QSAR integrated risk assessment – prioritization within the four CADASTER classes

Ullrika Sahlin PhD
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 evaluate 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

Linnaeus University
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
Uncertainty analysis in hazard assessment

Triazoles
BDE
PFC
Fragrances

QSAR integrated 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

expectation

conservative value

conservative value & out of AD

HC05 no QSAR uncertainty
Rank after PNEC with no uncertainty

Ranking after PNEC no uncertainty

BDE009
BDE028
BDE047
BDE099
BDE153
Uniconazole
Triadimeno-A
Diniconazole
Ssf 109
Diclobutrazol
BDE183
Ipazone
Fluoxam
BDE203
Sulfentrazone
BDE208
BDE209

neg Hazardous concentration
Rank after expected PNEC

Ranking after mean PNEC

Substances:
- BDE009
- BDE153
- Triadimenol-A
- Uniconazole
- Diniconazole
- Ssf 109
- Diclobutrazol
- Iponazole
- Flupoxam
- BDE203
- Sulfentrazone
- BDE208
- BDE209

neg Hazardous concentration
Rank after conservative bound

Ranking after conservative PNEC

- BDE009
- BDE028
- BDE015
- BDE047
- BDE099
- Triadimeno-A
- Uniconazole
- BDE153
- Diniconazole
- Ssf 109
- Diclobutrazol
- Iponazole
- BDE183
- Flupoxam
- Sulfentrazzone
- BDE203
- BDE208
- BDE209

neg Hazardous concentration
Rank after conservative bound & extra due to out of AD

Ranking after conservative PNEC & out of AD

Linnaeus University
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

VOI = 1.9

benefit
damage
welfare
MPL dist

welfare in emission units

Density in emission units

emission

MPL*

Linnaeus University
VOI given linear L+
beta1 = 0.1 beta2 = 0.5 c = 1.5

VOI given power L+
beta1 = 0.1 beta2 = 3 c = 1

MPL under perfect info = "1/Risk"

Variance in MPL = "Uncertainty"
VOI given linear $L^+$

\[ \text{beta1} = 0.1 \quad \text{beta2} = 3 \quad \text{c} = 1 \]

Variance in MPL = "Uncertainty"

MPL under perfect info = "1/Risk"

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?

### Ranking

Risk = $-\log MPL$

### Ranking considering out of AD

Risk = $-\log MPL$
Guide further testing – which endpoints to test

Which input parameters have the largest contribution to overall uncertainty?

Sensitivity analysis – relative contribution of QSAR uncertainty

**Ranking**

- pLC50_OMykis_NOR
- pEC50_PSubcapitata_NOR
- pEC50_PSubcapitata_CHI
- k-OH_CHI
- pEC50_DMagna_CHI
- k-OH_NOR
- pEC50_DMagna_NOR
- K-oc NOR
- conversion factor water-sediment
- K-oc CHI
- conversion factor water-soil
- BioDeg in water

Relative contribution
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.