline	Anionic surfac-tant	Esters (dithio-phos-phates)	Esters (monothi-phos-phates)	Imidazole	Neutral organic	Phenol	Quinone	Substitu-ted urea	Unknown /other
very low	0.08	0	0	0	0.25	0.455172	0	0	0	0
low	0.8	0.333333	0.184211	0.025641	0	0.344828	0.362745	0	0.45	0
medium	0.08	0.571429	0.263158	0.564103	0.75	0.165517	0.117647	0	0.05	0
high	0.04	0.095238	0.5	0.410256	0	0.02069	0.519608	1	0.5	0
very high	0	0	0.052632	0	0	0.013793	0	0	0	0
unknown	0	0	0	0	0	0	0	0	0	1
Sum	50	42	76	39	4	145	204	13	20	

Fig. 2. Examples of conditional probability tables (CPTs) and density functions (CDFs) for selected nodes, illustrating the different approaches used for parameterisation of the conditional dependencies. The colour code represents the scale from green (zero) to red (1 or 100%). (a) CPTs for the node "Membrane crossing": the probability of a substance crossing a biological membrane based on its physical properties (molecular weight and hydrophobicity). Probabilities are based on expert judgement. (b) Extract of the CPT for the node "Toxicity to fish predicted from chemical category". The probabilities are derived from frequency distributions in our

Examples of methods:

- Expert judgement
- Data: count of observations
- Theory, equations, algorithms
- Model predictions

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Our BN has both continuous values and categories

3) **Continuous nodes** for real input values = **evidence** (currently max. 10)

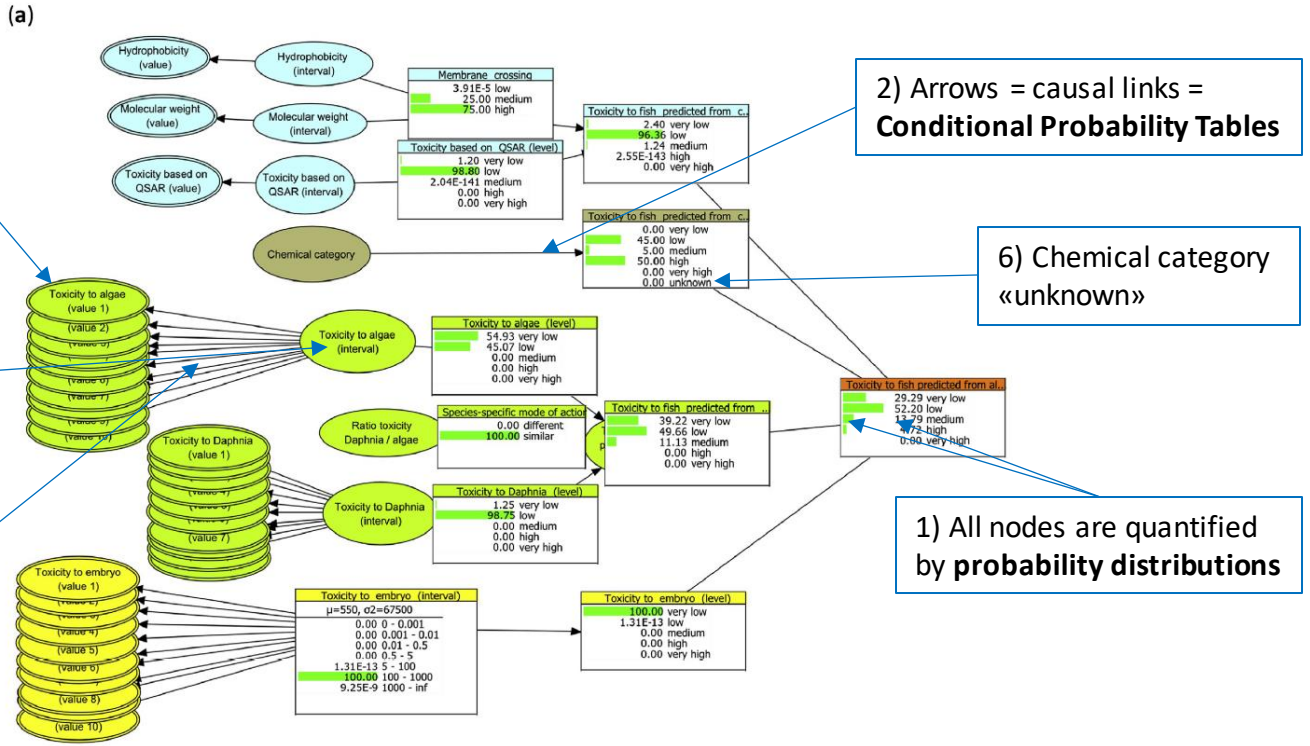
4) Transition from continuous to **discrete nodes** (intervals)

