SETAC EUROPE2021
SETAC EUROPE 31ST ANNUAL MEETING
3–6 MAY 2021 | VIRTUAL CONFERENCE

Weight of Evidence by Conditional Probabilities: A Bayesian network model for predicting fish acute toxicity based on fish embryo testing

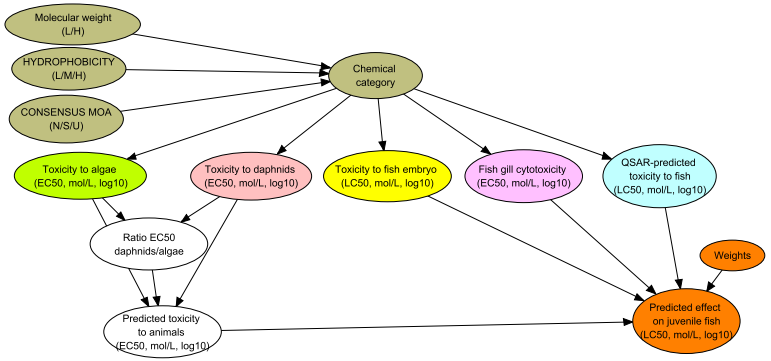
Jannicke Moe, Anders L. Madsen, Raoul Wolf, Kristin A. Connors, Jane M. Rawlings, Scott E. Belanger, Wayne G. Landis, T. Braunbeck, M. Embry, K. Schirmer, S. Scholz, Adam D. Lillicrap

Session 4.01: Artificial Intelligence Approaches in Environmental Risk Assessment: Bayesian Networks, Machine Learning and Predictive Modelling

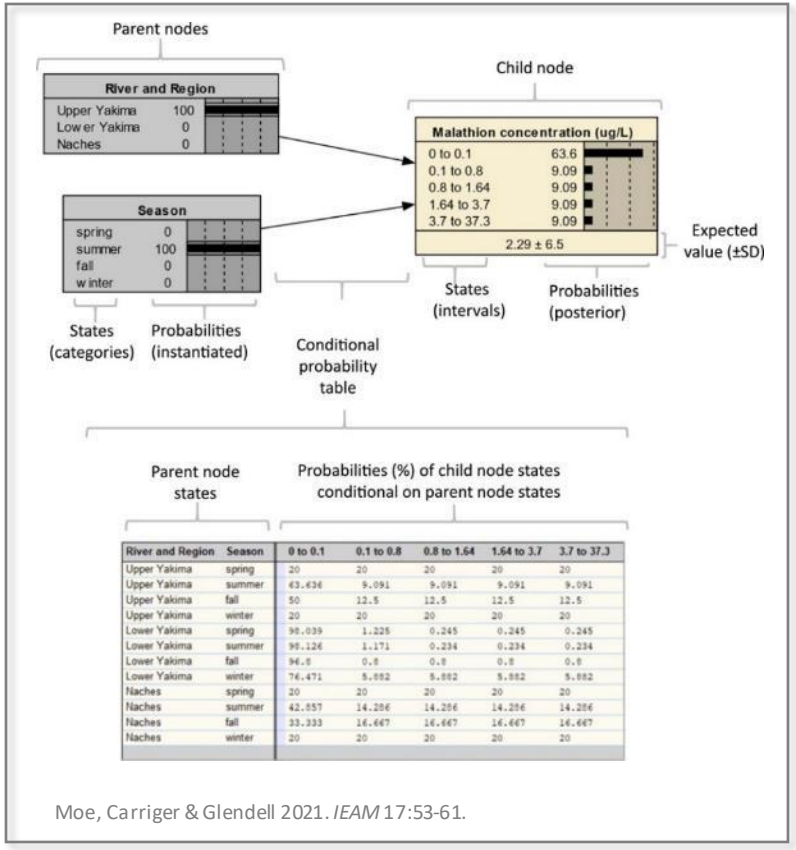
Presentation ID: 4.01.08

Highlights: We have developed a Bayesian network model which …

- ✓ integrates fish **embryo toxicity data** with other information on physical, chemical and toxicological properties of substances
- ✓ represents a **quantitative weight-of-evidence** approach
- ✓ predicts the **correct fish acute toxicity** intervals for most of test substances
- ✓ is **publicly available** for demonstration and testing in a web interface



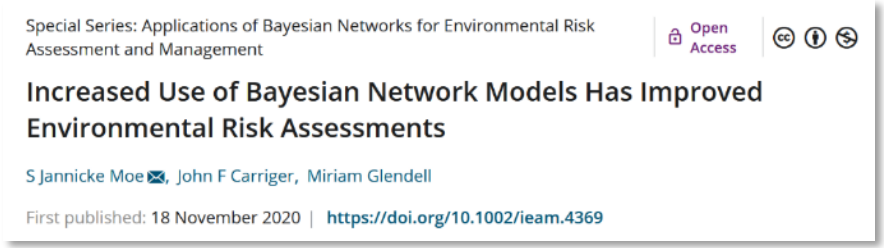
What is a Bayesian network?



