Inclusion of Toxicity Information into Identification of Alerting Chemicals

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Our Concerns

How to include toxicity information into the identification of alerting chemicals?

- **Prioritising: Screening**
- **Risk assessment: As precise as possible**

How to obtain toxicity information?

- **Experimental data**
- **Predictive models**

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Toxicity Prediction

- Many different organisms and endpoints
- Ecotoxicology vs. human health
- Toxicity depends on mode of action

- Quantitative models limited, restricted
- Alternatives:
  Structural alerts, read-across
- Advances approaches to be explored

Baseline Toxicity

- Reversible damage of cell membrane
- Toxicity driven by hydrophobicity
- Quantitative estimation possible

  Linear relationship hydrophobicity / toxicity (logarithmic scale)

  $\log EC_{50} = A \bullet \log K_{ow} + B$

Excess Toxicity

- **Significantly higher toxicity than estimated by baseline toxicity equation**
- **Reactive or specific modes of action**

Note: High toxicity ~ low EC_{50}

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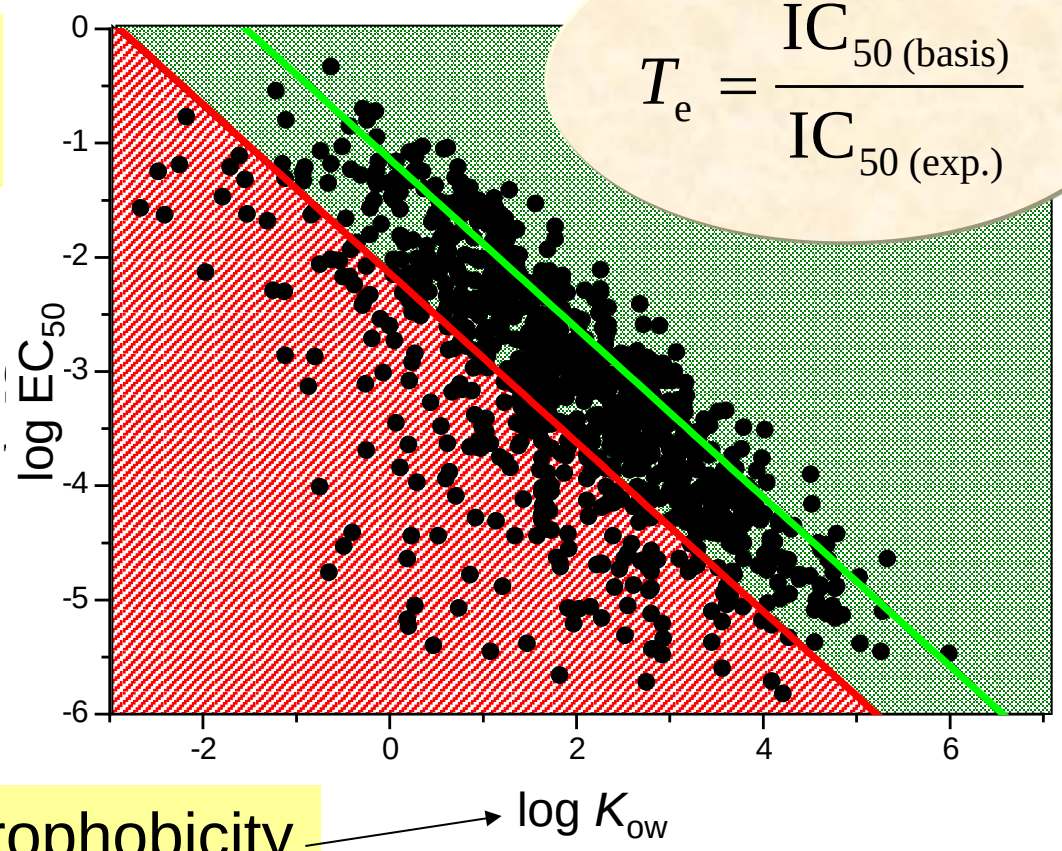
Baseline and Excess Toxicity