5) «**Backward** calculation»

2) Arrows = causal links = **Conditional Probability Tables**

6) Chemical category «unknown»

1) All nodes are quantified by **probability distributions**



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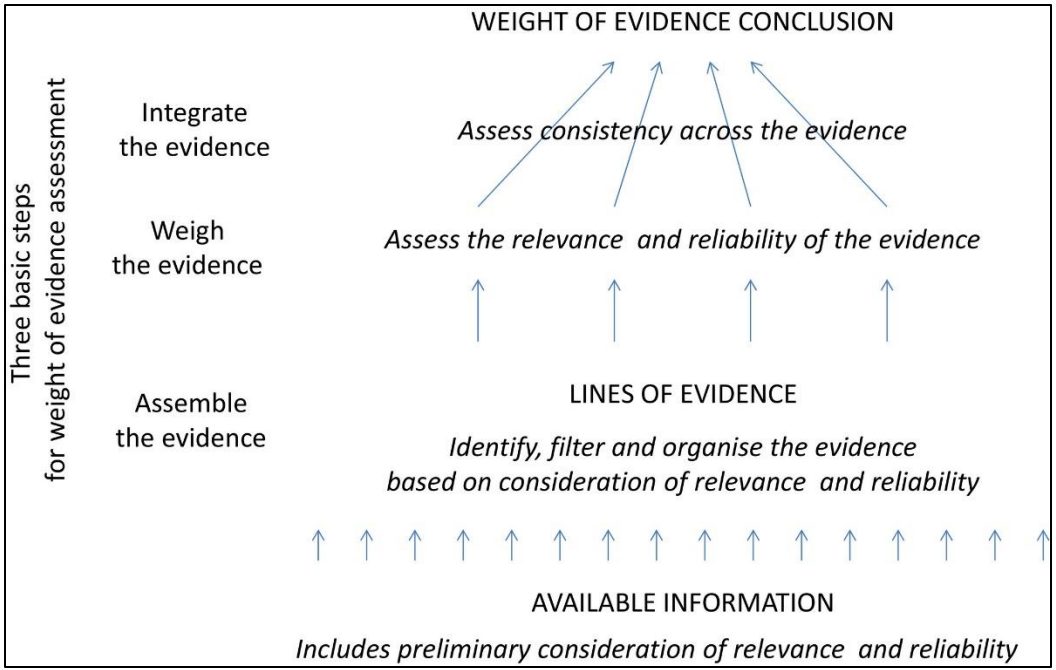
How can our BN be used in a WoE approach?