River and Region	Season	0 to 0.1	0.1 to 0.8	0.8 to 1.64	1.64 to 3.7	3.7 to 37.3
Upper Yakima	spring	20	20	20	20	20
Upper Yakima	summer	63.636	9.091	9.091	9.091	9.091
Upper Yakima	fall	50	12.5	12.5	12.5	12.5
Upper Yakima	winter	20	20	20	20	20
Lower Yakima	spring	90.039	1.225	0.245	0.245	0.245
Lower Yakima	summer	90.126	1.171	0.234	0.234	0.234
Lower Yakima	fall	96.8	0.8	0.8	0.8	0.8
Lower Yakima	winter	76.471	5.882	5.882	5.882	5.882
Naches	spring	20	20	20	20	20
Naches	summer	42.857	14.286	14.286	14.286	14.286
Naches	fall	33.333	16.667	16.667	16.667	16.667
Naches	winter	20	20	20	20	20

Moe, Carriger & Glendell 2021. *IEAM* 17:53-61.

- A joint probability distribution among variables (nodes) in a graphical format
- Relationships (arrows) are quantified by Conditional Probability Tables (CPTs)
- The nodes usually have discrete states
- The nodes and arrows form a directed acyclic graph; no feedback loops
- Many recent applications in ERA


Special Series: Applications of Bayesian Networks for Environmental Risk Assessment and Management

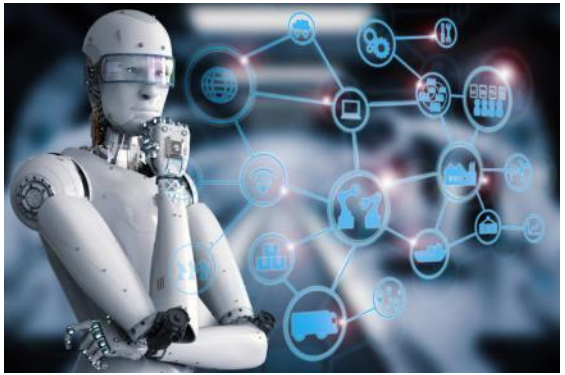
Open Access

Increased Use of Bayesian Network Models Has Improved Environmental Risk Assessments

S Jannicke Moe, John F Carriger, Miriam Glendell

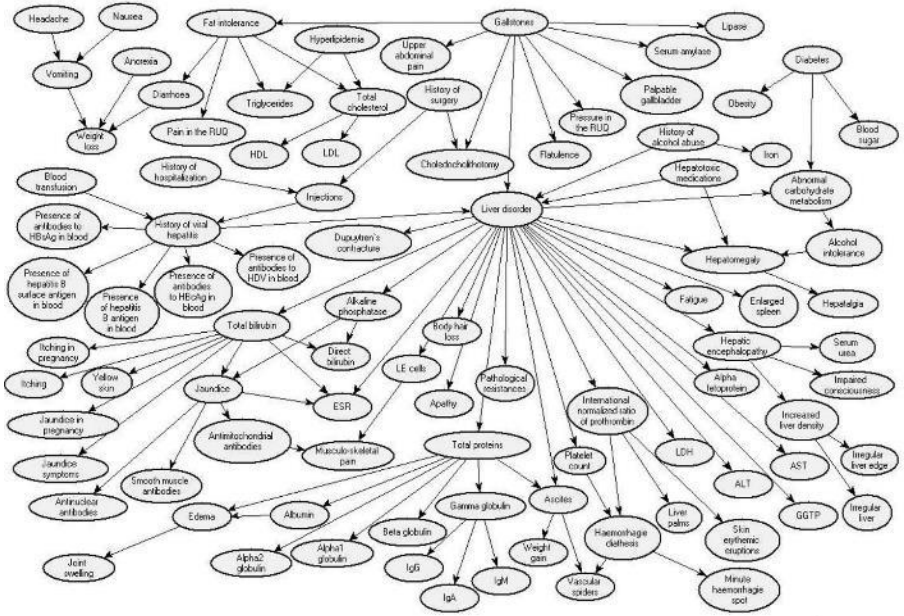
First published: 18 November 2020 | https://doi.org/10.1002/ieam.4369

BNs can use Artificial Intelligence for learning model structure and parameter values



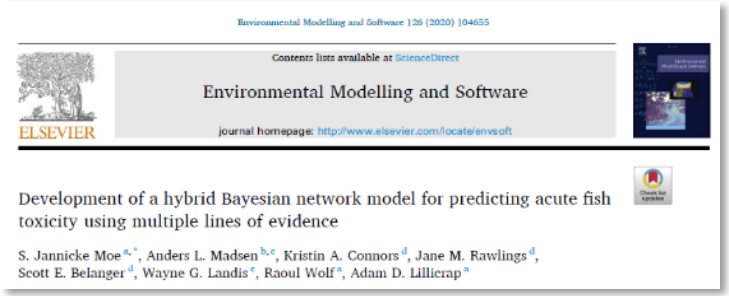
- Machine learning (ML) methods require large data sets
- Toxicity and exposure data are often limited
- ”Unlike most ML methods, BNs allow for direct **expert knowledge** input, to control the direction and existence of edges between nodes”
- ”BNs fill an important gap in the ML world, **bridging the divide** between simple models without probability information, and computationally heavy and data-hungry methods”

