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*

Progress meeting 11.03.2021

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How can our BN be used in a WoE approach?

EFSA JOURNAL

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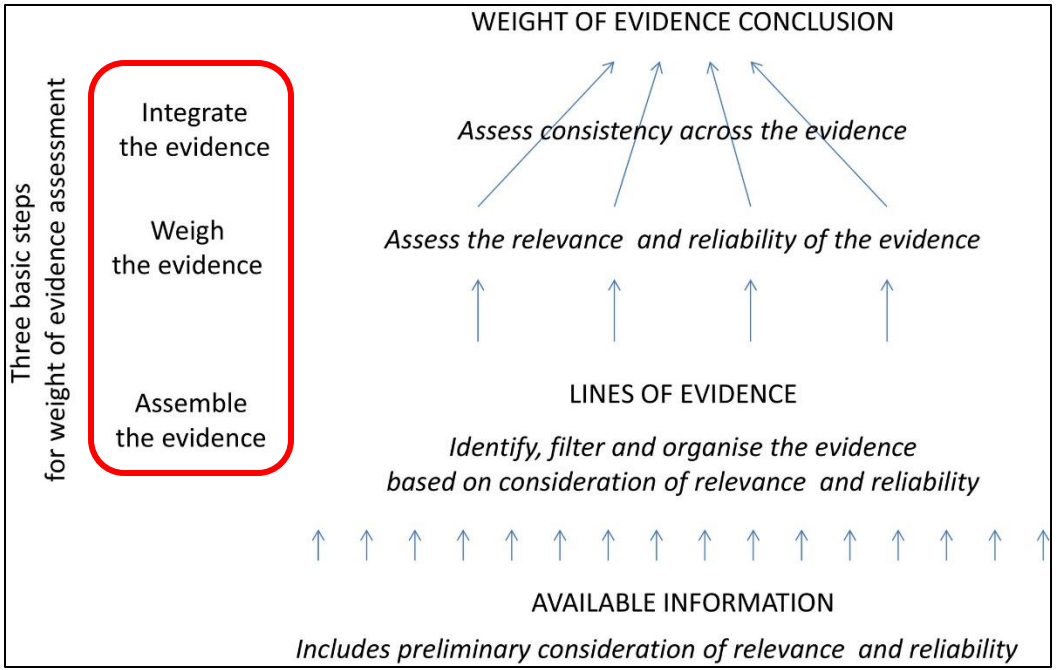
Guidance on the use of the weight of evidence approach in scientific assessments

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

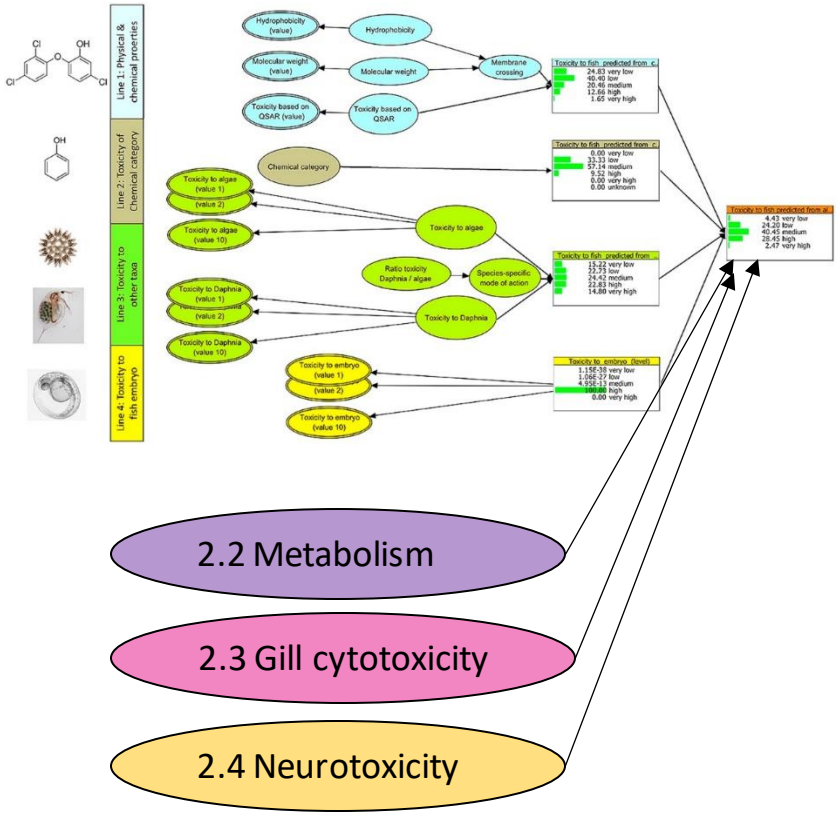
First published:03 August 2017 | https://doi.org/10.2903/j.efsa.2017.4971 | Citations: 47