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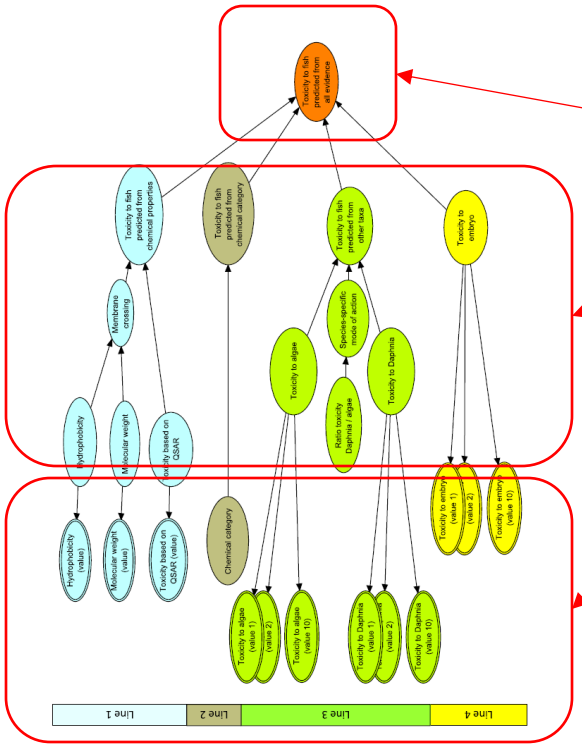

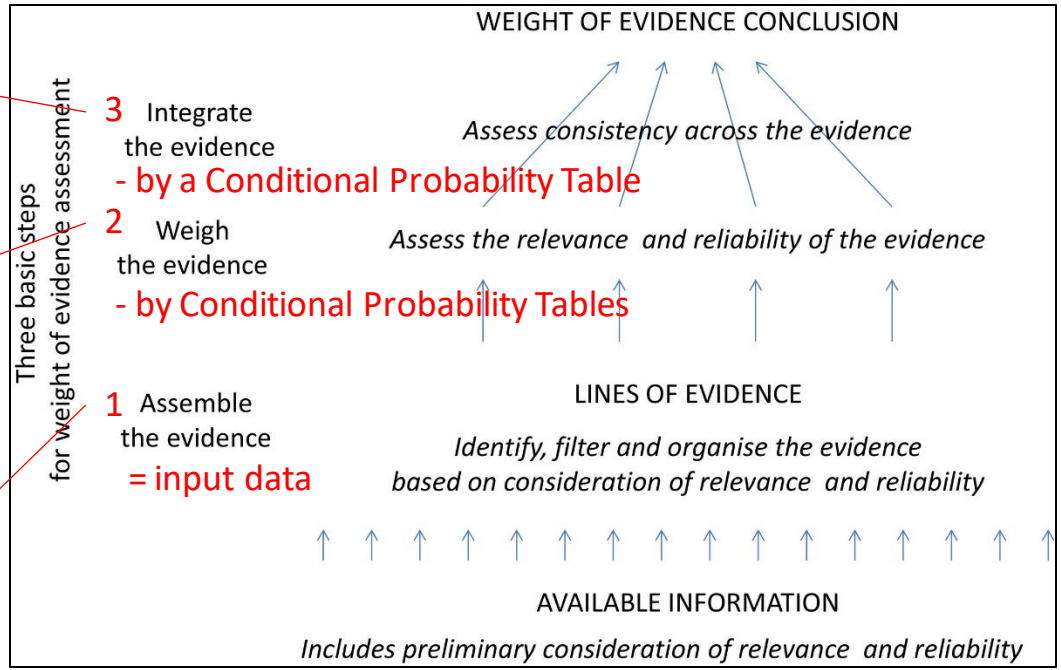

How can we use CPTs to weight the evidence?

Narrow probability distribution
= low uncertainty
= **high weight**
of the evidence
«Aniline»

Wide probability distribution
= high uncertainty
= **low weight**
of the evidence
«Neutral organic»

(b)

Toxicity to fish predicted from chemical category										
Chemical Category	Aniline	Anionic surfac-tant	Esters (dithio-phos-phates)	Esters (monothi-phos-phates)	Imidazole	Neutral organic	Phenol	Quinone	Substitu-ted urea	Unknown /other
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Sum	50	42	76	39	4	145	204	13	20	

Our CPTs can be **improved** by

- Involving more **experts**
- Using more **data**
- Using **equations**
- etc.