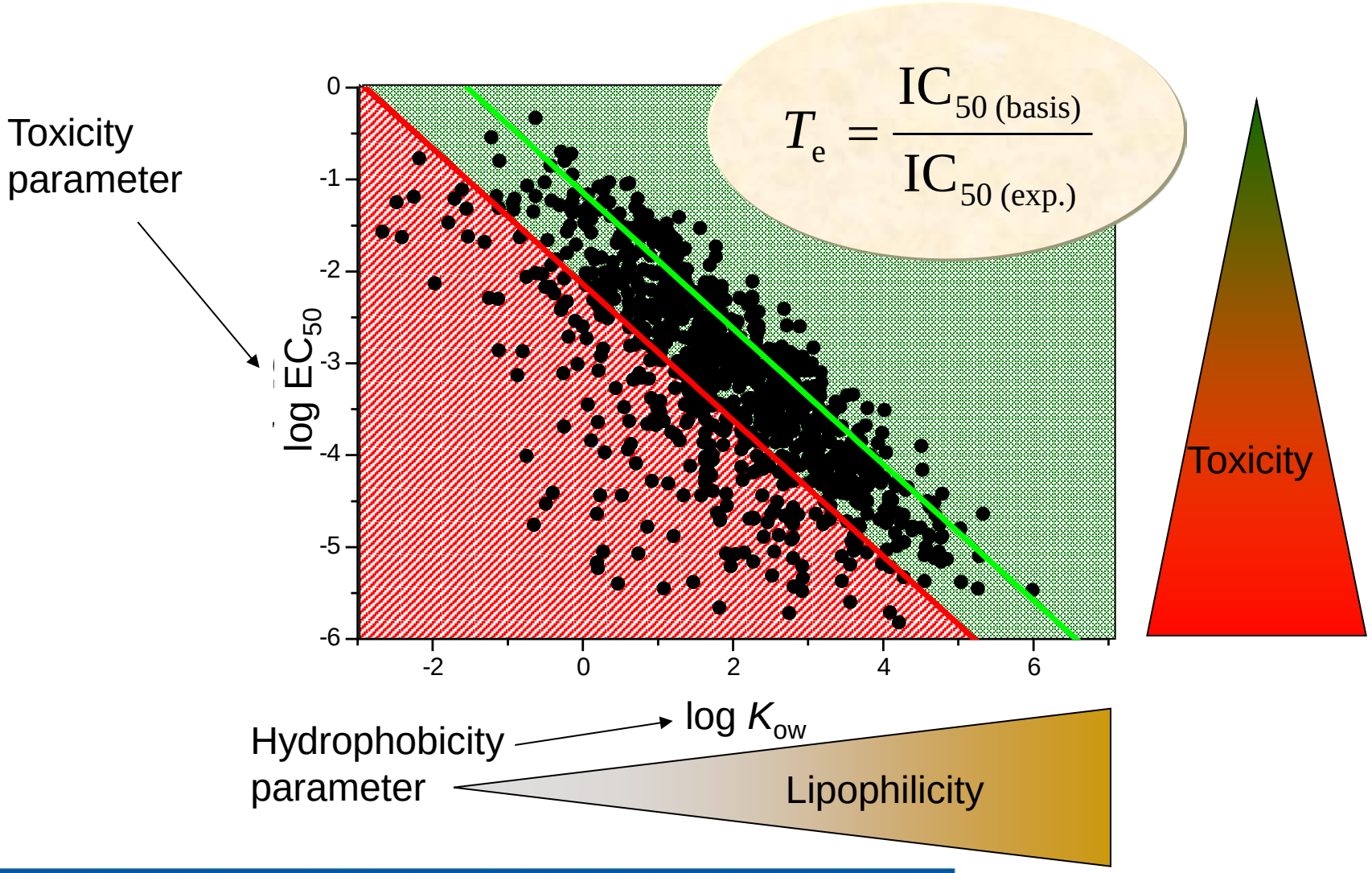
Toxicity parameter

$$T_e = \frac{IC_{50\ (basis)}}{IC_{50\ (exp.)}}$$



Hydrophobicity parameter

Baseline and Excess Toxicity



Baseline and Excess Toxicity

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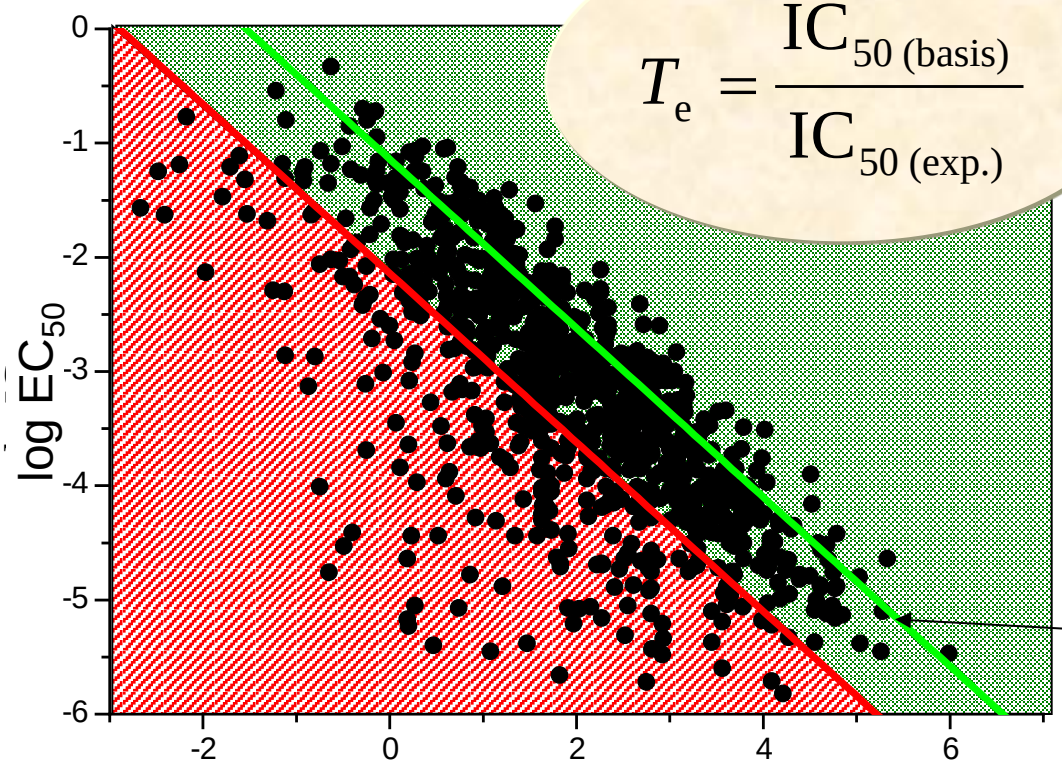
Toxicity parameter