WP3 progress & next steps

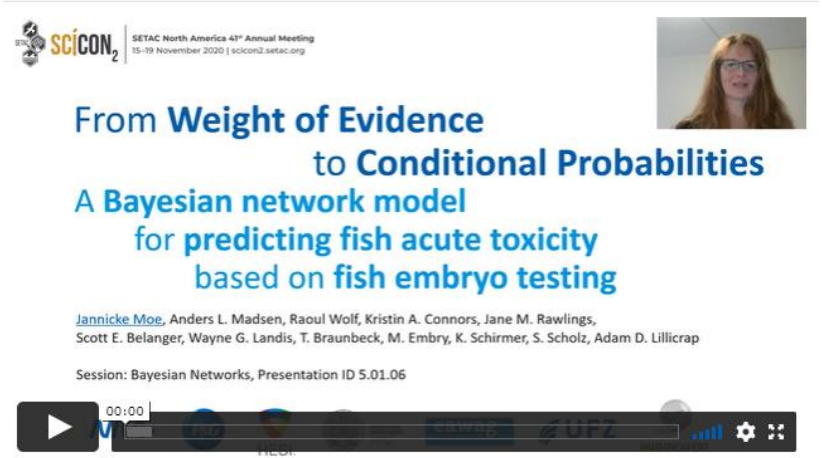
1) Revise the model **structure**
2) Revise the **intervals** of toxicity nodes
3) Revise the **Conditional Probability Tables**
4) Incorporate the **new lines** of evidence (from WP2)
5) **Integration** of lines: test & evaluate

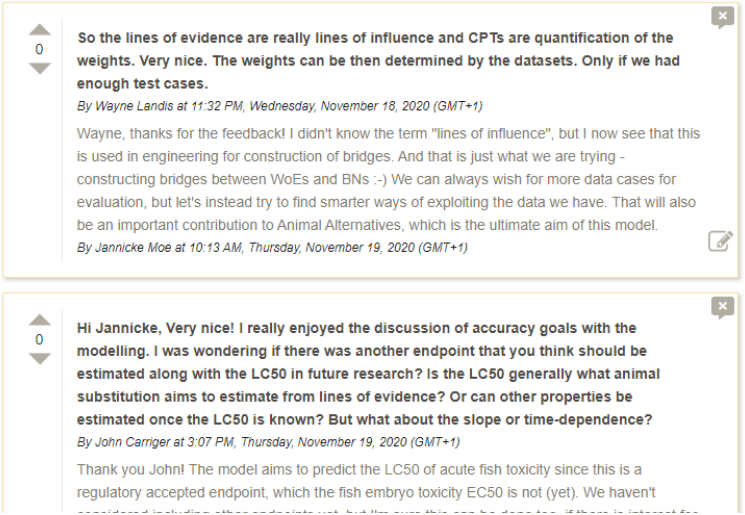
All model development so far is based on «old data» (described in Moe et al. 2020)



1) Revise the model structure

Presentations at SETAC SciCon2





https://setac.confex.com/setac/scicon2/meetingapp.cgi/Paper/3106

Aims for revised model structure

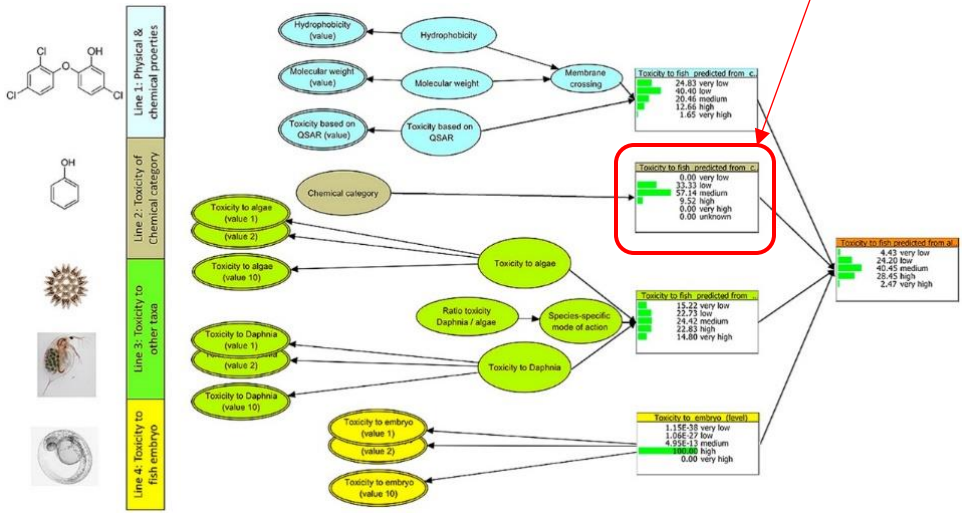
i. Arrows to represent causality?
   - If useful

ii. Avoid using Acute Fish Toxicity data
   - Only for model evaluation

iii. Better use of additional information
   - New definition of «chemical category» based on physical properties (Michelle)
   - Calculate prior probability of toxicity within each LoE and each category

iv. Better quantification of uncertainty
   - Hierarchical data analysis (Raoul)