After https://medium.com/eliiza-ai/bayesian-networks-combining-machine-learning-and-expert-knowledge-into-explainable-ai-efaf6f8e69b



https://www.norwegiancreations.com/2018/09/artificial-intelligence-bayes-network/

A BN model for predicting acute **fish toxicity** from **fish embryo toxicity** & other information



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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]

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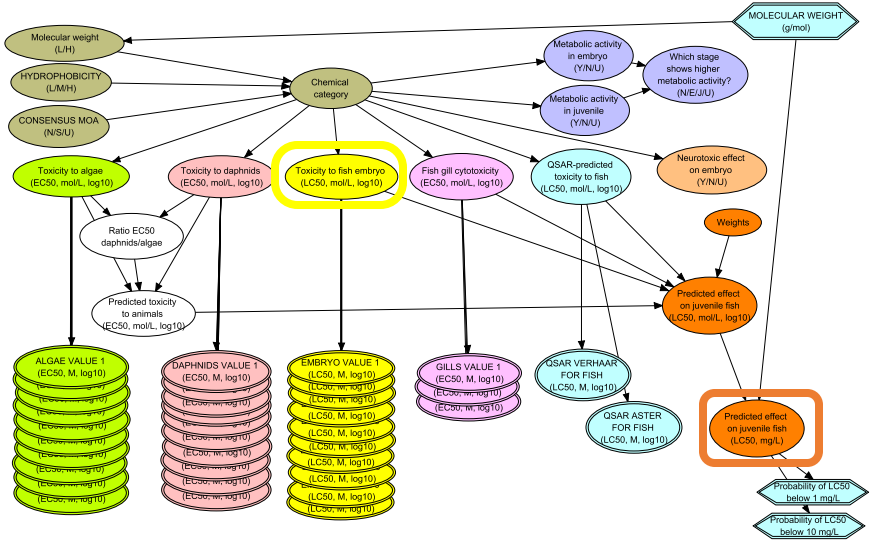
452 Received: 5 September 2019 | Returned for Revision: 21 November 2019 | Accepted: 20 February 2020

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‡



- Aim: replace the use of juvenile fish (OECD 203) with fish embryos (OECD 236) in toxicity testing
- Request: «strengthen the weight of evidence for fish embryo data»
- (More background information: presentation 1.01.07)

The SWiFT project (2020-2023)

LRI Long-Range Research Initiative | cefic The European Chemical Industry Council

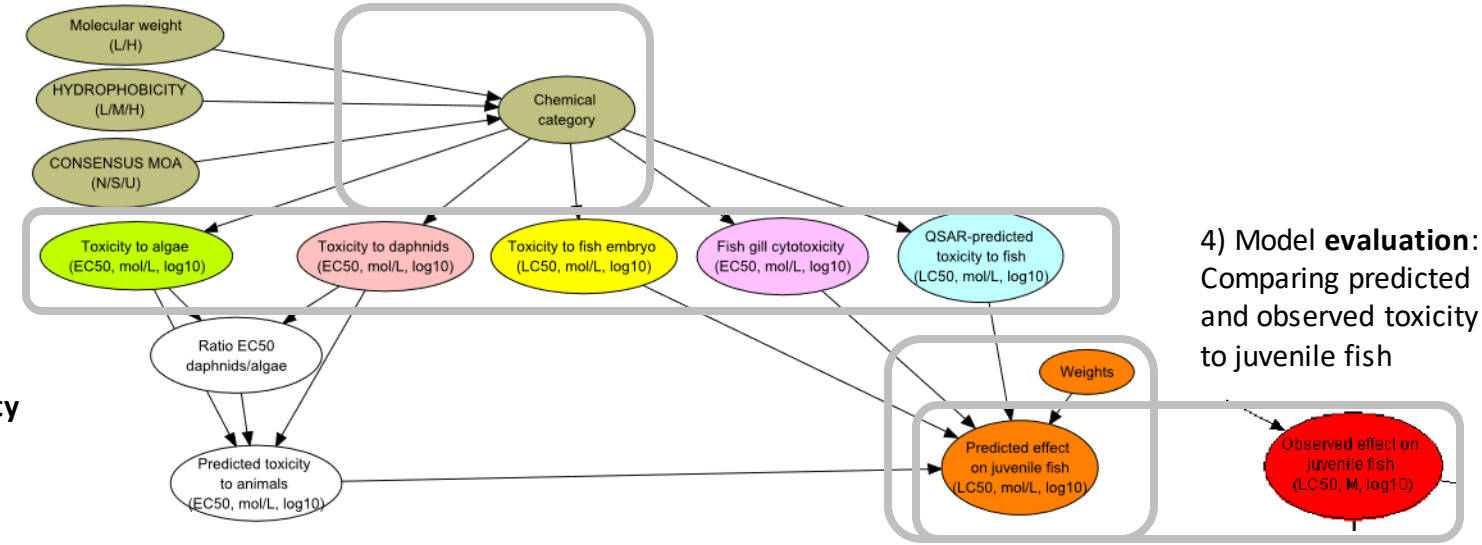
Strengthening **W**eight of ev**i**dence for FET data to replace acute **F**ish **T**oxicity (SWiFT)

