QSAR integrated risk assessment – prioritization within the four CADASTER classes

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Conclusions

Uncertainty in QSAR predictions

- can aid to verify experimental results
- can be used to generate conservative (safer) hazard and risk assessments
- may have an impact on decision making
- can aid to evalute policy strategies
- can help us to identify knowledge gaps
  - including learning more about chemistry :)

The need to consider QSAR uncertainty needs motivation

- from a knowledge oriented perspective
- by consideration of net-benefits to increasing knowledge
- through CAse-studies

Why consider uncertainty in QSAR predictions?

"There must be greater appreciation of QSAR "quality" and the appropriateness of their use, both in terms of the chemical domain described, and in terms of the precision of the estimates that are produced."

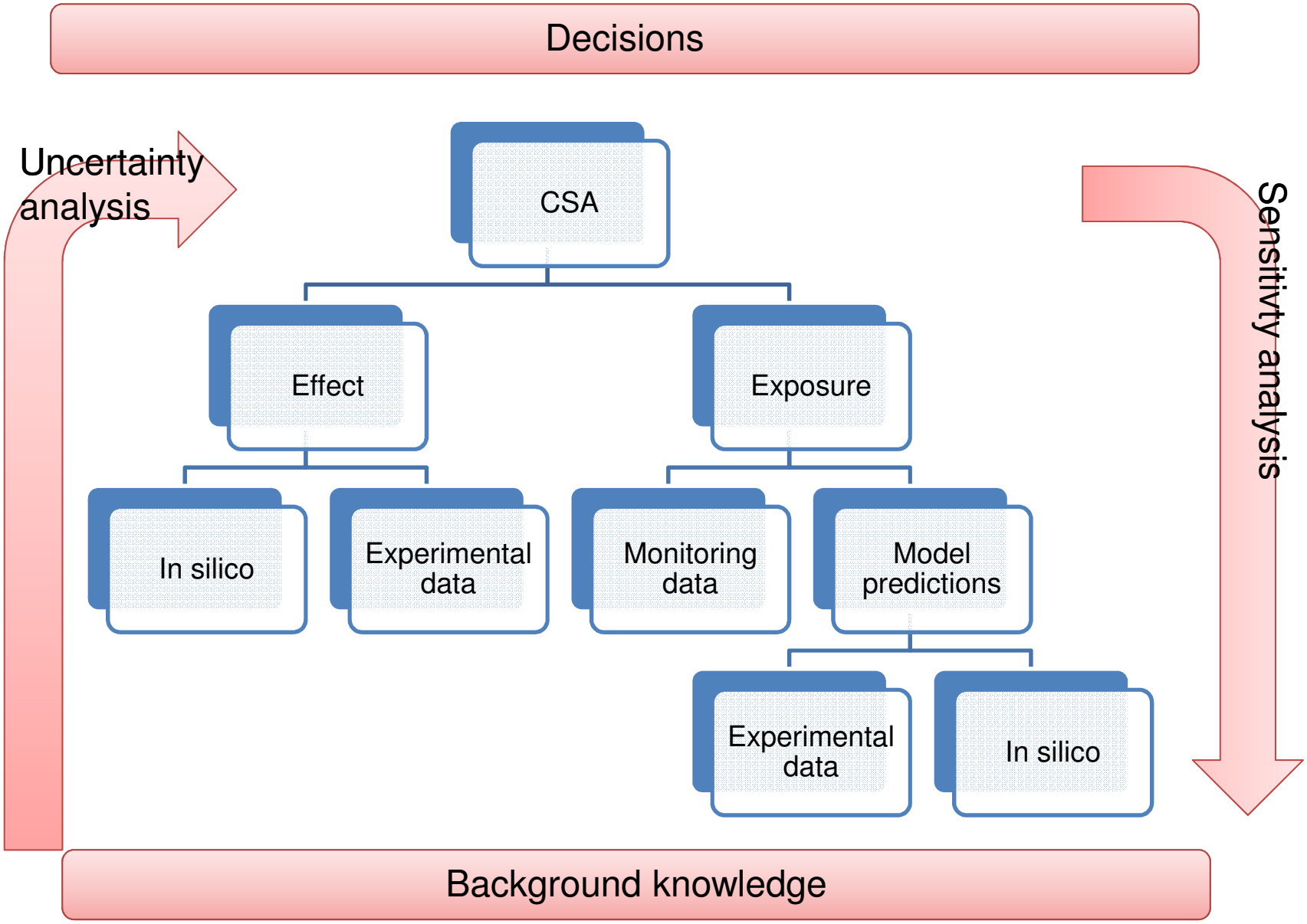
Cronin et al 2003 Environmental Health Perspectives

