# A hybrid Bayesian network model for predicting acute fish toxicity using multiple lines of evidence

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## Highlights

- ★ We developed a Bayesian network (**BN**) to **predict acute toxicity** of chemicals to juvenile fish
- ★ The BN uses **fish embryo toxicity data** in a quantitative weight-of-evidence approach
- ★ The BN **integrates information** on physical and toxicological properties of chemicals
- ★ The BN has **continuous nodes** for capturing the variability of input values
- ★ The BN predicts **correct toxicity intervals** for 69-80% of the test cases
- ★ The BN model is **publicly available** for testing through a web interface: http://demo.hugin.com/example/FET

## Background

- **Reduction, Replacement or Refinement of animal testing** wherever possible is required by legislations (e.g. EU Directive 2010/63/EU).
- **Fish Embryo Toxicity** (**FET**) testing could be an **alternative to juvenile fish** in acute toxicity testing. However, FET data are not yet accepted as a replacement for regulatory purposes such as REACH.
- The European Chemicals Agency (ECHA) has therefore recommended development of a **weight-of-evidence** (**WoE**) approach for FET data.

## Objectives

1. To **develop and evaluate a BN model** for predicting toxicity of substances to juvenile fish from embryo toxicity data in combination with other relevant information (Moe et al. 2019)
2. To **apply the BN model in a WoE approach** which can support replacing juvenile fish toxicity testing with fish embryo toxicity testing
3. To make a **publicly available user interface to the BN** for demonstration, testing and feedback

## Conceptual model

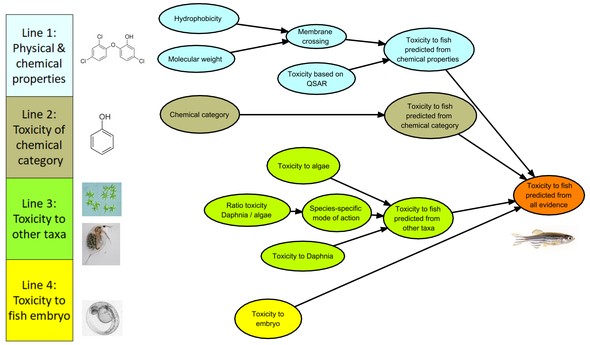



**Figure 1.** Conceptual version of the BN model

## Data and Methods

- The model has four lines of evidence (Figure 1)
- Toxicity data for 237 substances include QSAR, EC50 for algae and Daphnia, and LC50 for embryo and juvenile fish (Rawlings et al. 2019)
- Toxicity values are discretized to **5 intervals**:
  - very low: >100 mg/L
  - low: 5-100 mg/L
  - medium: 0.5-5 mg/L
  - high: 0.01-0. 5 mg/L
  - very high: <0.01 mg/L
- The links between nodes are quantified by **conditional probability tables** (**CPT**), where the probabilitites are obtained by various methods, e.g.
  - Count of observations (e.g. Table 1a),
  - Equal weighting (e.g. Table 1b)
- The BN includes **continuous nodes**, to account for variability in input values
- **Model evaluation** was performed with different subsets of the dataset

**Table 1.** Examples of conditional probability tables (subsets) based on different approaches. (**a**) **Counts of observations** of toxicity to juvenile fish (shown for 9 out of 42 chemical categories). (**b**) **Expert judgement:** the algorithm for combining two out of the four lines of evidence by equal weighting.

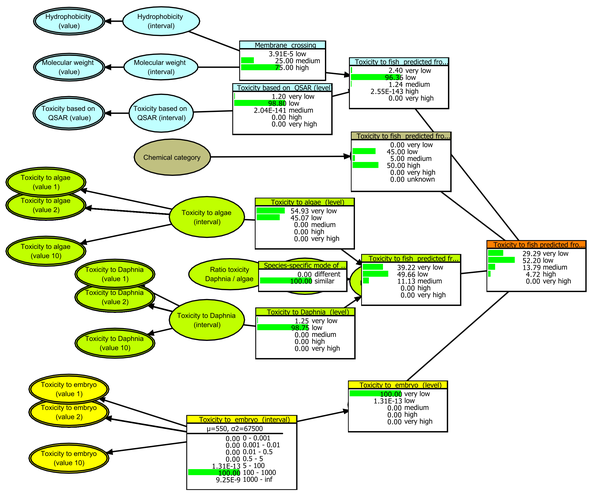
**(a) Count of observations**

| 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 | 0.455 | 0 | 0 | 0 | 0 |
| low | 0.80 | 0.333 | 0.184 | 0.026 | 0 | 0.345 | 0.363 | 0 | 0.45 | 0 |
| medium | 0.08 | 0.571 | 0.263 | 0.564 | 0.75 | 0.166 | 0.118 | 0 | 0.05 | 0 |
| high | 0.04 | 0.095 | 0.500 | 0.410 | 0 | 0.021 | 0.520 | 1 | 0.5 | 0 |
| very high | 0 | 0 | 0.053 | 0 | 0 | 0.014 | 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 | |