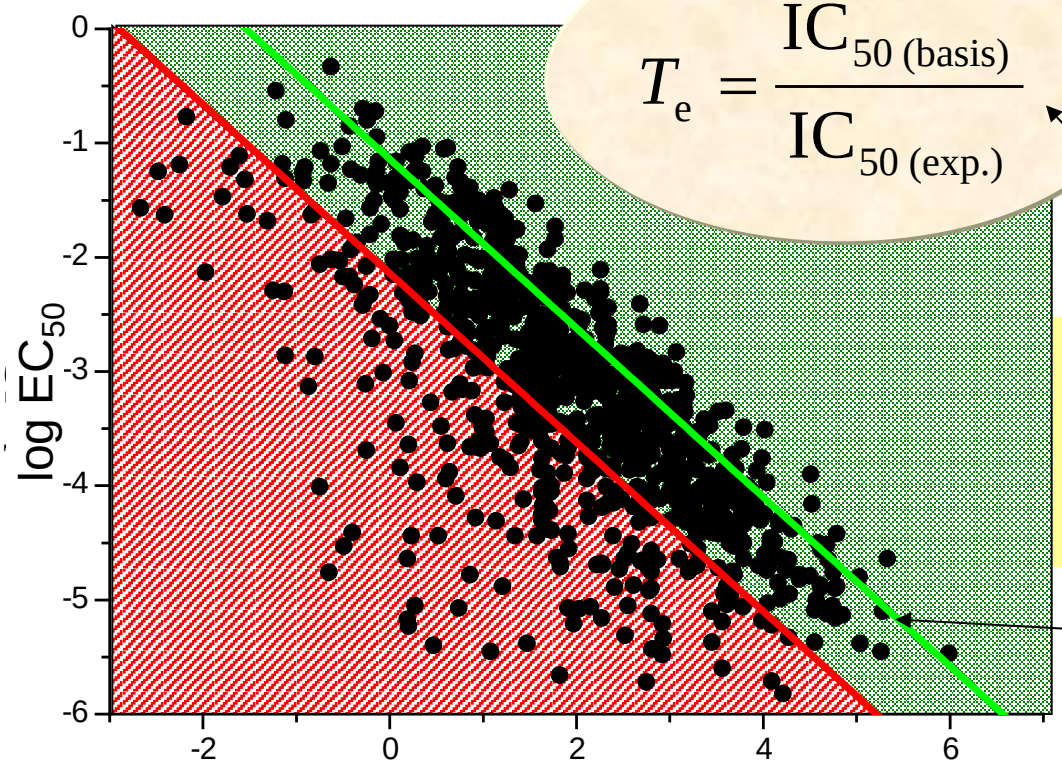
Baseline toxicity

Hydrophobicity parameter

Baseline and Excess Toxicity

Toxicity parameter

$$T_e = \frac{IC_{50\ (basis)}}{IC_{50\ (exp.)}}$$

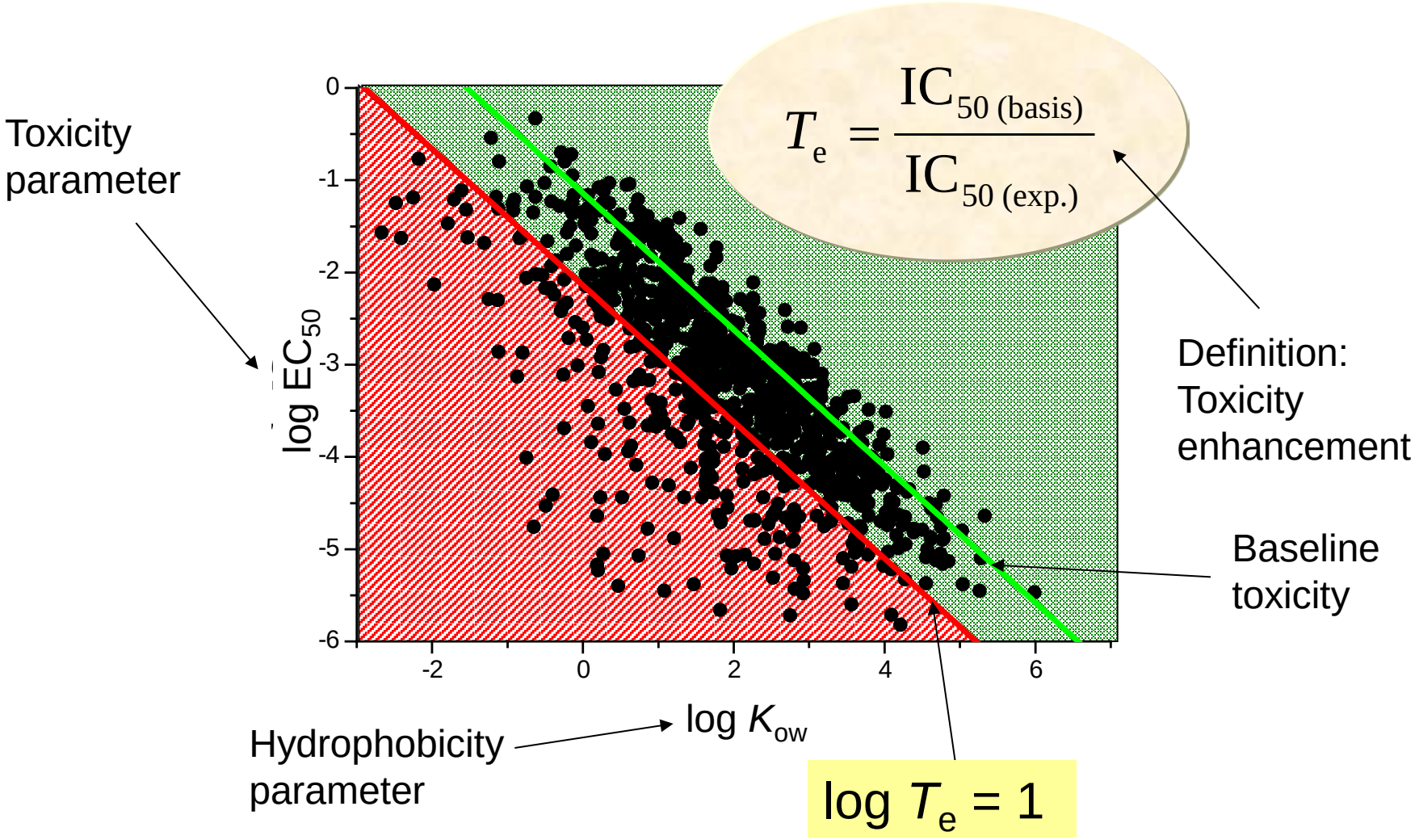


Definition:
Toxicity enhancement

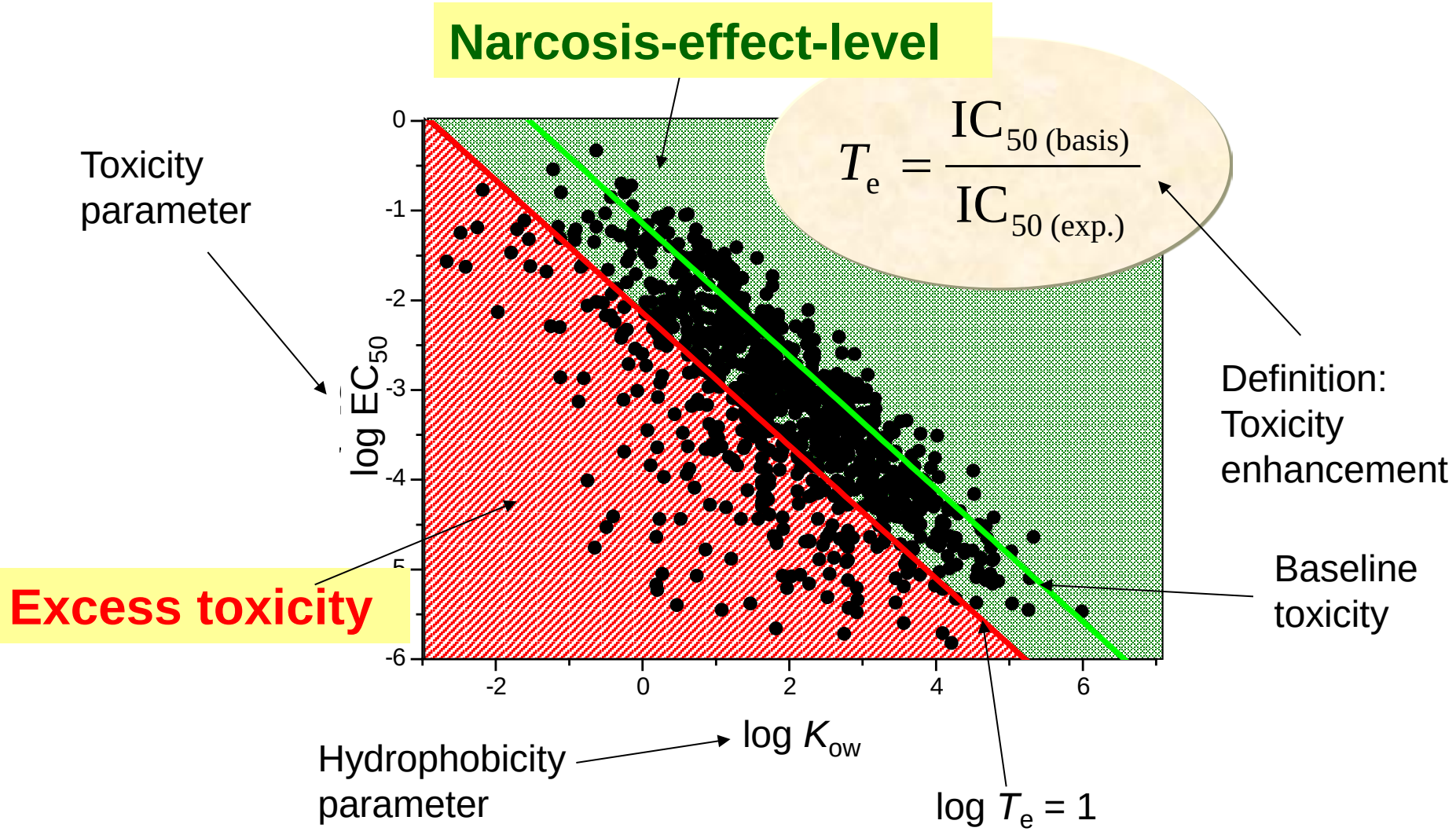
Baseline toxicity

Hydrophobicity parameter

Baseline and Excess Toxicity



Baseline and Excess Toxicity



Structural Alerts for Predicting Aquatic Excess Toxicity

Hypothesis

Molecular **reactivity** related to **excess** toxicity

General Approach

Reactive **functional groups** as basis for excess toxicity model

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New Structural Alert Model for Fish