Decision making

- Single hazard or risk assessment
- Prioritization of chemicals

Examples

- Uncertainty analysis
- Value of information analysis

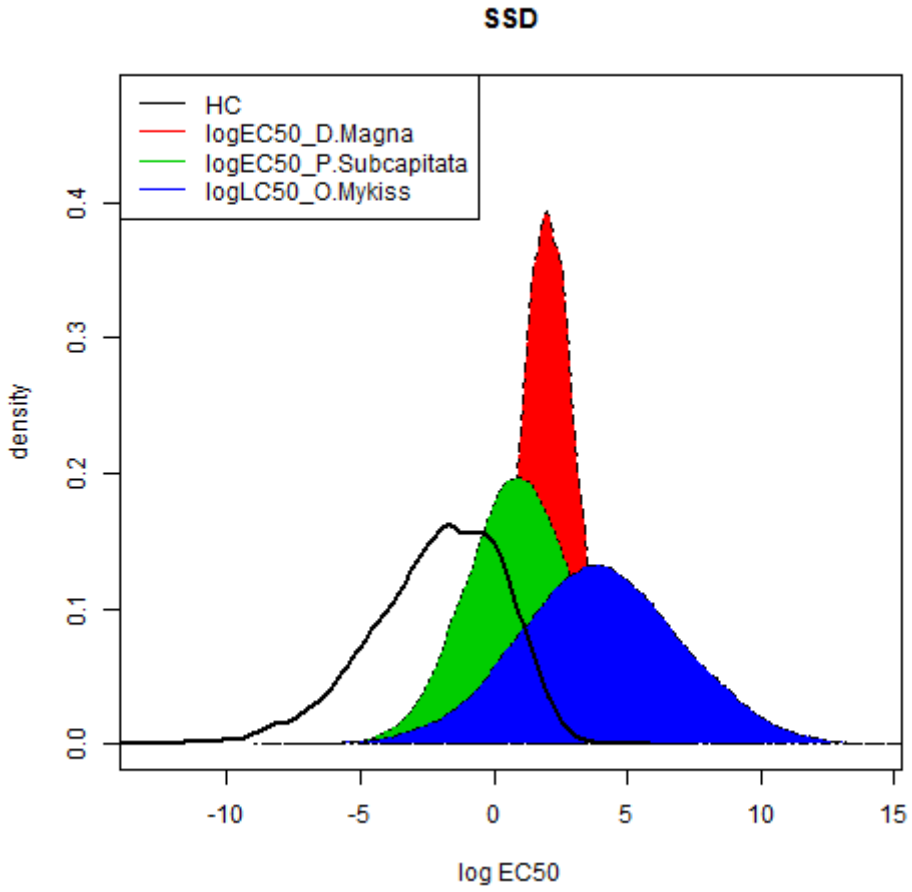

Decisions
Uncertainty analysis
CSA
Effect
Exposure
In silico
Experimental data
Monitoring data
Model predictions
Experimental data
In silico
Sensitivity analysis
Background knowledge

Uncertainty analysis in hazard assessment

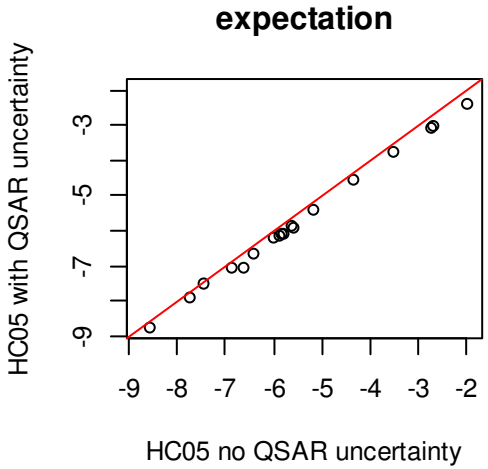
Triazoles
BDE
PFC
Fragrances

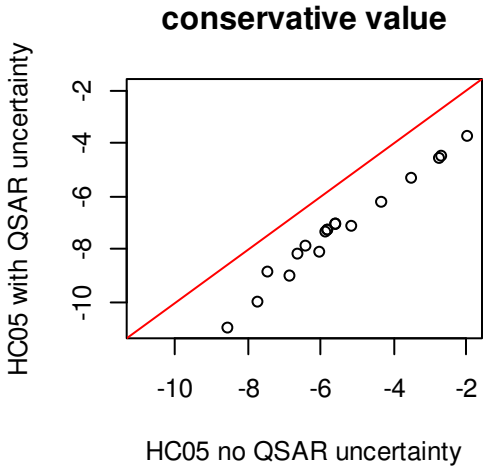
QSAR intergrated SSD

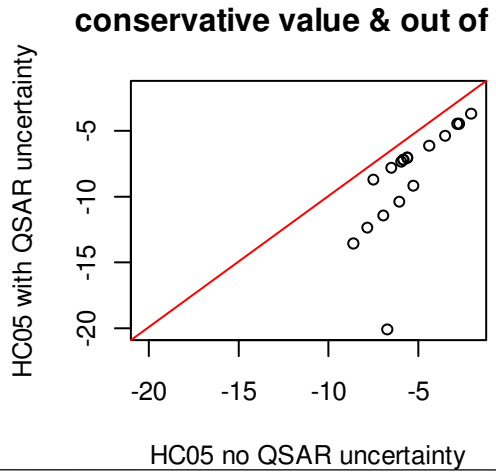
- MC sample for predictive distributions from each species QSAR on aquatic toxicity
- for each species-triplet - derive an hazardous concentration