«Chemical cateogory» was based on AFT data (juvenile)



A BN model structure does not need to represent causality

en.wikipedia.org/wiki/Bayesian_network

Causal networks [edit]

Although Bayesian networks are often used to represent causal relationships, this need not be the case: a directed edge from u to v does not require that X_v be causally dependent on X_u. This is demonstrated by the fact that Bayesian networks on the graphs:

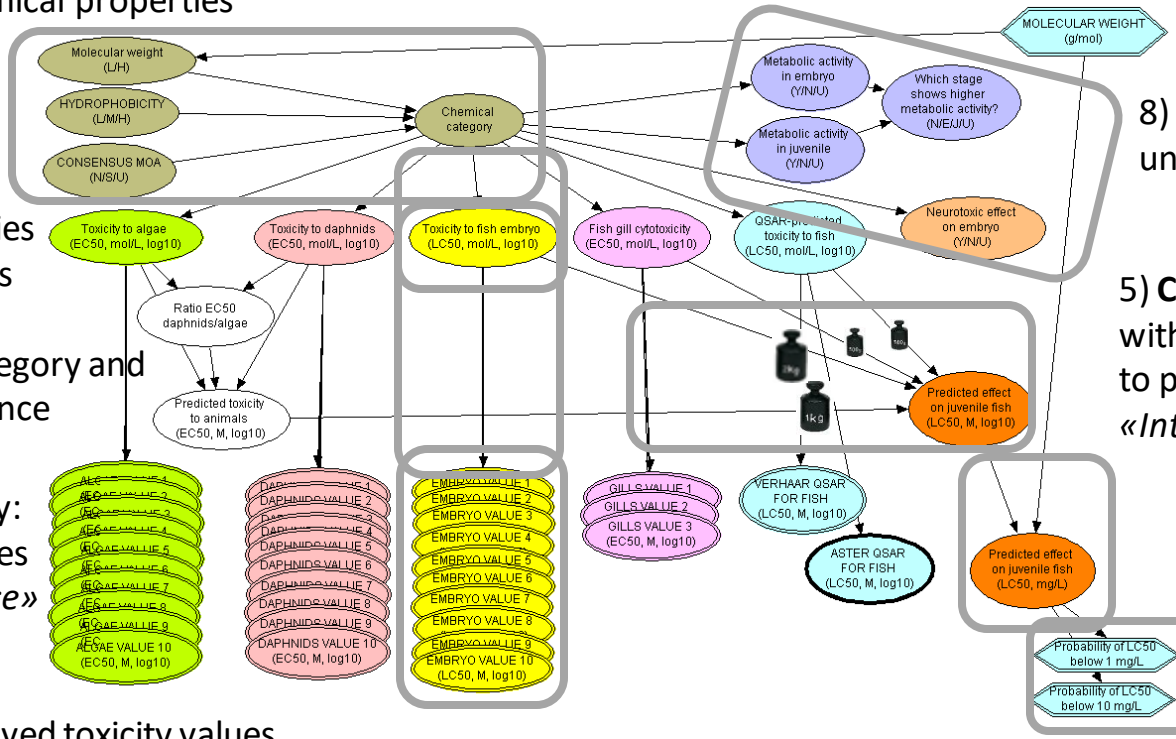
$$a \rightarrow b \rightarrow c \qquad \text{and} \qquad a \leftarrow b \leftarrow c$$

are equivalent: that is they impose exactly the same conditional independence requirements.

A causal network is a Bayesian network with the requirement that the relationships be causal. The additional semantics of causal networks specify that if a node X is actively caused to be in a given state x (an action written as do($X = x$)), then the probability density function changes to that of the network obtained by cutting the links from the parents of X to X, and setting X to the caused value x.[1] Using these semantics, the impact of external interventions from data obtained prior to intervention can be predicted.