Demonstration of the web interface (WP4)

HUGIN Demo | Demos (finance) | Demos (ecosystem services) | Demos (misc) | Demos (projects) | About

A Bayesian network model to predict fish acute toxicity from multiple lines of evidence

By: Jannicke Moe, Raoul Wolf and Adam Lillicrap (Norwegian Institute for Water Research)
WWW: Anders L Madsen

April 2019

Latest update: April 2020

Introduction page | Enter values | Results | Additional information

Bayesian networks (BNs) are gaining popularity in ecotoxicology and ecological risk assessment, because of their ability to integrate different types of data and other information, and to predict the probability of specified states. This example demonstrates the use of a Bayesian network to provide scientific support for decisions on animal testing in ecotoxicology. European legislations require Reduction, Replacement or Refinement of animal testing wherever possible. The use of fish embryos for toxicity testing is considered a promising alternative to the use of juvenile or adult fish. However, fish embryos are not yet accepted as an alternative for regulatory purposes. The European Chemicals Agency (ECHA) has therefore recommended the development of a weight-of-evidence (WoE) approach to evaluate Fish Embyo Toxicity (FET) data in combination with other types of information as a replacement for juvenile fish toxicity data.

We have developed a probabilistic WoE model: a BN to predict the acute toxicity of a substance to juvenile fish based on four lines of evidence (Figure 1). The purposes of this online demonstration version are:

- To demonstrate the functionality of the model by the example substances given below
- To let users predict juvenile fish toxicity for new substances by entering their own data.
- To get feedback from users for improvement of the tool.

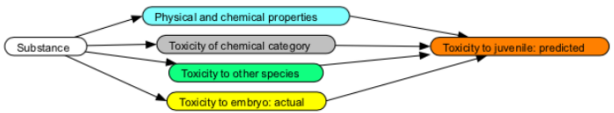


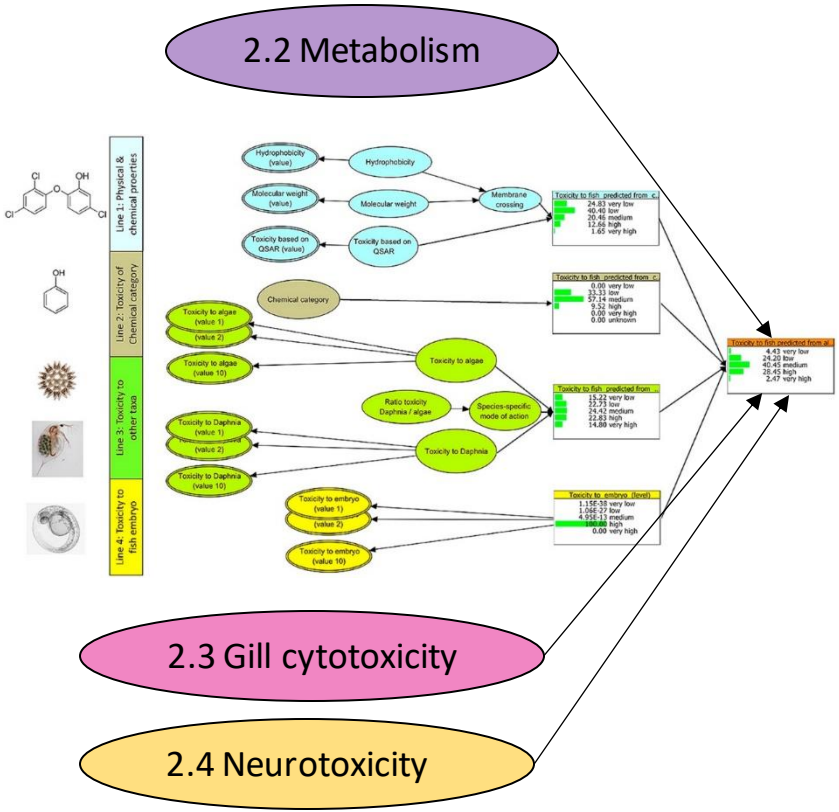
Figure 1.