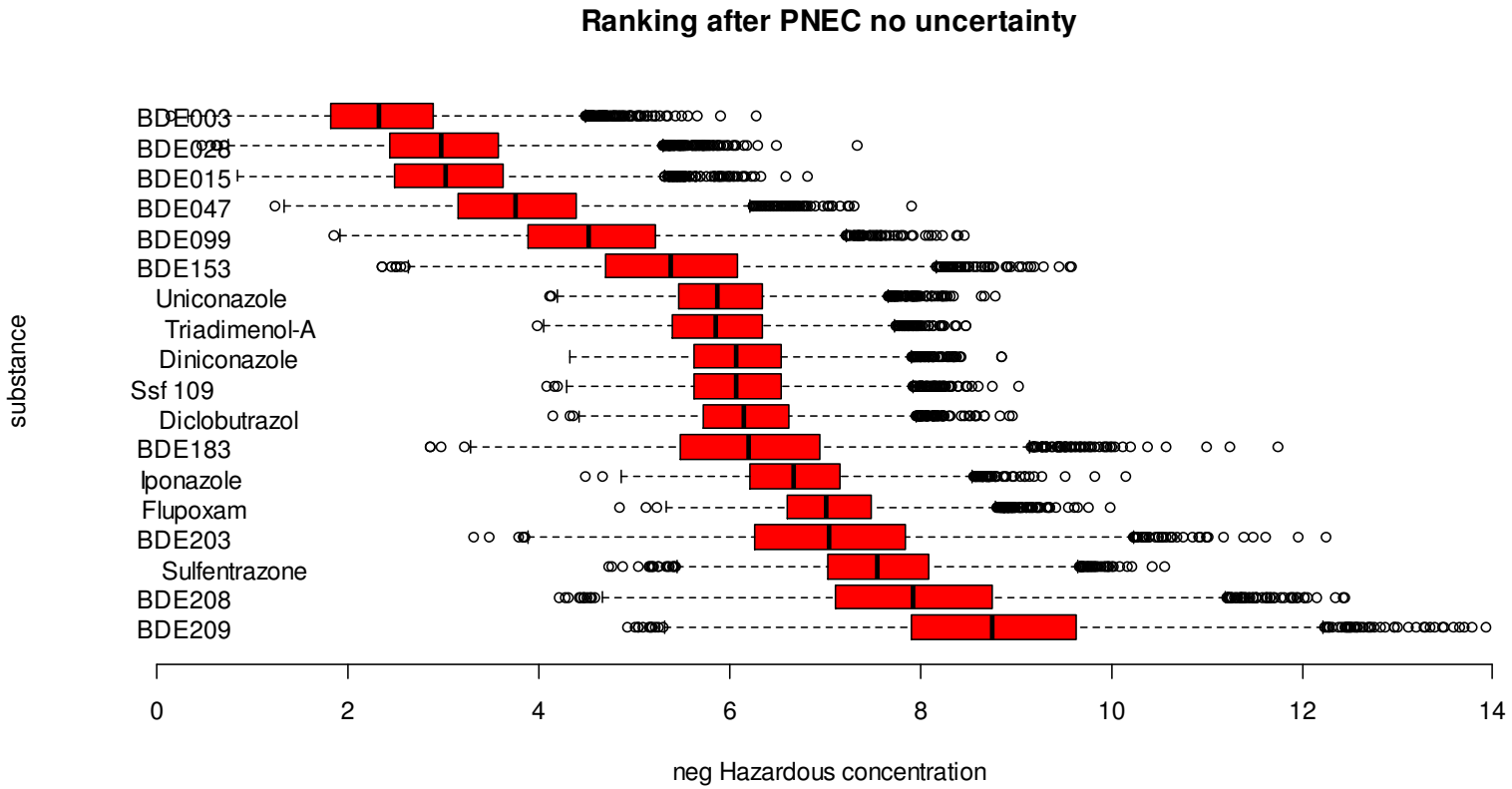
Uncertainty -> Rank after hazard



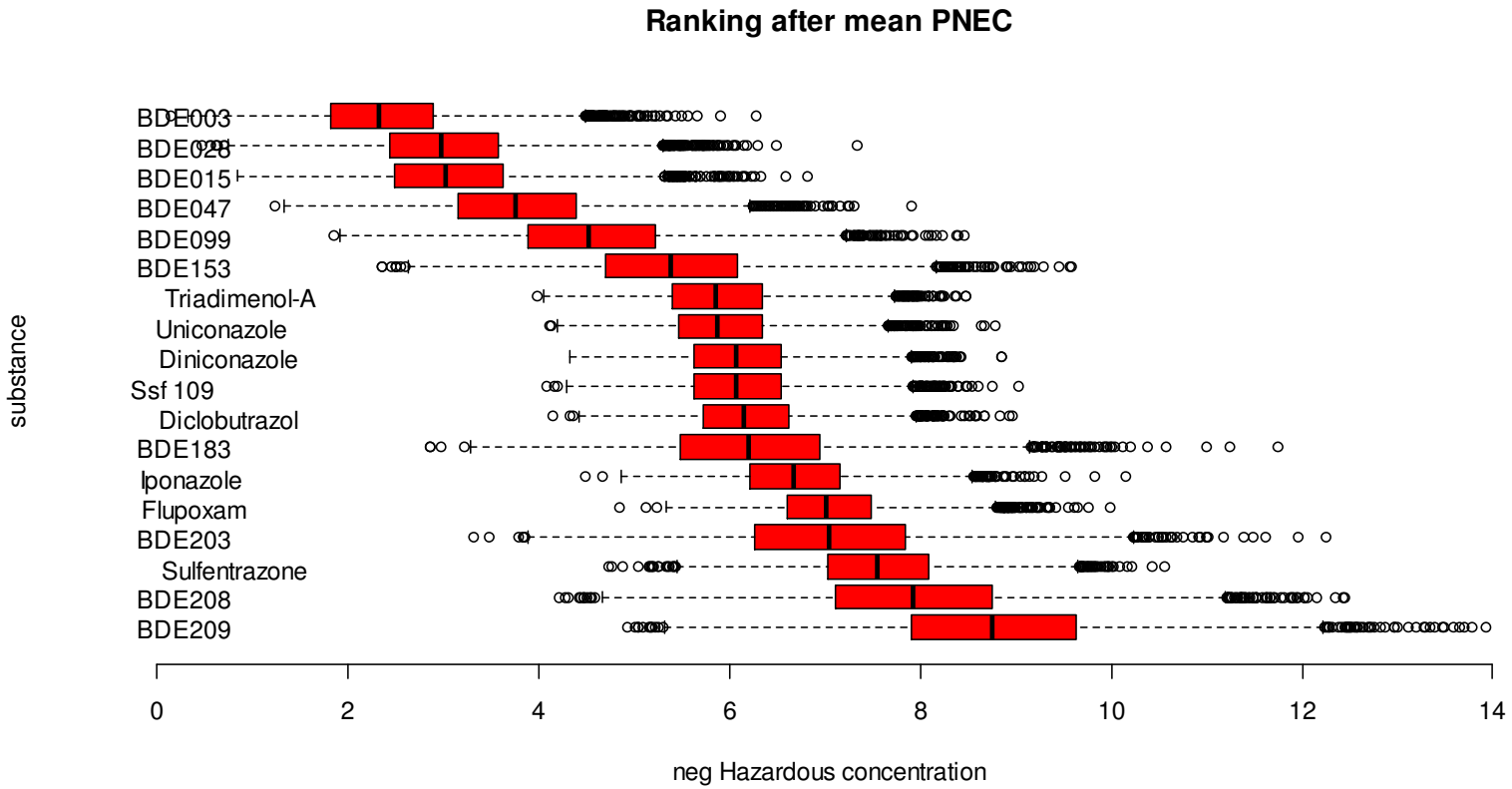




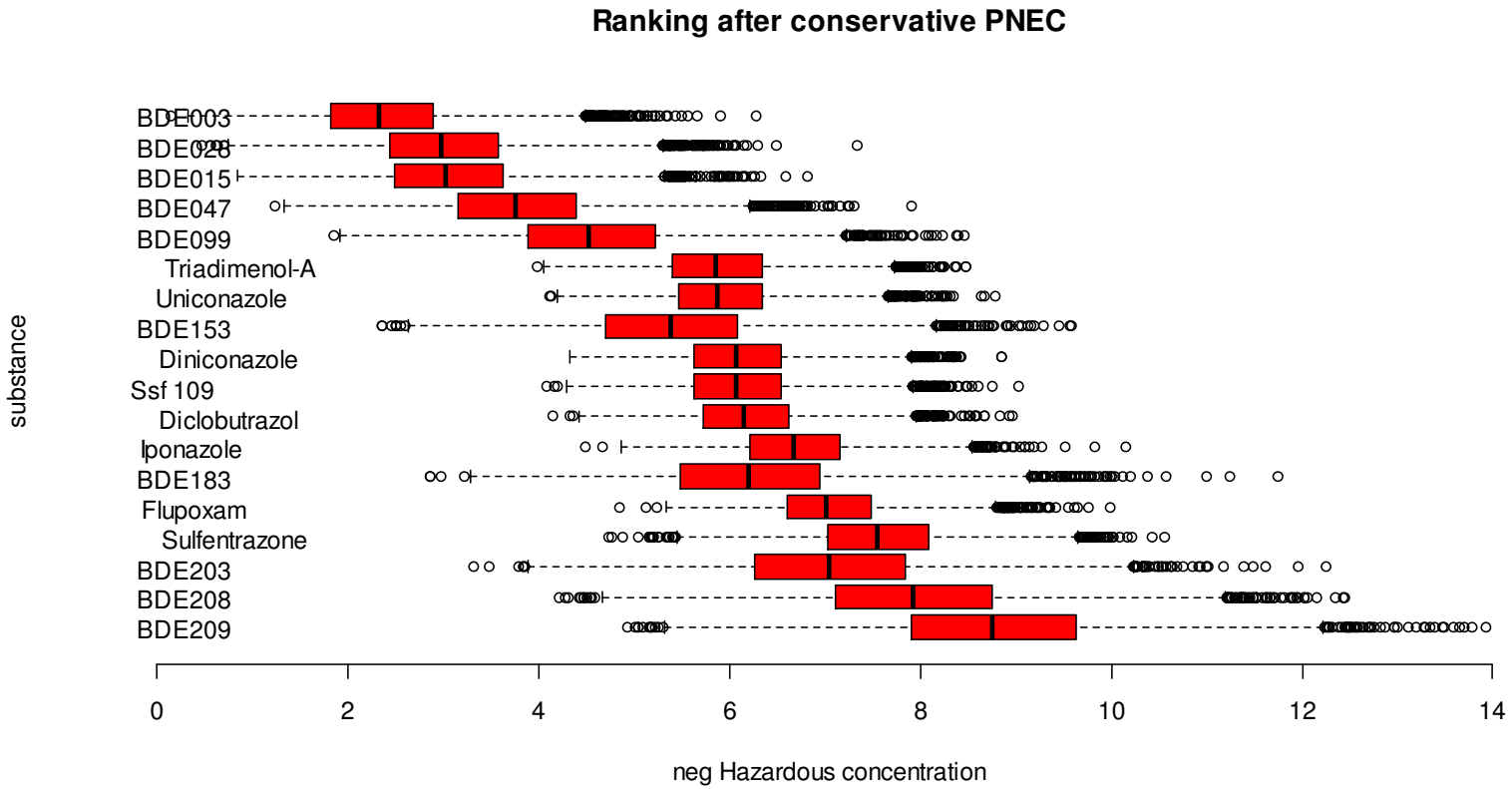
Rank after PNEC with no uncertainty



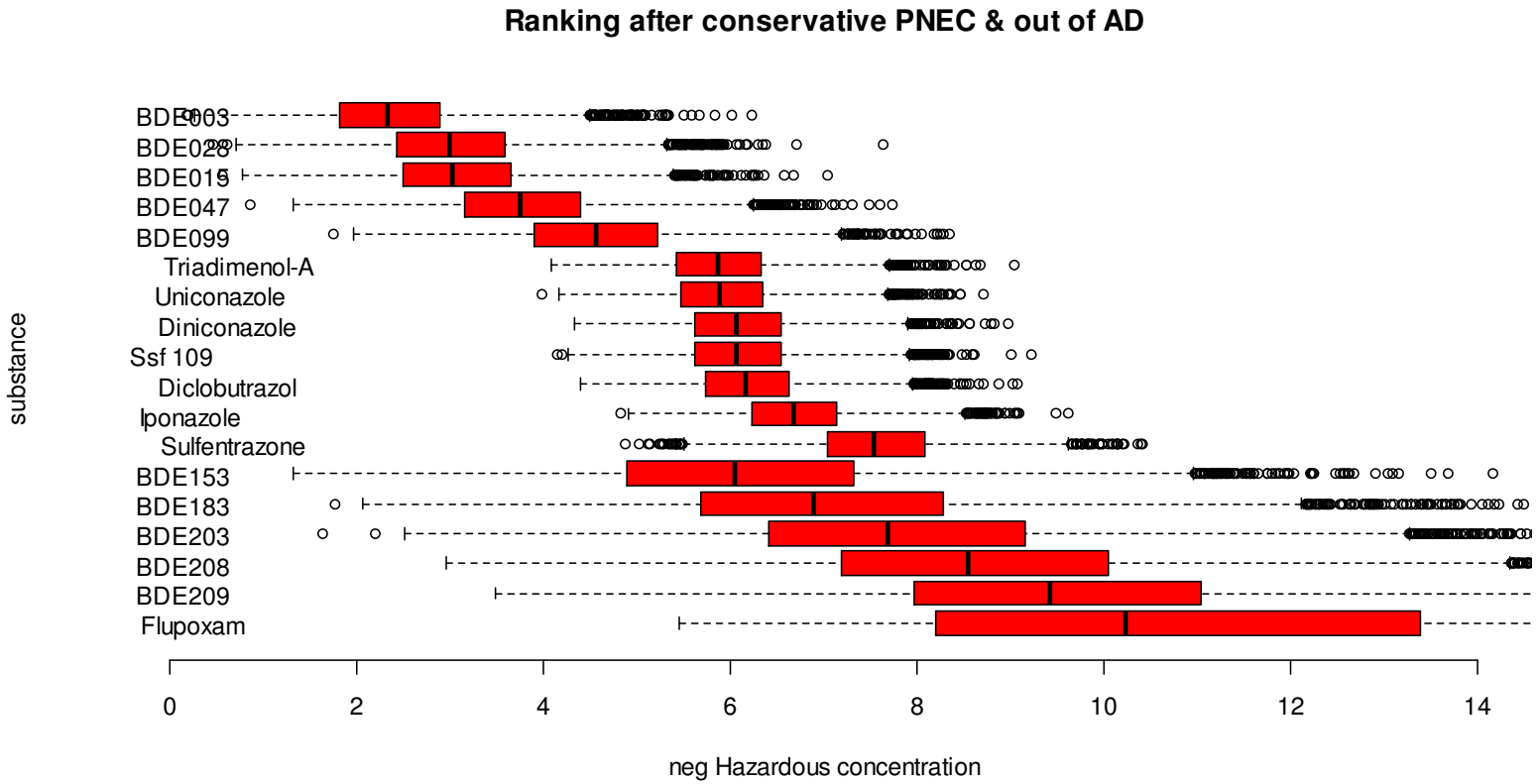
Rank after expected PNEC



Rank after conservative bound



Rank after conservative bound & extra due to out of AD



Rank to improve information

Losses needs to be compared to benefit from using the substance and reduced cost for regulatory decision making, saved animal lives.

Value of information analysis considers

- expected loss of making wrong decisions
- error of type I and II
- net-benefit of a decision

- Classification
- Non-classification

Value of information analysis given Maximum Permissable Load

Action alternatives

- Load (production of a chemical)