23 Structural Alerts for Excess Toxicity

T_e (Toxicity Enhancement) Threshold

- Log LC_{50} ≤ log LC_{50}, baseline **– 1**

Training Set

- Validated LC_{50} (fathead minnow) for **693 cpds**

Data Sources

- **Duluth** database (*n* = **526**)
  ECOTOX/Aquire database (*n* = **170**)

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Structural Alert Model for Fish: Model Performance

Fathead minnow *n* = 693

Narcosis-Effect-Level : No structural alert

Good prediction power (95%)

Excess Toxicity: At least 1 of 23 structural alerts

Good prediction power (90%)

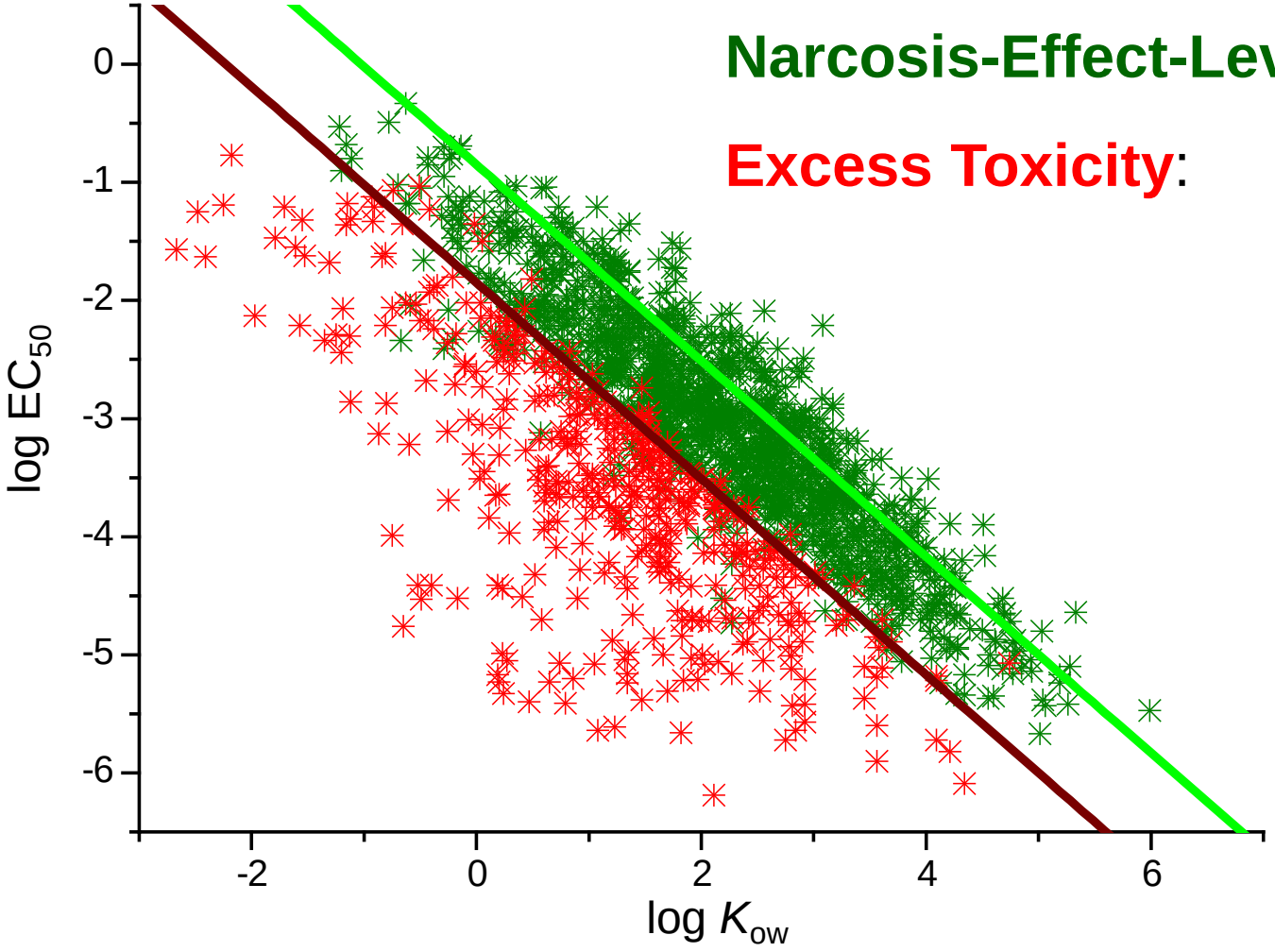
EINECS Compounds: Structural Alerts for Excess Toxicity

Fathead minnow:
Acute Toxicity, 96-h exposure, log LC_{50} (*n* = 72520)

less strict dom.	*all cpds*	*not strictly out of domain*	*in domain*
Alert	12630	7954	**3153**
No alert	59890	35313	**16065**
No result	0	29253	**53302**