Next steps:
WP3 (BN model) & WP4 (web interface)

Planned activities: WP3 (BN model)

Task 3.1 Model refinement

- Add **new lines** of evidence from WP2
  - Develop a **sub-model** for each LoE
  - Object-oriented Bayesian network
- Include more **data** from WP1
  - Toxicity data + metadata
  - Uncertainty
- **Prior probabilities** and **conditional probability tables** will be improved
  - new data, methods and/or **experts**
- Toxicity **intervals** will be refined



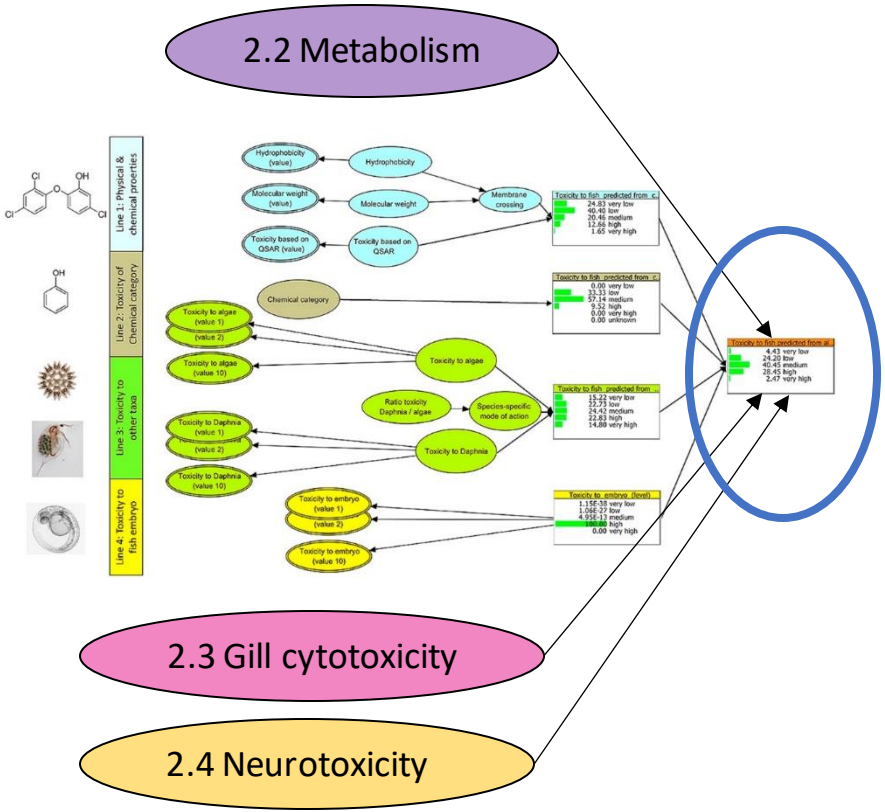
Planned activities: WP3 (BN model)

Task 3.2 Model calibration

- Improve the **integration** of lines of evidence: optimize the weighting

Task 3.3 Model evaluation

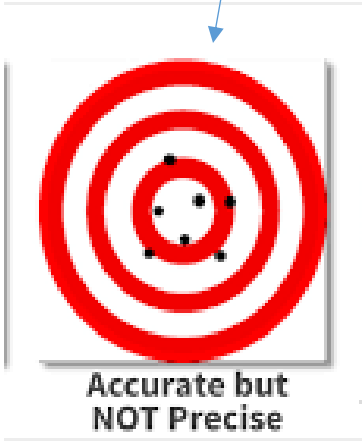
- Assess the **accuracy** of the BN predictions
- **Sensitivity** analysis
- **Value-of-information** analysis



«It’s better to be roughly right than precisely wrong»