Decision rule

- Maximize load keeping risk below safety margin

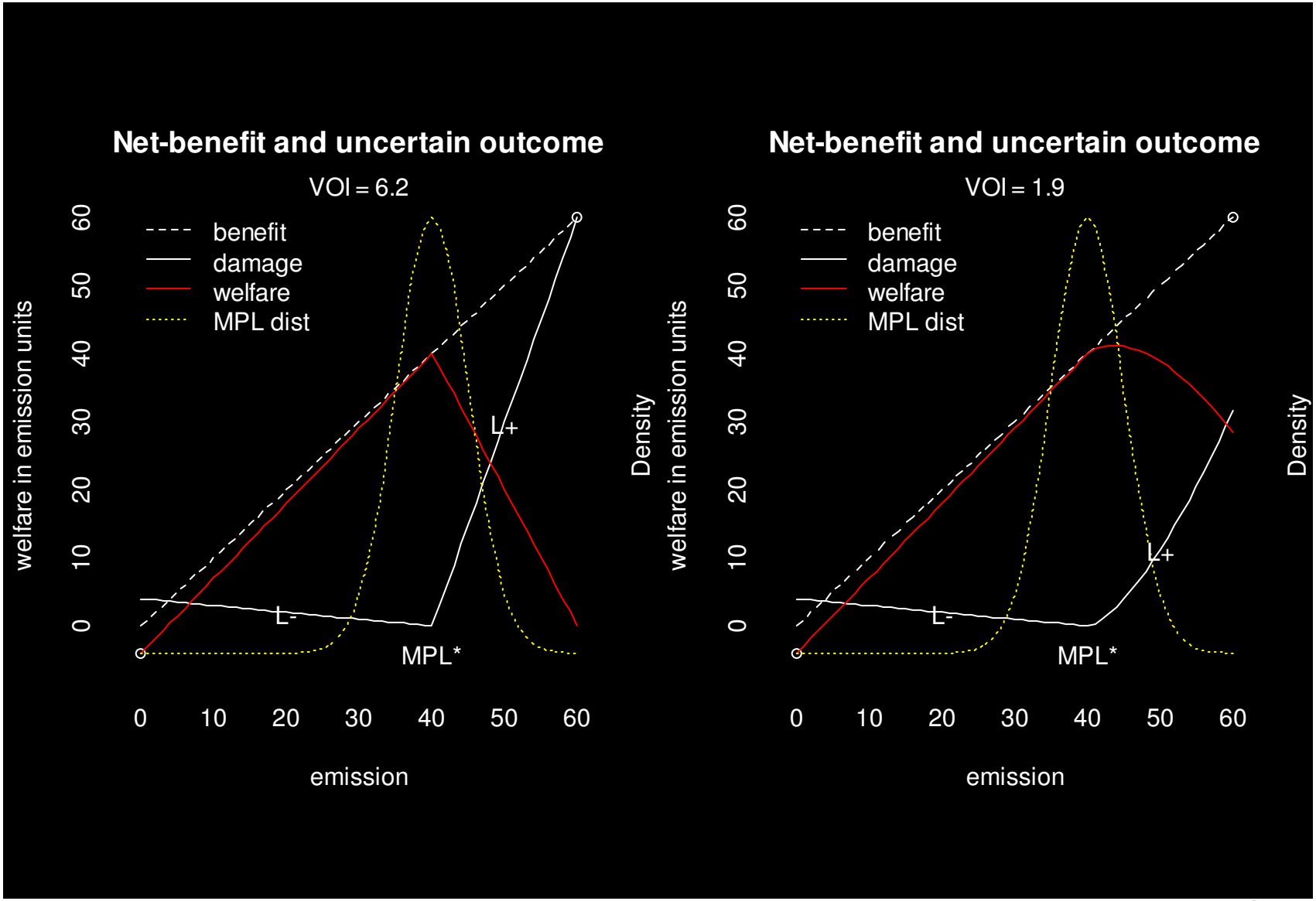
Uncertain outcome

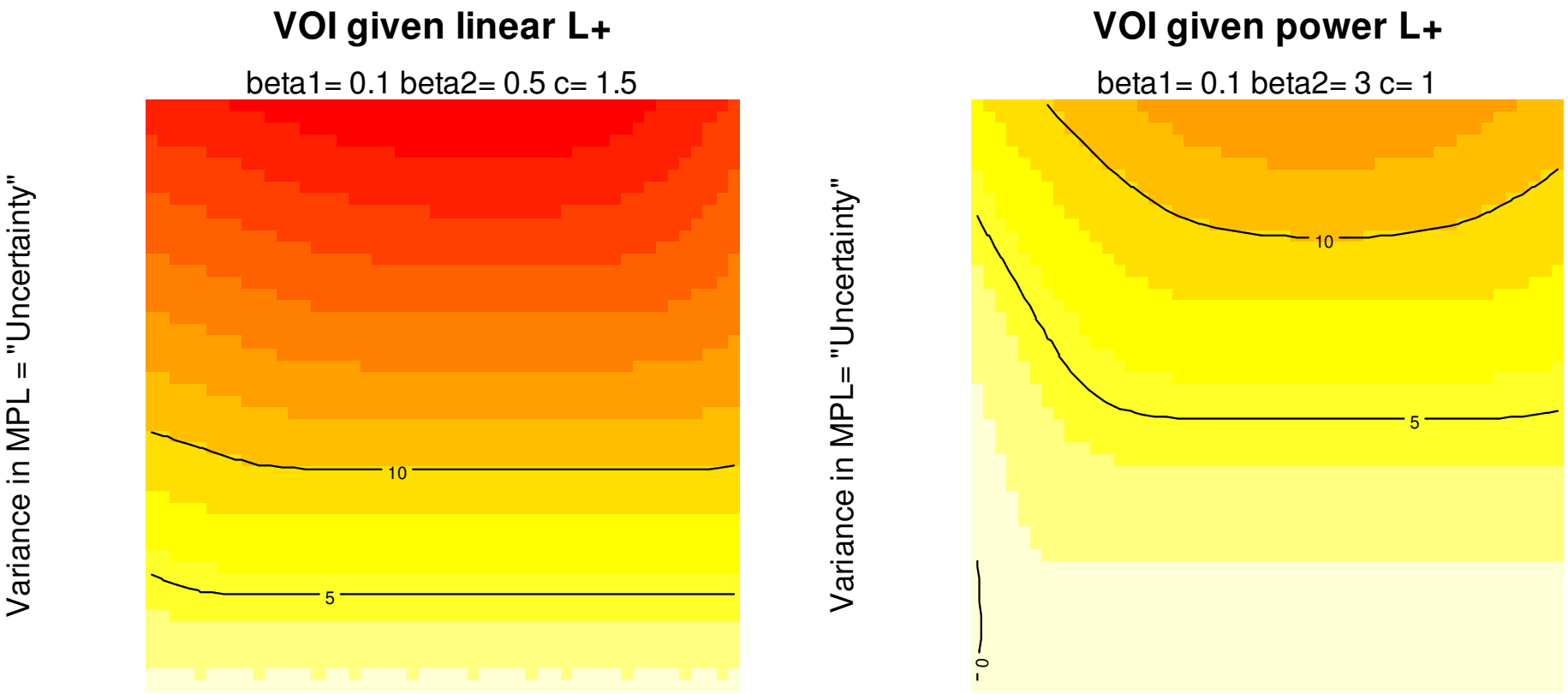
- Maximum permissable load (MPL) from a probabilistic risk assessment