→ **Prediction for (only) 60%,**
with 49% narcosis-level, and 11% excess-toxic

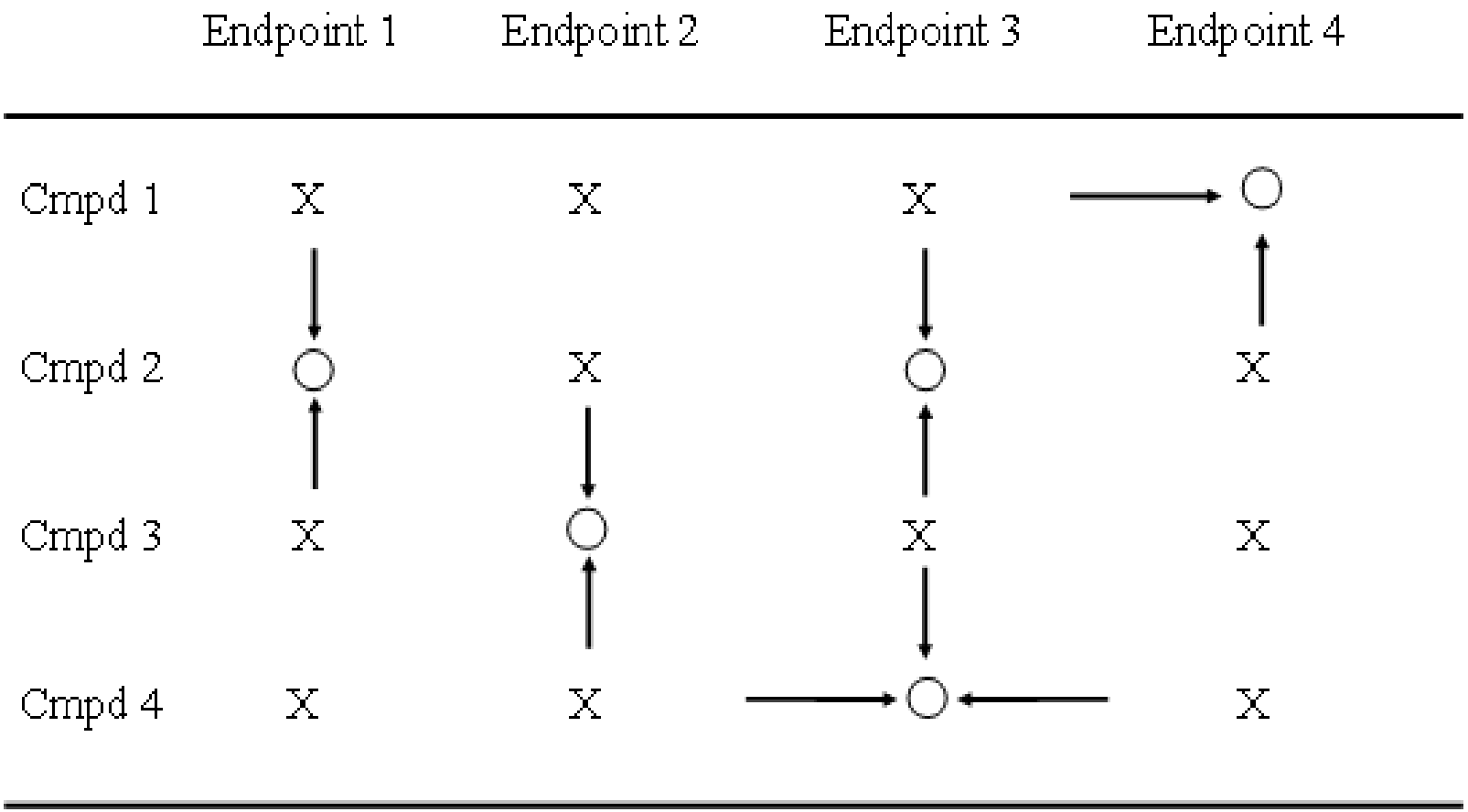
Predicitivity SA model *T.pyriformis*



Narcosis-Effect-Level: 96%

Excess Toxicity: 91%

Read-across


Endpoint 1
Endpoint 2
Endpoint 3
Endpoint 4
Cmpd 1
Cmpd 2
Cmpd 3
Cmpd 4
X

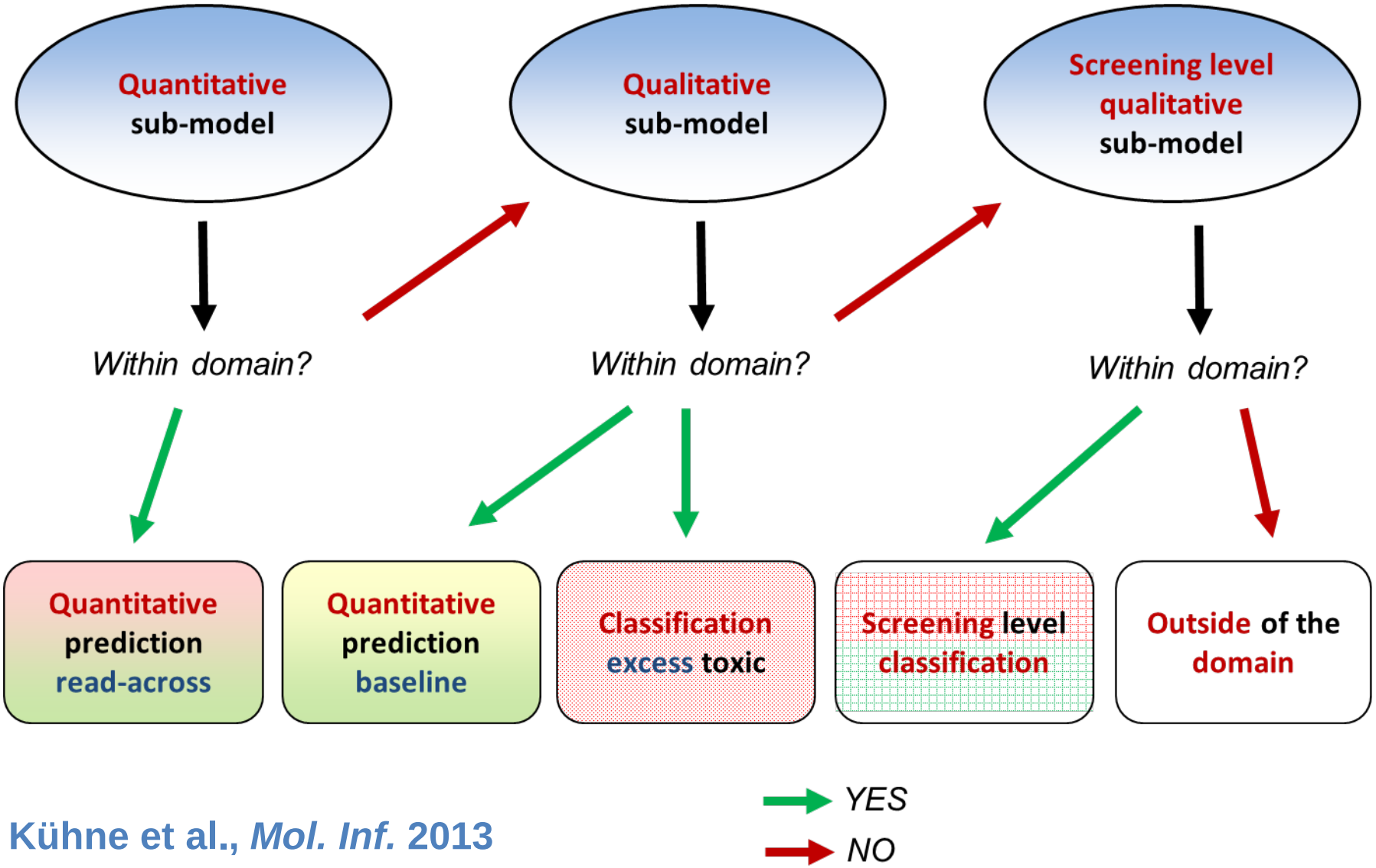
Fish Toxicity: Read-across

Fathead Minnow:
Acute Toxicity, 96-h exposure, log LC_{50} (*n* = 692)

	*n*valid	r^2 LOO	q^2 LOO	*rms* LOO	*bias*	*mne*	*mpe*
Similarity Threshold							
No	692	0.73	**0.72**	**0.73**	0.03	-2.31	4.29
Moderate	419	0.78	**0.76**	**0.60**	0.00	-2.92	3.99
High	230	0.84	**0.87**	**0.43**	-0.01	-1.34	1.73