Revised model structure: flow of information

1) **Chemical category** of a substance: defined by its physical & chemical properties



2) **Prior** probabilities of toxicity intervals calculated for each chemical category and each Line of Evidence

4) **Predicted** toxicity: updated probabilities *«Weigh the evidence»*

3) **Evidence:** Observed toxicity values, to be entered by user *«Assemble the evidence»*

8) New LoEs: under development

5) **Combine the LoEs** with different weights to predict Acute Fish Toxicity *«Integrate the evidence»*

6) **Back-transformation** to original scale (mg/L)

7) Generate **conclusions** for website and report

2) Revise the **intervals** of toxicity nodes

Transformation of toxicity scale

Original model:

- Scale of toxicity values (LC50 or EC50): mg/L
- Interval size increased exponantially

Problem 1:

- Combinig toxicity values for substances with different mol. weight, within chemical category

Solution 1:

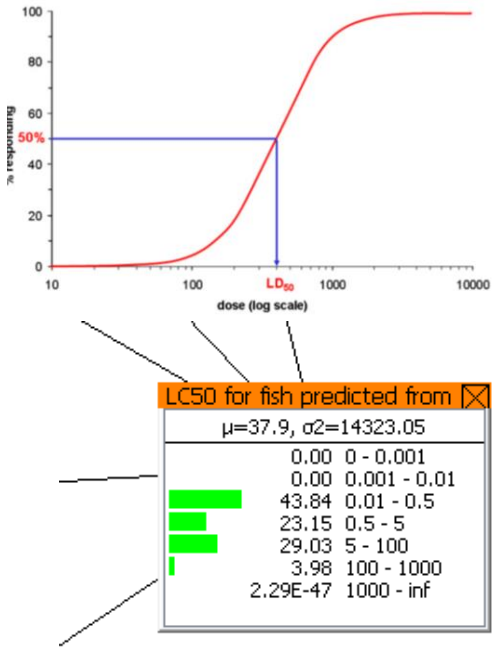
- Convert scale from mg/L to mol/L

Problem 2:

- Exponentially increasing intervals caused bias in the updated probability distributions (Moe et al. 2000)

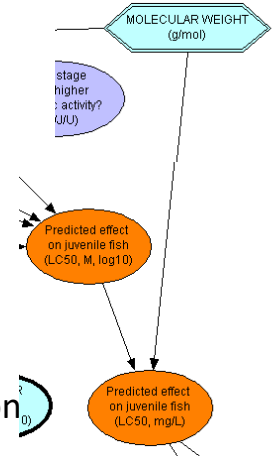
Solution 2:

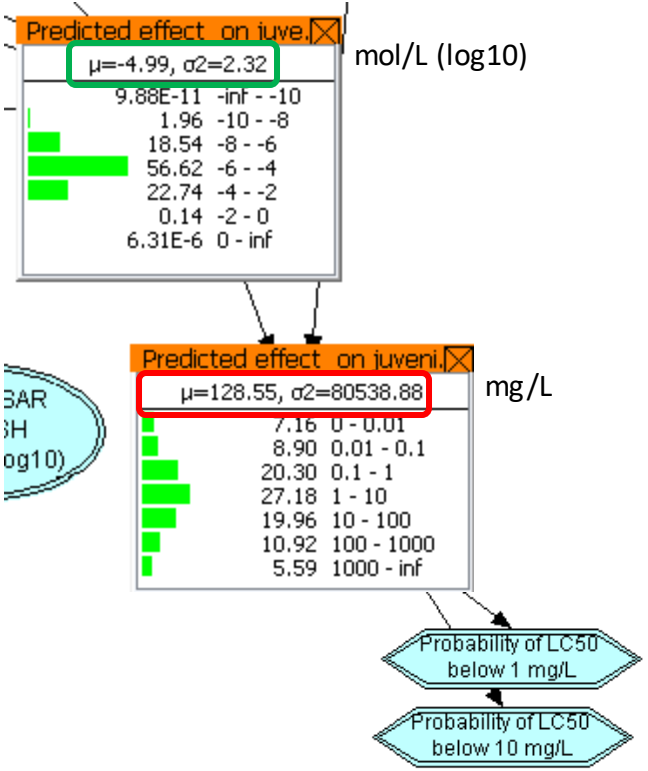
- Log10-transform all values before calculation



Transformation of toxicity values

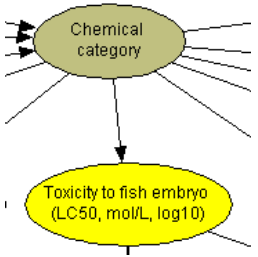
- Input by users:
  - Still enter values in mg/L
  - No transformation needed
- Inside the model:
  - Conversion from mg/L to mol/L
  - log10-transformation
  - Back-transformation and back-conversion
- Output in web site – two alternative views:
  - mol/L (log10)
  - mg/L





3) Revise the Conditional Probability Tables

Revise CPTs: data-based



Current:

- Probability distributions calculated directly from counts of observations
  Categories with no observations: calculated from overall distribution

Toxicity to fish embryo (LC50, mol/L, log10)

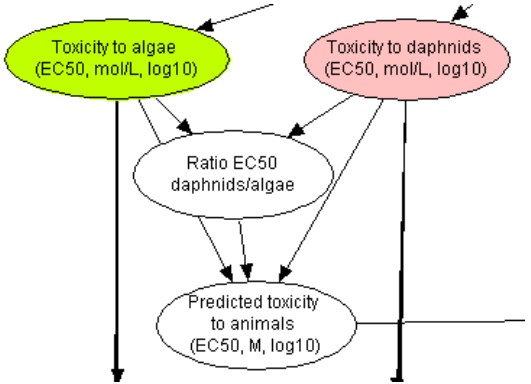
Chemical c...	LLN	LLS	LLU	LMN	LMS	LMU	LHN	LHS	LHU	HLN	HLS	HLU	HMN	HMS	HMU	HHN	HHS	HHU
-inf - -10	9.997003E-5	9.996996E-5	9.996994E-5	9.996002E-5	9.996001E-5	9.996002E-5	9.995002E-5	9.995002E-5	9.994004E-5	9.997997E-5	9.997997E-5	9.994004E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5
-10 - -8	0.238024	0.049368	0.041654	9.996002E-5	9.996001E-5	9.996002E-5	9.995002E-5	9.995002E-5	9.994004E-5	0.169168	0.169168	9.994004E-5	0.169168	0.169168	0.169168	0.169168	0.169168	0.169168
-8 - -6	0.414842	0.209814	0.291579	0.173843	9.996001E-5	0.11428	9.995002E-5	9.995002E-5	9.994004E-5	0.296519	0.296519	9.994004E-5	0.296519	0.296519	0.296519	0.296519	0.296519	0.296519
-6 - -4	0.320833	0.654124	0.49986	0.608453	0.878437	0.571201	0.666334	9.995002E-5	0.9994	0.435274	0.435274	0.9994	0.435274	0.435274	0.435274	0.435274	0.435274	0.435274
-4 - -2	0.017002	0.086394	0.166617	0.217304	0.090873	0.28256	0.333166	0.49976	9.994004E-5	0.077931	0.077931	9.994004E-5	0.077931	0.077931	0.077931	0.077931	0.077931	0.077931
-2 - 0	9.997003E-5	9.996996E-5	9.996994E-5	9.996002E-5	0.030291	9.996002E-5	9.995002E-5	0.49976	9.994004E-5	0.020908	0.020908	9.994004E-5	0.020908	0.020908	0.020908	0.020908	0.020908	0.020908
0 - inf	9.997003E-5	9.996996E-5	9.996994E-5	9.996002E-5	9.996001E-5	9.996002E-5	9.995002E-5	9.995002E-5	9.994004E-5	9.997997E-5	9.997997E-5	9.994004E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5	9.997997E-5
Experience	294	81	24	23	33	7	3	2	2	0	0	1	0	0	0	0	0	0

Ongoing (Raoul):

- Use hierarchical Bayesian models (statistical) to estimate probability distribution, accounting for variability at different levels
- Can be supplemented with expert judgement

Revise CPTs: expert-based

- Original: manually assigned probabilities
- Current: «Expressions» (equations and algorithms)
- Next steps:
  - Refinement of expressions
  - Model testing and evaluation
  - Feedback from monitoring team?



Predicted toxicity to animals (EC50, M, log10)