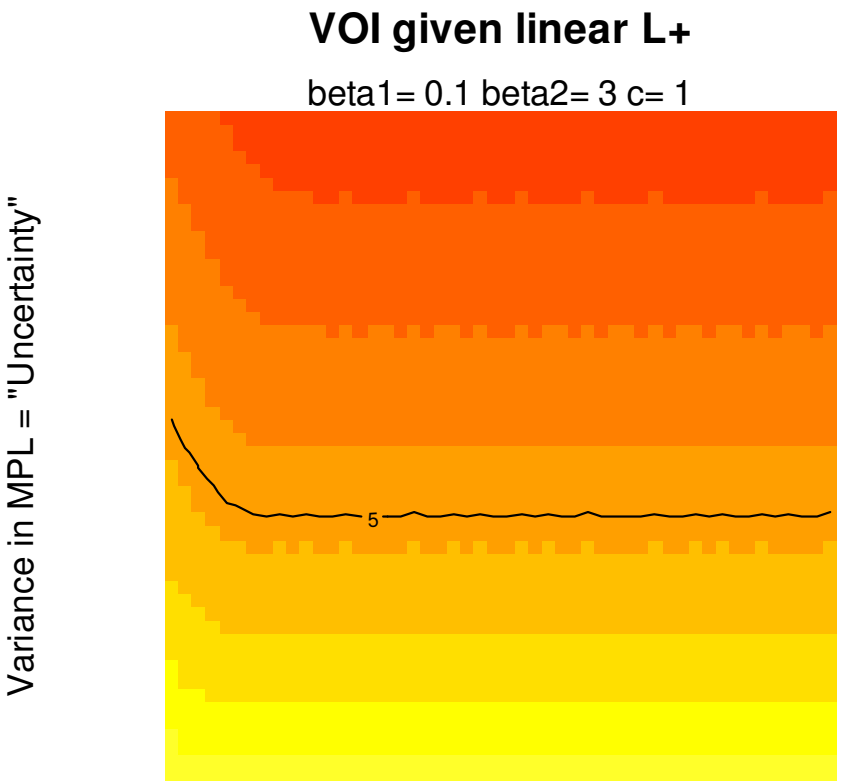
Loss function

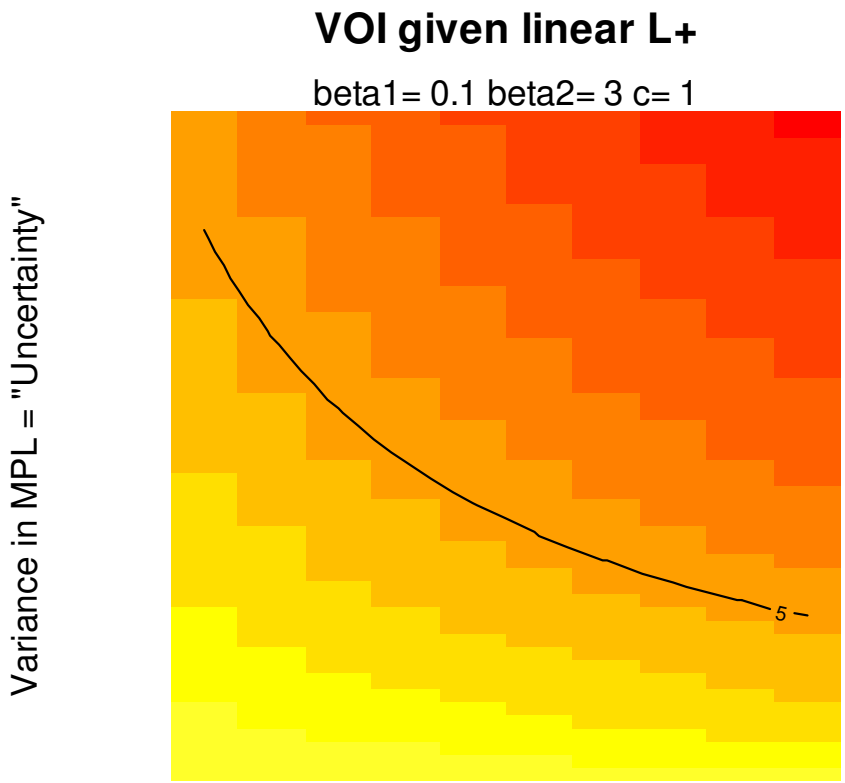
L^- : Loss of missed opportunities following an over-estimated risk

L^+ : Loss due to undesireable damages resulting from an over-production following an under-estimated risk


Net-benefit and uncertain outcome
VOI = 6.2
benefit
damage
welfare
MPL dist
L+
L-
MPL*
welfare in emission units
Density
emission
0
10
20
30
40
50
60
Net-benefit and uncertain outcome
VOI = 1.9
benefit
damage
welfare
MPL dist
L+
L-
MPL*
welfare in emission units
Density
emission


VOI given linear L+
beta1= 0.1 beta2= 0.5 c= 1.5
Variance in MPL = "Uncertainty"
10
5
MPL under perfect info = "1/Risk"
VOI given power L+
beta1= 0.1 beta2= 3 c= 1
Variance in MPL= "Uncertainty"
10
5
0
MPL under perfect info = "1/Risk"


VOI given linear L+
beta1= 0.1 beta2= 3 c= 1
Variance in MPL = "Uncertainty"
5
MPL under perfect info = "1/Risk"