**(b) Expert judgement**

| Toxicity to fish predicted | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| line 1 | very low | | | | | low | | | | | medium | | | | |
| line 2 | very low | low | med-ium | high | very high | very low | low | med-ium | high | very high | very low | low | med-ium | high | very high |
| very low | 1 | 0.5 | 0.33 | 0.25 | 0.2 | 0.5 | 0 | 0 | 0 | 0 | 0.33 | 0 | 0 | 0 | 0 |
| low | 0 | 0.5 | 0.33 | 0.25 | 0.2 | 0.5 | 1 | 0.5 | 0.33 | 0.25 | 0.33 | 0.5 | 0 | 0 | 0 |
| medium | 0 | 0 | 0.33 | 0.25 | 0.2 | 0 | 0 | 0.5 | 0.33 | 0.25 | 0.33 | 0.5 | 1 | 0.5 | 0.33 |
| high | 0 | 0 | 0 | 0.25 | 0.2 | 0 | 0 | 0 | 0.33 | 0.25 | 0 | 0 | 0 | 0.5 | 0.33 |
| very high | 0 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0.25 | 0 | 0 | 0 | 0 | 0.33 |

**(a) Carbamazepine: low observed toxicity level**




**(b) Triclosan: high observed toxicity level**

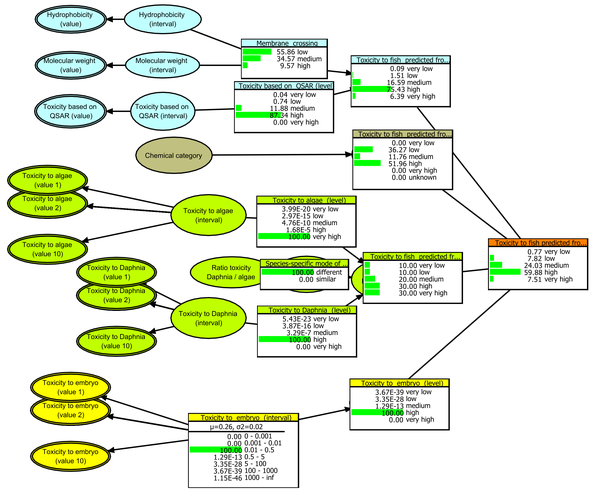



**Figure 2.** Examples of model predictions for two substances:
(**a**) Carbamazepine, which has **low observed toxicity level** to juvenile fish;
(**b**) Triclosan, which has **high observed toxicity level** to juvenile fish.
For simplicity, only 3 out of 10 continuous input nodes are displayed.

## Results

- The BN model can predict toxicity to juvenile fish **more accurately** than fish embryo data alone (e.g. Figure 2a)
- **Sensitivity analysis** indicate that the model predictions are most influenced by components based on data, and less by those based on expert judgement
- The BN predicted **correct toxicity interval** to juvenile fish for **69-71%** of the substances in the three largest data subsets (n = 77, 106, 159)
- The BN predicted **correct toxicity interval** for **80%** in the smallest data subset, with the strictest quality criteria (n = 20)
- In the 4 cases of incorrect predictions, the BN underestimated the toxicity level
  - 2,4-Dichlorophenol, 4-Chlorophenol, Malathion and Naphthalene
  - However, these 4 substances are **more toxic to algae or Daphnia**, which will therefore drive the risk assessment

## Further developments

- Higher resolution of toxicity intervals
- Use of machine learning to optimize the weighting of the lines of evidence
- Model validation with fish embryo and juvenile toxicity data from more sources
- Expand the BN model with more lines of evidence
- Refinement of the web interface based on feedback from users

## References

Moe, S.J., A.L. Madsen, K.A. Connors, J.M. Rawlings, S.E. Belanger, W.G. Landis, R. Wolf, A.D. Lillicrap. 2019. Development of a hybrid Bayesian network model for predicting acute fish toxicity using multiple lines of evidence. *Environmental Modelling and Software* (in review).
Preprint: https://www.biorxiv.org/content/10.1101/750935v1

Rawlings, J.M., S.E. Belanger, K.A. Connors, G.J. Carr. 2019. Fish embryo tests and acute fish toxicity tests are interchangeable in the application of the threshold approach. *Environmental Toxicology and Chemistry* 38: 671-681.

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**This poster** | **Moe et al. preprint** | **Web interface to BN model** | **NIVA's Section for Ecotoxicology and Risk Assessment**