Researcher Team:
Adam Lillicrap (PI, WP2), Kristin Connors (WP1), Jannicke Moe (WP3), Anders Madsen (WP4), Raoul Wolf, Thomas Braunbeck, Kristin Schirmer, Michelle Embry, Scott Belanger, Stefan Scholz

Advisory Team:
Noemie Croze, Christopher Faßbender, Sylvia Gimeno, Marlies Halder, Sarah Hughes, Joop de Knecht, Mark Lampi, Wayne Landis, Teresa Norberg-King, Martin Paparella, Audrey Pearson, Eleonora Simonini, Marta Sobanska, Susanne Walter-Rohde

Main properties of the BN model, run for one chemical substance

0) Enter info on physical & chemical properties of the substance
➔ define chemical category
➔ get **prior probability** of toxicity for each Line of Evidence (LoE)



1) Enter toxicity values (= **evidence**) for one or more Lines of Evidence

2) combine with priors
➔ **posterior probability** of toxicity for each LoE

3) **Integration** and predition: Weighting of each LoE

4) Model **evaluation**: Comparing predicted and observed toxicity to juvenile fish

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

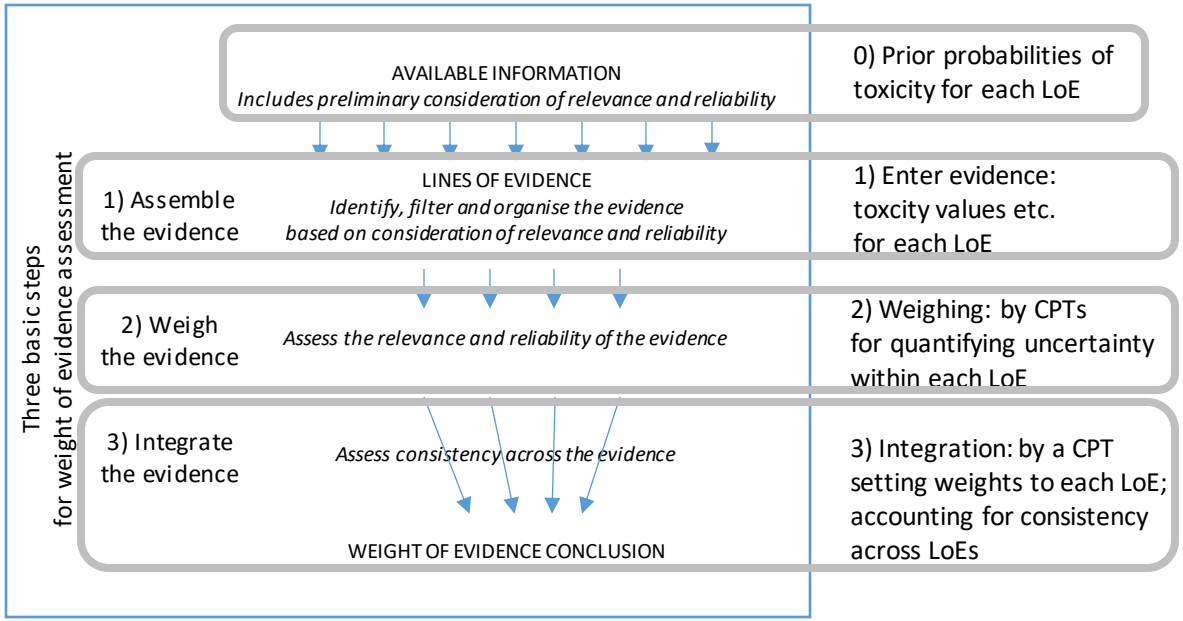
EFSA Scientific Committee, Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn ... See all authors

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

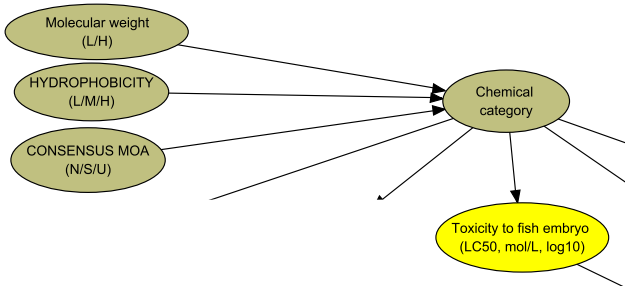
Our BN-WoE should be

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

Main steps of the BN model:



0) Prior probability of toxicity: existing toxicity data grouped by chemical category



Definition of chemical categories:

- Molecular weight (**L**ow/**H**igh)
- Hydrophobicity (**L**ow/**M**edium/**H**igh)
- Mode of action (**N**arcotic/**S**pecific/**U**nspecified)