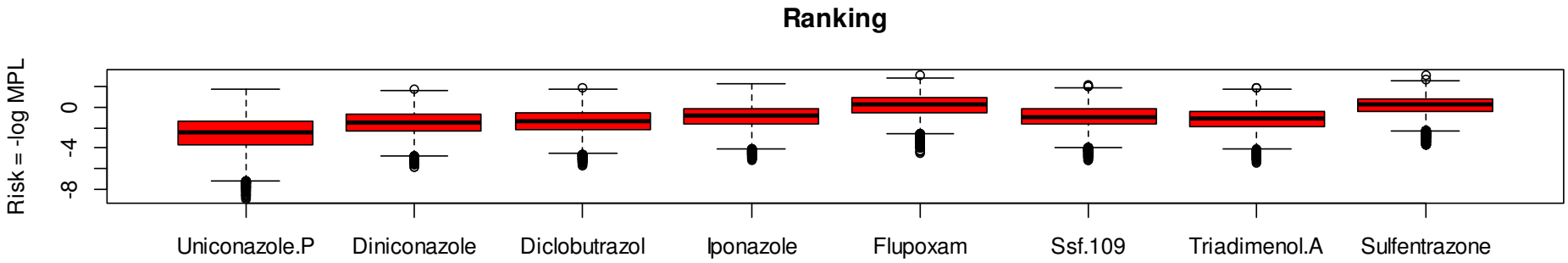

VOI given linear L+
beta1= 0.1 beta2= 3 c= 1
Variance in MPL = "Uncertainty"
5
Extent of extrapolation from AD

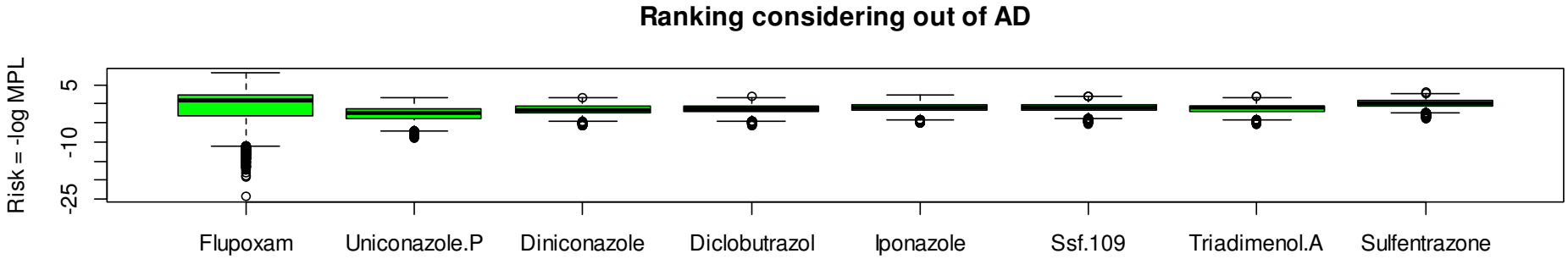
Guide further testing – several substances

Test those believed to be of largest risk?

with the largest uncertainty?

those that provide additional QSAR data for building better QSARs?

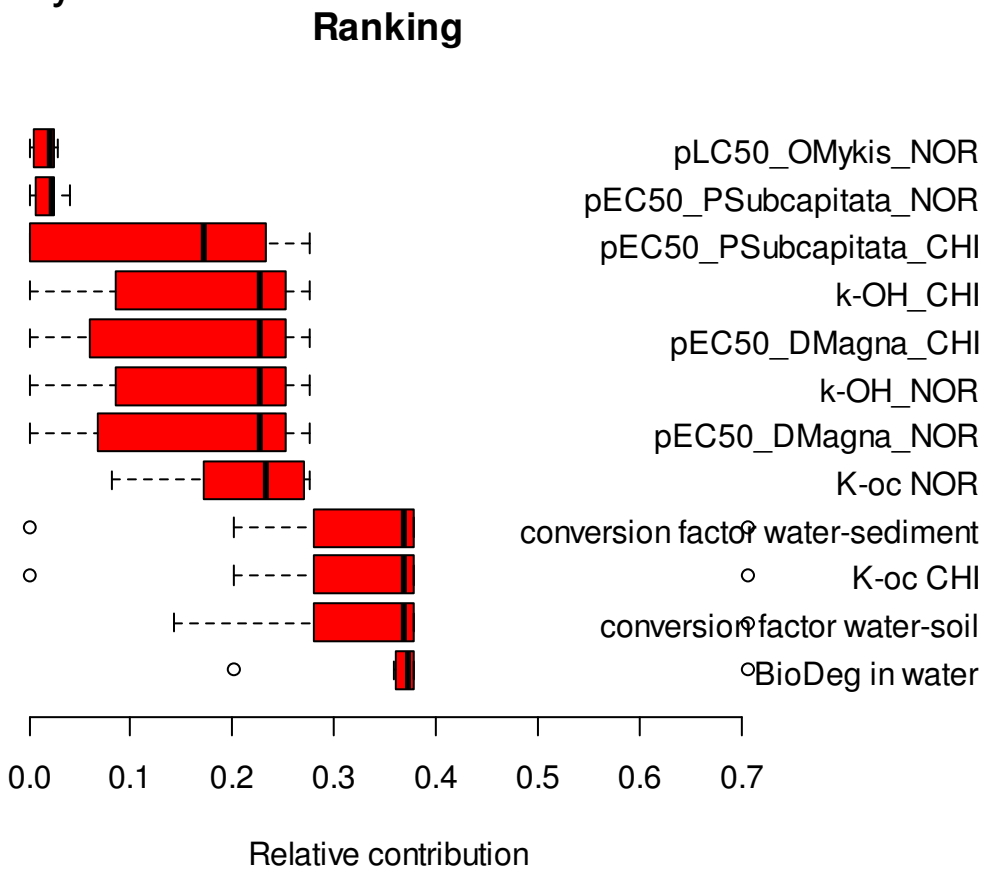




Guide further testing – which endpoints to test

Which input parameters have the largest contribution to overall uncertainty?

Sensitivity analysis – relative contribution of QSAR uncertainty



Conclusion 2

There are lessons to be learnt by considering
uncertainty from QSAR predictions in hazard and risk assessment

by showing impacts on decision making

Linnæus University