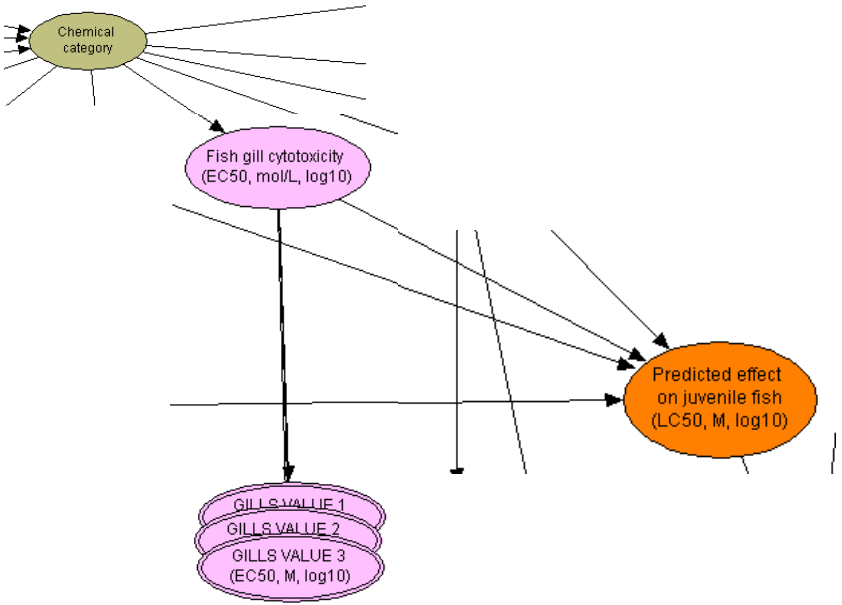
Ratio EC50 ...	0 - 0.5										0.5 - 2										2 - inf									
Expression	Daphnids_EC50_M_log10										0.5 * Daphnids_EC50_M_log10 + 0.5 * Algae_EC50_M_log10										Daphnids_EC50_M_log10									
Ratio EC50 ...	0 - 0.5		0.5 - 2																											
Toxicity to d...	0 - inf		-inf - -10								-10 - -8								-8 - -6								-6 - -4			
Toxicity to a...	-2 - 0	0 - inf	-inf - -10	-10 - -8	-8 - -6	-6 - -4	-4 - -2	-2 - 0	0 - inf	-inf - -10	-10 - -8	-8 - -6	-6 - -4	-4 - -2	-2 - 0	0 - inf	-inf - -10	-10 - -8	-8 - -6	-6 - -4	-4 - -2	-2 - 0	0 - inf	-inf - -10	-10 - -8	-8 - -6	-6 - -4	-4 - -2	-2 - 0	0 - inf	-inf - -10
-inf - -10	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-10 - -8	0	0	0	1	1	0	0	0	0	1	1	0.48	0	0	0	0	1	0.48	0	0	0	0	0	0	0	0	0	0	0	0
-8 - -6	0	0	0	0	0	1	1	0	0	0	0	0.52	1	0.48	0	0	0	0.52	1	0.48	0	0	0	1	1	0.48	0	0	0	1
-6 - -4	0	0	0	0	0	0	0	1	1	0	0	0	0	0.52	1	0.48	0	0	0	0.52	1	0.48	0	0	0	0.52	1	0.48	0	0
-4 - -2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.52	0	0	0	0	0	0.52	1	0	0	0	0	0.52	1	0.48
-2 - 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.52
0 - inf	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

4) Incorporate new lines of evidence

Option 1:
Use as predictor variable for toxicity to juvenile fish (AFT)

Fish gill cytotoxicity

- Existing data (from EAWAG):
  - Can be used set prior probability distribution for each chemical category
- New data from users:
  - Can entered as evidence to update the probability distribution

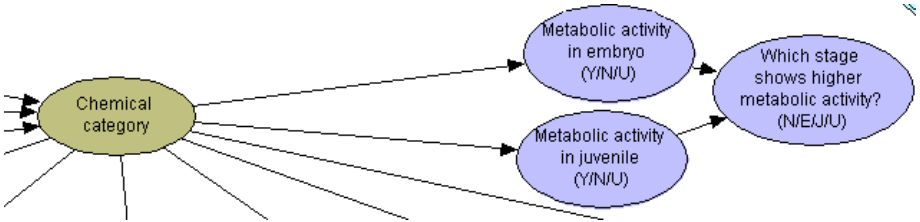


Option 2:
Use as qualitative additional information

Metabolic activity

- New data from users:
  Not expected

- Existing data (from Uni Heidelberg):
  - Can be used generate an «alert» for selected chemical categories
  - Can be included in report
  - User can take into account for interpretation of model prediction

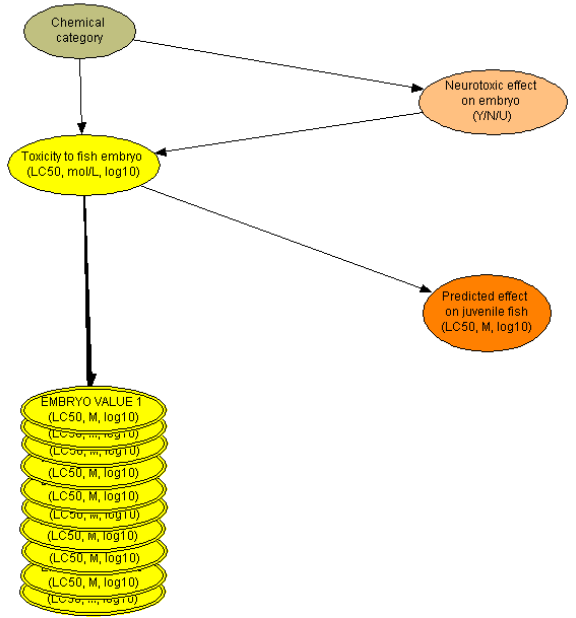


Option 3:
Use to influence other lines of evidence

Neurotoxicity

- New data from users:
  Can be recommended

- Existing data (from UFZ):
  - (i) Per category: can generate qualitative «alert»
  - **(ii) Per category: can influence the CPT for embryo**
  -