Category «LLU»: Wide probability distribution = high uncertainty

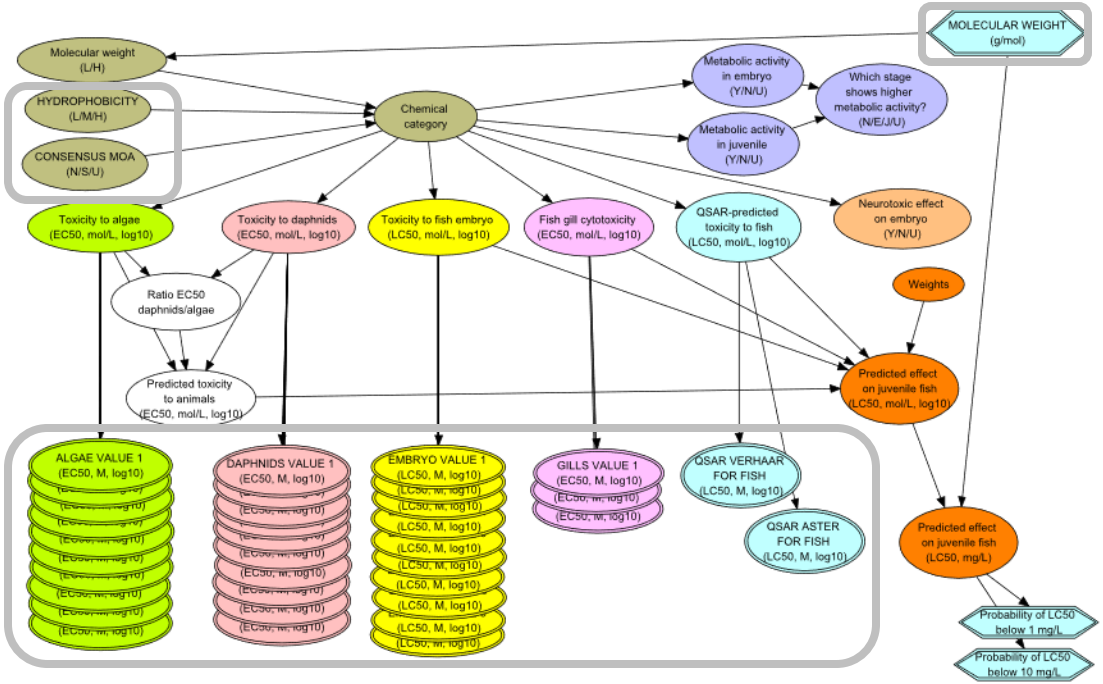
Category «LMS»: Narrow probability distribution = low uncertainty

- Training data set: 237 substances (Moe et al. 2020)
- Current method: count of observations
- In development: hierarchical Bayesian estimation (Presentation 1.01.07)

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 - -9	9.998001E-5	9.998005E-5	9.99801E-5	9.997994E-5	9.996002E-5	9.997001E-5	9.994993E-5	9.994004E-5	9.994004E-5	9.998005E-5	9.998005E-5	9.994004E-5	9.998005E-5	9.998005E-5	9.998005E-5	9.998005E-5	9.998E-5	9.998E-5
-9 - -6	0.017003	0.086403	0.166633	0.217348	0.121164	0.235629	0.353167	0.9994	9.994004E-5	0.09884	0.09884	9.994004E-5	0.09884	0.09884	0.09884	0.09884	0.09884	0.09884
-6 - -5	0.064613	0.185148	0.208292	0.434696	0.605818	0.428443	0.666334	9.994004E-5	0.9994	0.171068	0.171068	9.994004E-5	0.171068	0.171068	0.171068	0.171068	0.171068	0.171068
-5 - -4	0.265253	0.469042	0.231608	0.173878	0.272618	0.142814	9.994993E-5	9.994004E-5	9.994004E-5	0.264206	0.264206	0.9994	0.264206	0.264206	0.264206	0.264206	0.264206	0.264206
-4 - -3	0.319664	0.135775	0.166633	0.130409	9.996002E-5	0.142814	9.994993E-5	9.994004E-5	9.994004E-5	0.220488	0.220488	9.994004E-5	0.220488	0.220488	0.220488	0.220488	0.220488	0.220488
-3 - 0	0.383267	0.123432	0.166633	0.104347	9.996002E-5	9.997001E-5	9.994993E-5	9.994004E-5	9.994004E-5	0.245198	0.245198	9.994004E-5	0.245198	0.245198	0.245198	0.245198	0.245198	0.245198
0 - inf	9.998001E-5	9.998005E-5	9.99801E-5	9.997994E-5	9.996002E-5	9.997001E-5	9.994993E-5	9.994004E-5	9.994004E-5	9.998005E-5	9.998005E-5	9.994004E-5	9.998005E-5	9.998005E-5	9.998005E-5	9.998005E-5	9.998E-5	9.998E-5
Experience	294	81	24	23	33	7	3	2	2	0	0	1	0	0	0	0	0	0

1) Assemble the evidence



Enter evidence for one substance:

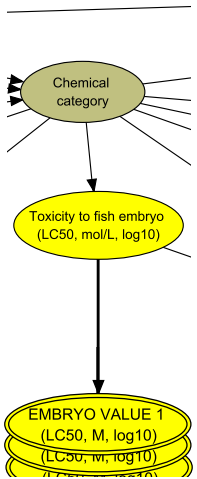
- Molecular weight (g/mol)
- Hydrophobicity (L/M/H)
- Mode of action (N/S/U)
- Algae (EC50, mg/L)
- Daphnids (EC50, mg/L)
- Embryo (LC50, mg/L)
- Gill cytotoxicity (EC50, mg/L)
- (Neurotoxicity EC50)

Built-in data processing:

- conversion from mg/L to mol/L
- log10 transformation

2) Weigh the evidence

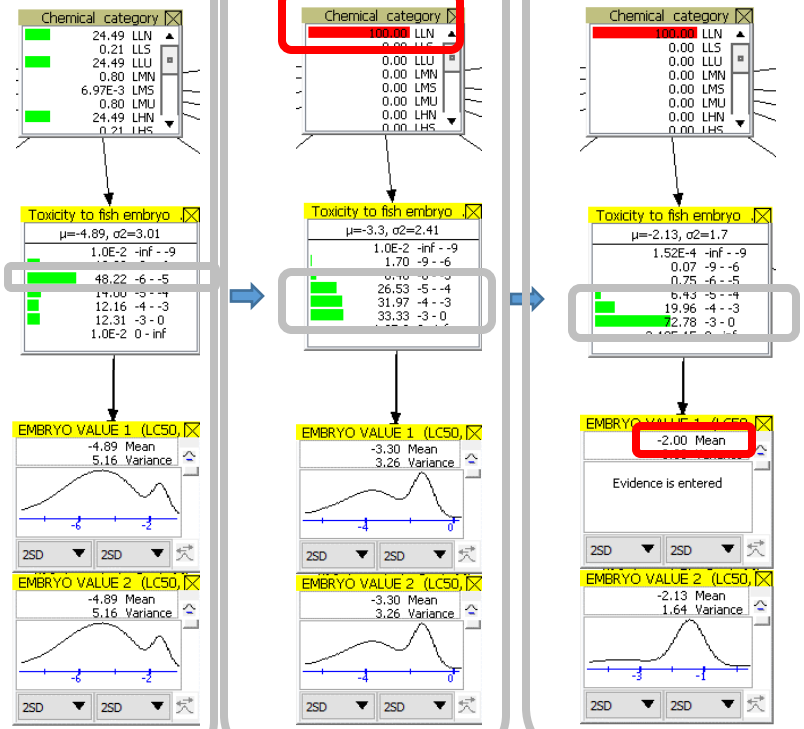
Example:
Embryo toxicity



i) Prior probability

ii) Info on chemical category
➔ updated probability

iii) Evidence: measured embryo toxicity
➔ updated probability



iv) More evidence
➔ updated probability
etc.

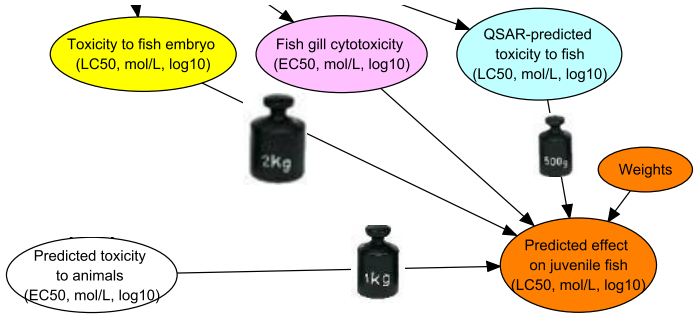
More consistent prior & evidence

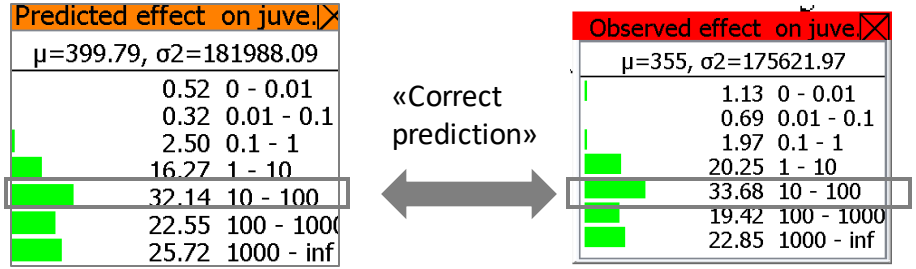
More consistent evidence values

narrower posterior probability distribution

higher **weight** for this line of evidence

3) Integrate & weight the lines of evidence





How to optimise the weighting of the LoEs?

- Optimisation of weights by **machine learning**?
  - Problem: requires >10^6 test cases
- We have max. 237 test substances
  - depending on the criteria for data selection
- Solution: define a limited set of scenarios with alternative weights
  - Evaluate model performance for alternatives
- Match the predicted vs. observed interval of LC_{50} for juvenile fish
  - Compare the most probable interval
  - How high precision is needed?