Schüürmann et al., *EST* 2011

Daphnid Toxicity: Decision Tree

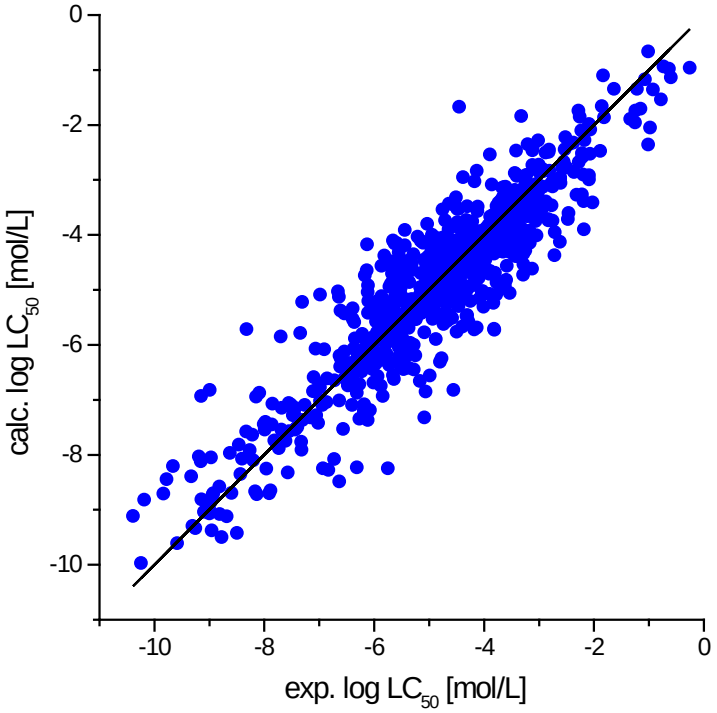


Kühne et al., *Mol. Inf.* 2013

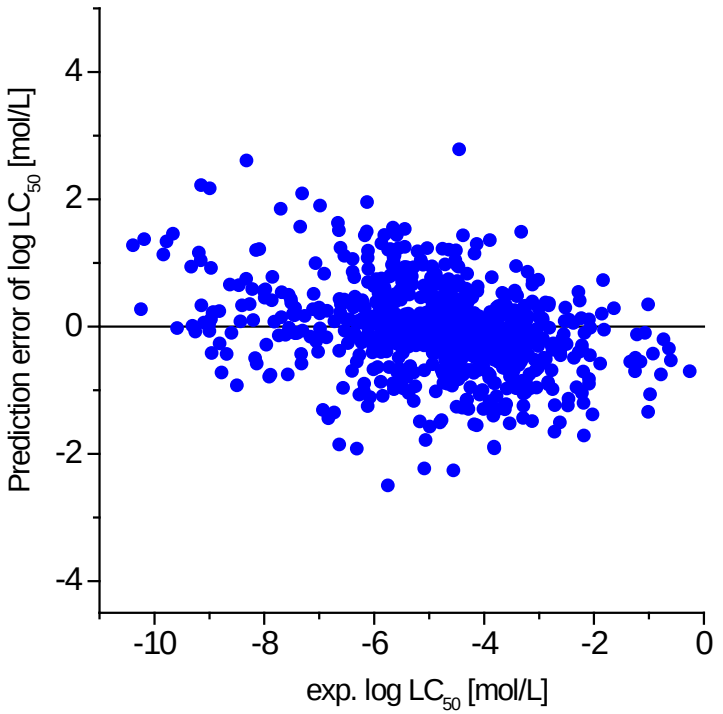
Daphnid Toxicity: Quantitative Model

Log LC_{50} (mol/L)

Calculated vs experimental



Residues vs experimental



n = 759 r^2=0.83 q^2=0.83 *rms* = 0.68 *bias* = -0.04

Kühne et al., *Mol. Inf.* 2013

Daphnid Toxicity: Qualitative Model

- **Excess toxicity prediction**

  ***n* = 50, 47 of them (94%) correctly classified**

- **Screening level classification (*n* = 271)**

  Narcosis level

  Sensitivity 86% Predictivity 82%

  Excess toxicity

  Sensitivity 78% Predictivity 83%

  Concordance 82%

- **Out of domain *n* = 285 (21%)**

Kühne et al., *Mol. Inf.* 2013

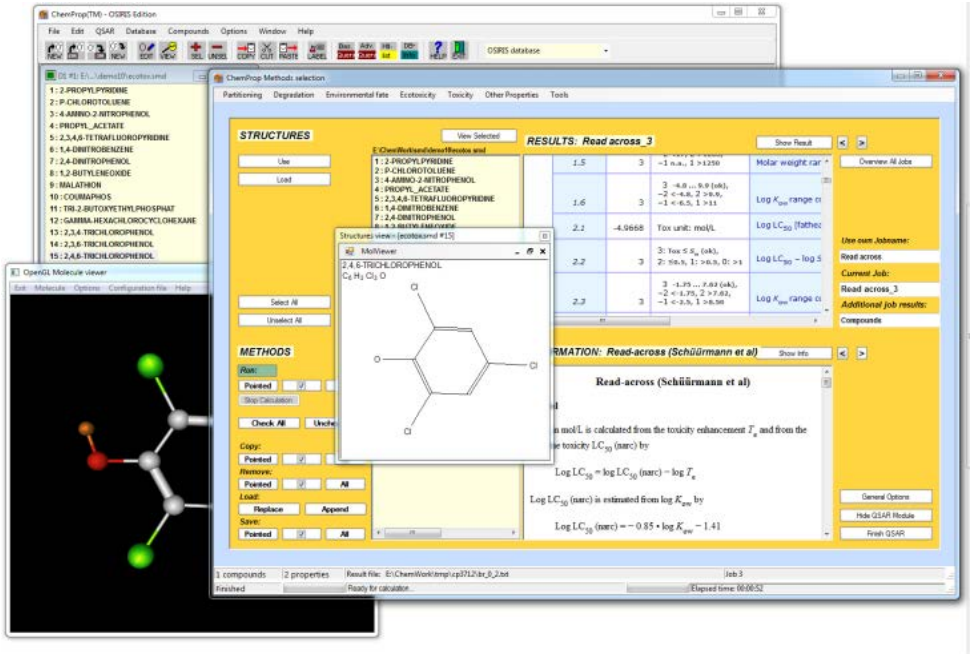
Fish Toxicity: Consensus Modeling for Excess Toxicity Probability

Read-across; **ECOSAR**; **Structural alerts**

Model T_e pred.	*N*	*Pred. prob. excess*	*exp. excess*
+ + +	75	100%	95%
+ + −	29	80%	21%
+ − +	21	98%	76%
− + +	38	99%	89%
+ − −	33	22%	12%
− + −	48	27%	8%
− − +	23	83%	83%
− − −	427	3%	3%

QSAR Software

- **ChemProp (UFZ)**



- **ToxTree, OECD Toolbox, EPISUITE**
- **Commercial software (e.g. DEREK, Multicase, …)**

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Beyond LC_{50}

Nominal concentrations do not reflect amount of chemical at target site

- **Physiologically based pharmacokinetics (PBPK) or PBTK**
- **Replace concentrations by activities**

Response from cell up to ecosystem

- **Adverse Outcome Pathways (AOP)**

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Integrating Approaches

- **Integrated Testing Strategies (ITS)**

- **Integrating knowledge across human and environmental risk assessment**

Exposome

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Take Home Messages

- Toxicity data limited
- Quantitative models typically restricted to Mode of Action
- Structural alerts useful screening tool
- QSAR models complemented by read-across
- Consensus of different approaches preferable
- Crucial: Applicability domain

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