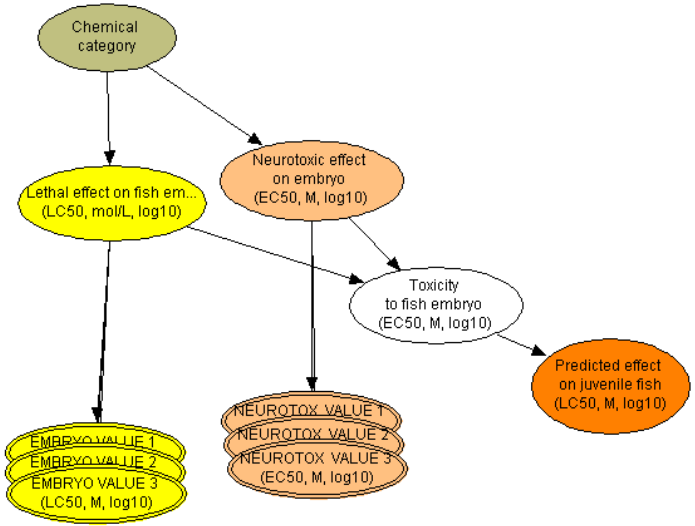


Option 3:
Use to influence other lines of evidence

Neurotoxicity

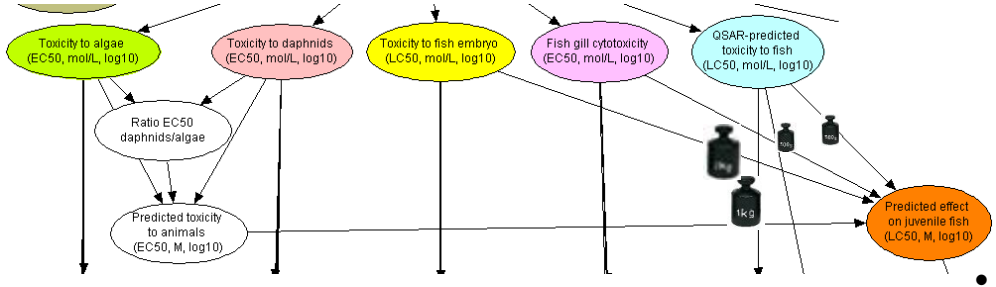
- New data from users:
  - Can be recommended?

- Existing data (from UFZ):
  - (i) Per category: can generate qualitative «alert»
  - (ii) Per category: can influence the CPT for embryo
  - **(iii) Per substance: can used as predictor of EC50 value**



5) Integration of lines: test & evaluate

How to optimise the weighting of the Lines of Evidence?



- Compare the predicted vs. observed LC_{50} for juvenile fish
  - Compare the post probable LC_{50} interval of both
  - LC_{50} = lethal concentration to 50% of the test population

159 test substances

- Toxicity data for both embryo + juvenile fish

Automatic calibration of weights not possible

- Requires >10^6 test cases

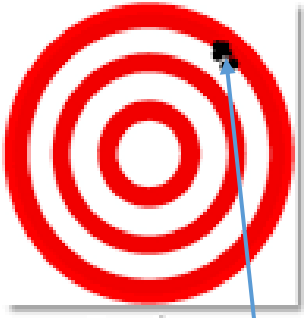
- Test a limited set of alternative weights
  - Compare model performance: accuracy and precision

What is the **aim** of the BN model predictions?