Precision vs. accuracy of the BN model predictions

HIGH ACCURACY,
HIGH PRECISION

Ideal situation

HIGH ACCURACY,
LOW PRECISION

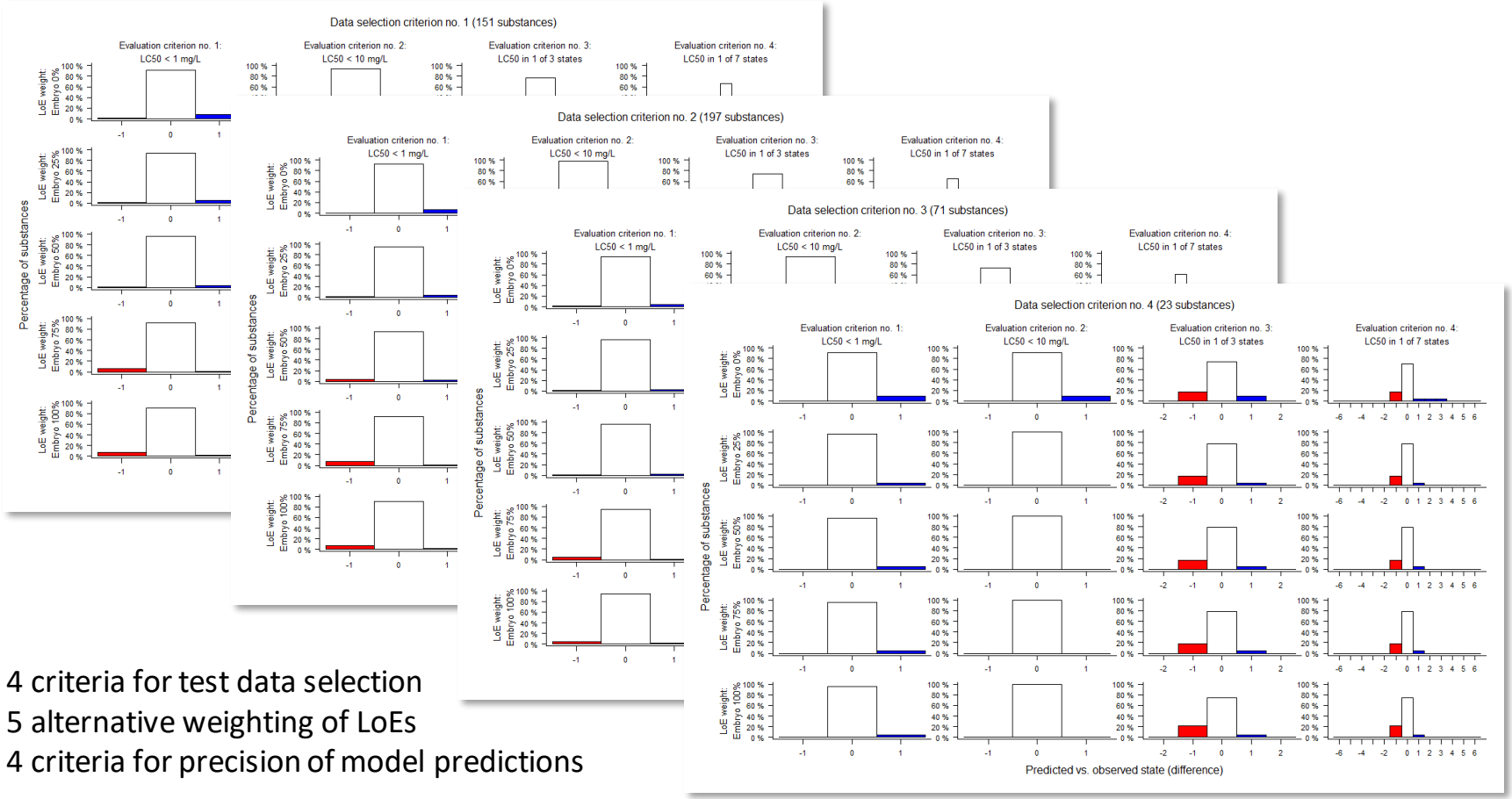
Realistic situation:
aim of our BN model