Ideal situation

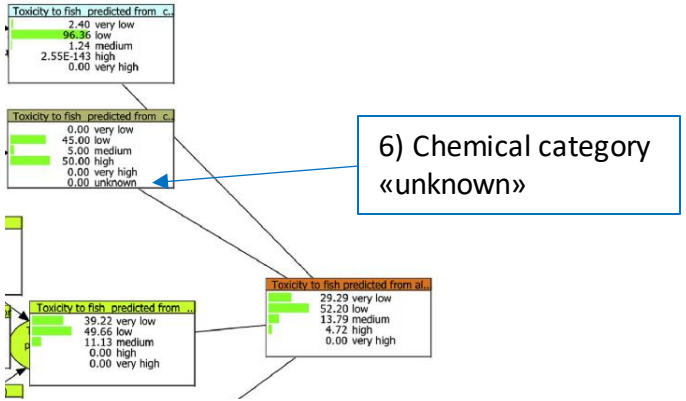
Typical situation:
point estimate
without uncertainty



Realistic situation:
aim of our BN model

If we remove the chemical category «unknown» …

- We can **combine the lines** of evidence more efficiently by equations
- We can more easily **add more lines** of evidence
  ← from WP2
- We can use new data and methods to **optimize the integration** of lines
  ← from WP1



Planned activities: WP4 (web interface)

- The BN model will be deployed with a **publicly available web-based user interface**
- Evaluation and testing via partnerships with the project **Monitoring Team, Scientific Advisors, Research Team, and additional experts**

Task 4.1: Web-based user interface

- Create and maintain dedicated web-site: http://swift.hugin.com (*NEW*)
- Adjust and extend interface to additional lines of evidence
- Additional functionality to import data and explorative visualization tools

Task 4.2: Technical user manual

- Technical user interface (Wiki-style): continuous improvements based on user feedback
- Introduction to technology and explanation of BN model
- Case examples of BN model usage
- Guidelines on using the BN model and its web interface

From correlations to causal relationships

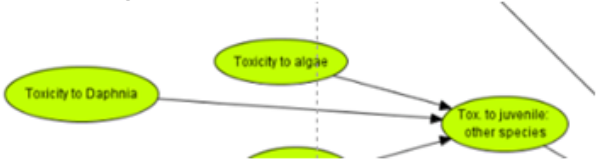
RE: WP4 slide and demo backup

Jannicke Moe
To Anders L Madsen
Cc Raoul Wolf; Adam David Lillicrap

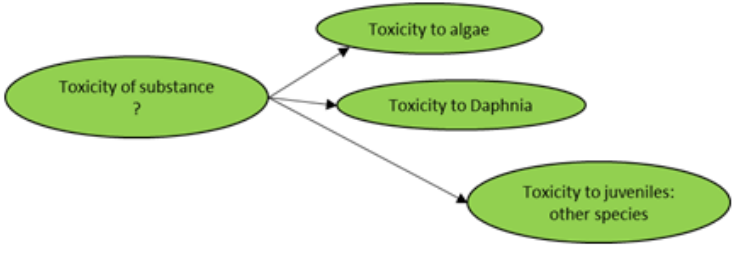
Reply | Reply All | Forward | ...

tir. 28.04.2020 14.32

Well we say that the arrows represent causal links, so I thought they should be - ideally?
Here is an example:



It looks as if toxicity of a substance to juvenile fish is "caused by" toxicity to Daphnia and toxicity algae.
In reality, it is some property of this substance that is causing the toxicity to both Daphnia, algae and juvenile fish.
I was thinking could restructure the model this way – arrows from the physical/chemical properties to Daphnia, to algae and to juvenile fish. The Daphnia and algae could still be input nodes, and the flow of information would go from Daphnia & algae backwards to some kind of general toxicity node, and forwards again juveniles. See picture:



I don't intend to show such a figure or explain it at the meeting, but this is what I had in mind and we can discuss it later.