HIGH PRECISION,
HIGH ACCURACY

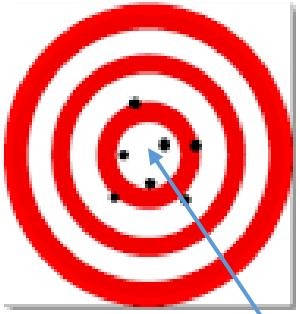
Ideal situation

HIGH PRECISION,
LOW ACCURACY



Typical situation:
point estimate
ignoring uncertainty

HIGH ACCURACY,
LOW PRECISION

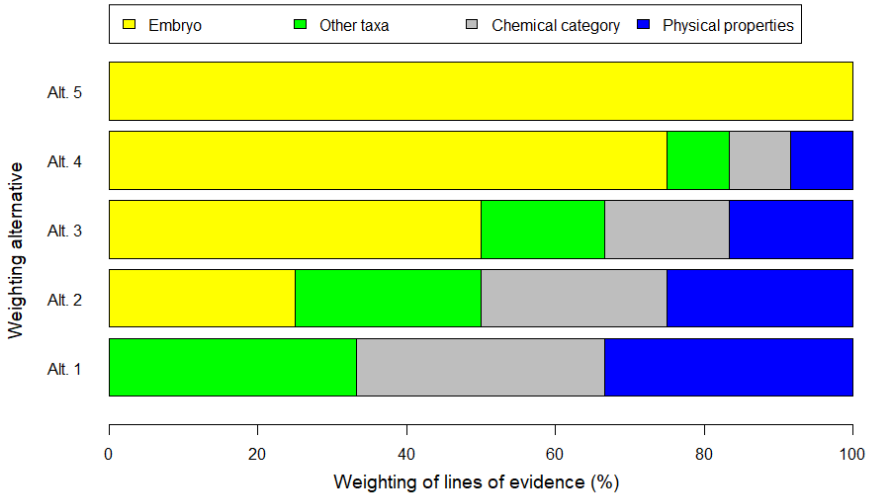


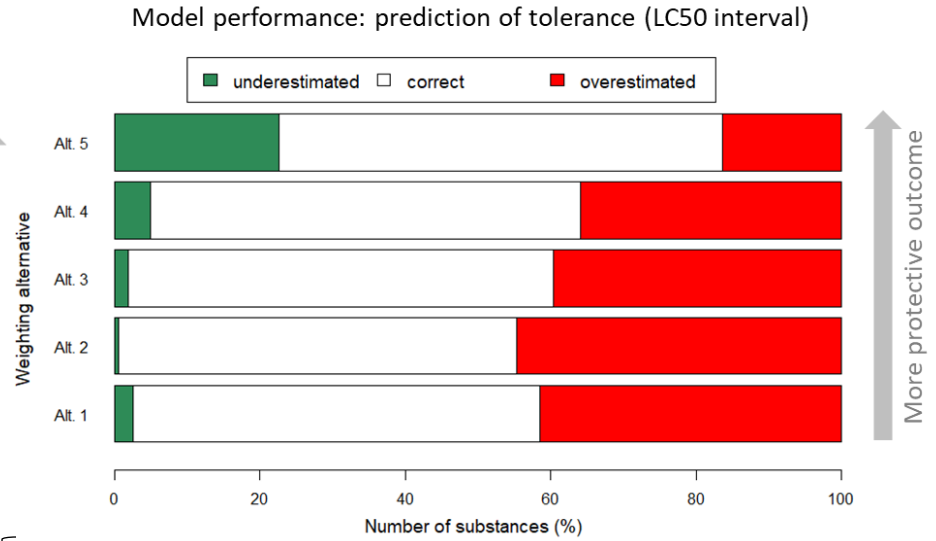
Realistic situation:
aim of our BN model

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

The weighting alternatives affect the accuracy of the model predictions

NB: Results from old model





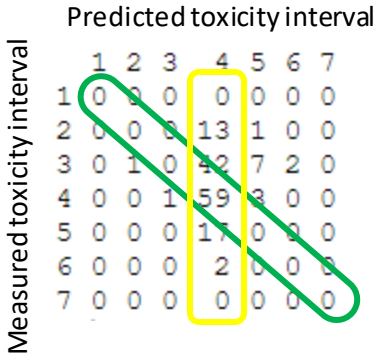
Higher weight to the Embryo Line of evidence

- ➔ lower overestimation of tolerance
  - ➔ more protective assessment
- ➔ slightly higher accuracy (% correct predictions)
- ➔ better balance in over- vs. underestimation

Preliminary outcome

- Comparison of predicted vs. measured toxicity
  - Prediction: interval with highest probability
  - Measured: interval with average of toxicity observations
  - Scale: mol/L (log10)

- Predicted toxicity values:
  - mostly in a reasonable interval (mM - µM)
  - too much centred in this interval



Preliminary outcome

- Main reason for lower sensitivity of model:
  - AFT data no longer use in model parametrisation (chemical category)

- Model performance can still be improved in various ways
  - Further refinement of chemical categories
  - Further refinement of CPTs (hierarchical data analysis)
  - Further use of additional information / expert judgement
  - Alternative weighting of LoEs
  - Alternative criteria for selection of test dataset

Predicted toxicity interval

Measured toxicity interval

	1	2	3	4	5	6	7
1	0	0	0	0	0	0	0
2	0	0	0	13	1	0	0
3	0	1	0	42	7	2	0
4	0	0	1	59	3	0	0
5	0	0	0	17	0	0	0
6	0	0	0	2	0	0	0
7	0	0	0	0	0	0	0