LOW ACCURACY,
HIGH PRECISION

Common situation:
point estimate
ignoring uncertainty

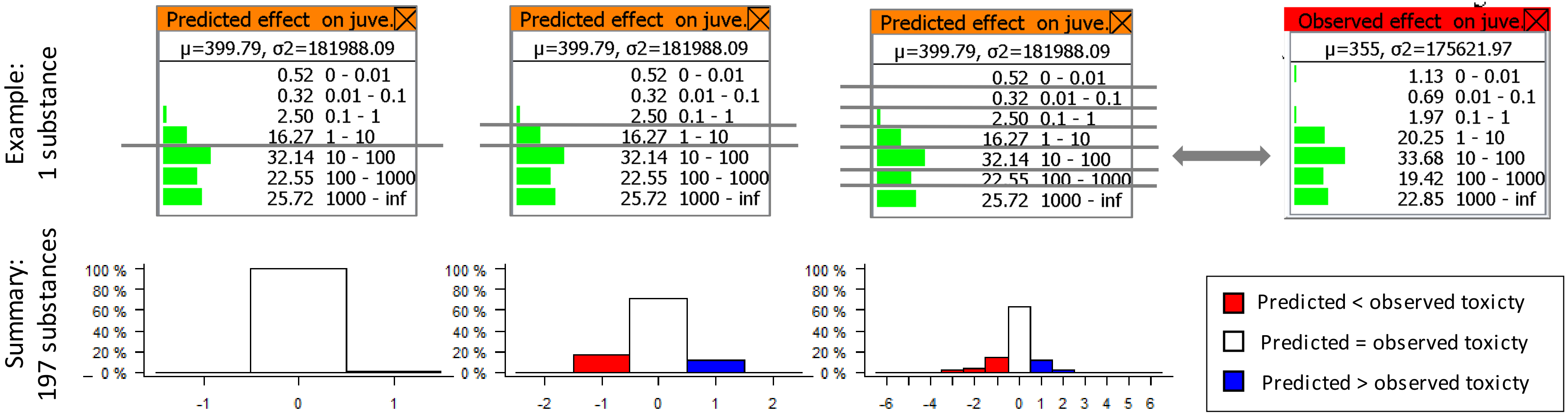
«It's better to be **roughly right**
than **precisely wrong**»

Scenarios for model evaluation



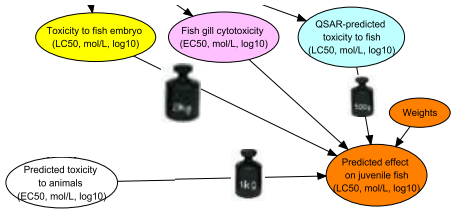
- 4 criteria for test data selection
- 5 alternative weighting of LoEs
- 4 criteria for precision of model predictions

The model’s success rate depends on the required **precision** of predicted toxicity

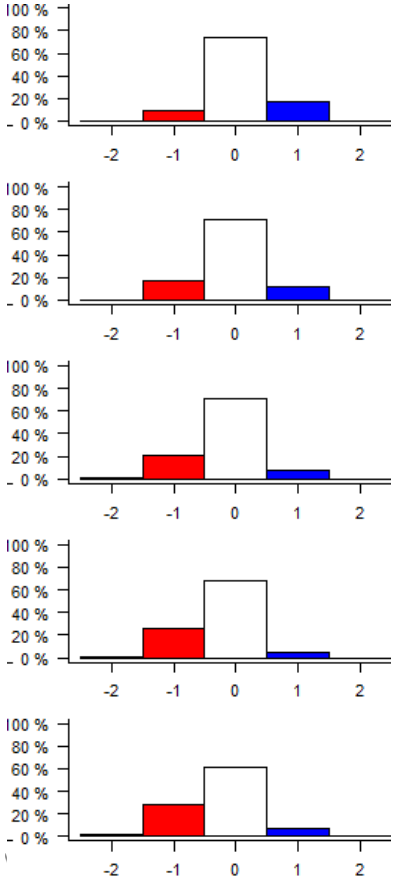


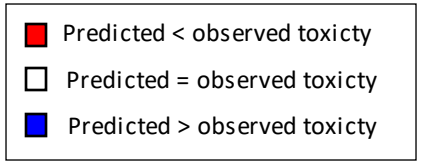
- Higher required resolution of predicted toxicity ➔ lower success rate
- To be decided by stakeholders

The model's success rate depends on the **weighting** of lines of evidence



Weight sceanario	Fish embryo	Algae & daphnids	QSAR fish
1	**0 %**	50.0 %	50.0 %
2	**25 %**	37.5 %	37.5 %
3	**50 %**	25.0 %	25.0 %
4	**75 %**	12.5 %	12.5 %
5	**100 %**	0 %	0 %





- Intermediate weight to Embryo (25-50%) ➔ highest accuracy
- Higher weight to Embryo ➔ more underestimation of acute fish toxicity

Conclusions

- Limited amount of test data (observed acute toxicity to juvenile fish)
  ➔ limited possibility of machine learning for this BN
  ➔ explore alternative approaches for training and testing
- The BN currently has a success rate of ca. 70-80 % of test substances, for predictions aggregated to 3 intervals (0-1, 1-10, 10-inf mg/L)
  - Balanced weighting of lines of evidence ➔ higher success
  - Lower resolution accepted for predicted toxicity ➔ higher success
- The BN-WoE approach is promising for supporting the use of fish embryo toxicity data instead of fish acute toxicity data.

Next steps

- Further exploration of model evaluation
  - Forthcoming larger test data set ➔ explore machine learning methods?
  - Compare the whole distributions of predicted vs. observed toxicity
- Incorporate additional lines of evidence
  - Gill cytotoxicity; neurotoxicity; metabolic activity (presentation 1.01.07)
- Better account for uncertainty and variability in data
  - Hierarchical Bayesian regression (presentation 1.01.07)
- Further development of demonstration model with web interface
  - See Q&A field for updated information
  - Feedback appreciated!

Thanks for your attention!

Contact:

jmo@niva.no

More information on the SWiFT project:

https://www.niva.no/swift

http://swift.hugin.com/

or visit the NIVA online stand at SETAC Europe 2021