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QSAR Uncertainty in the Maximum Permissible Emission of Triazoles

QSAR Uncertainty in the Maximum Permissible Emission of Triazoles

Risk of Chemicals

- A Risk Ratio (RR) can be estimated as the ratio of
  - Predicted Environmental Concentration (PEC) and [kg/m^3]
  - Predicted No Effect Concentration (PNEC) [kg/m^3]

Looking at a *unit emission* rather than *real emission data*

- A safe Maximum Permissible Emission (MPE) can be estimated as the ratio of
  - PNEC and [kg/m^3]
  - PEC [kg/m^3] per unit emission [kg/day] [day/m^3]
- Hence: Emission [kg/day] / MPE [kg/day] = RR

Maximum Permissible Emission

Emission to agricultural soil

Emission
1 kg/day

Concentration in the Environment

PEC: Predicted Environmental Concentration

Effects on Aquatic Species

PNEC: Predicted No Effect Concentration

$$MPE = PNEC / PEC_{unit\ emission}$$

Triazoles

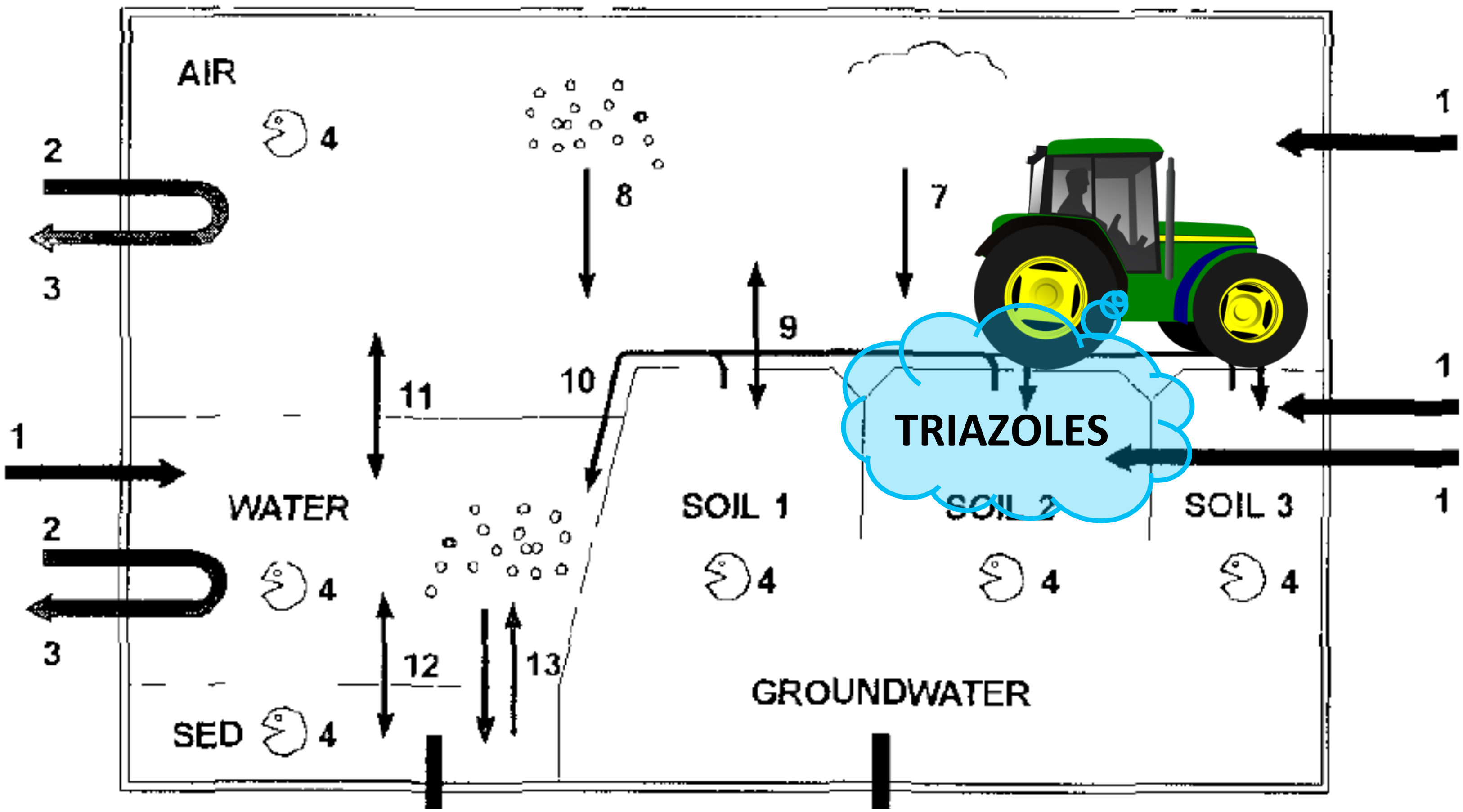
- Fungicides that interfere with fungi cell membrane
- Contamination of the aquatic environment

- Various effects in non-target organisms

Problem setting

- Chemical monitoring data and toxicity measurement data of triazoles are available to a limited extent only
- Substance properties can be predicted, e.g. with QSARs
- QSARs are uncertain
- The goals of this study:
  1. Quantify uncertainty ranges in the maximum permissible emisson of 8 triazoles
  2. Determine the relative importance of the individual QSARs to the overall uncertainty

Multimedia Fate Model



Simplebox Den Hollander HA, Van Eijkeren JCH, Van de Meent D (2004): SimpleBox 3.0: multimedia mass balance model for evaluating the fate of chemicals in the environment. RIVM, Bilthoven, NL

Multimedia Fate Model

Information requirements:

- Partitioning between environmental compartments
- Biodegradation in different compartments

QSAR Predictions for Substance Properties

For instance: vapor pressure

$$\text{Log VP} = 17.30 - 15.67 \cdot \text{BELp2} + 0.44 \cdot \text{RBN} + 1.38 \cdot \text{B09[N-Cl]}$$

descriptors of molecular structure

Other QSARs with same principle for :

- soil sorption partition coefficient
- aqueous solubility
- melting point
- biodegradation in air (rate constant for hydroxyl radical reaction)

Predictions of Biodegradation in Water

D. Aronson et al. / Chemosphere 63 (2006) 1953–1960

EPI Suite™ Biowin3	median (days)
days-weeks	4.65
weeks	8.35
weeks-months	14.9
months	85
recalcitrant	88
recalcitrant	281

Extrapolation to Soil and Sediment

Biodegradation half-life in water

Extrapolation Factor of 1

Extrapolation Factor of 1

Biodegradation half-life in soil

Biodegradation half-life in sediment

- Assumption is reasonable for screening purposes
- Confirmed by dataset

- Sediment has been reported to *enhance* and to *inhibit* degradation

Predicted No Effect Concentration

Assessment Factor Method

$$PNEC = \frac{\text{lowest } L(E)C50}{1000}$$

QSARs for toxicity

- LC50 *Onchorynchus Mykiss*
- EC50 *Daphnia Magna*
- EC50 *Pseudokirchneriella Subcapitata*

Uncertainty in QSAR Predictions

- Uncertainty in prediction Y_p follows a student-t distribution

$$Y_p \sim \overline{Y_p} + t_{n-k-1} \cdot SE(Y_p - \overline{Y_p})$$

- Distribution specified by
  - the predictive mean ($\overline{Y_p}$)
  - the predictive error ($SE(Y_p - \overline{Y_p})$)
  - the number of data points in the training data set (n)
  - the number of descriptors in the linear regression model (k)
- Based on experimental data underlying the QSAR regressions

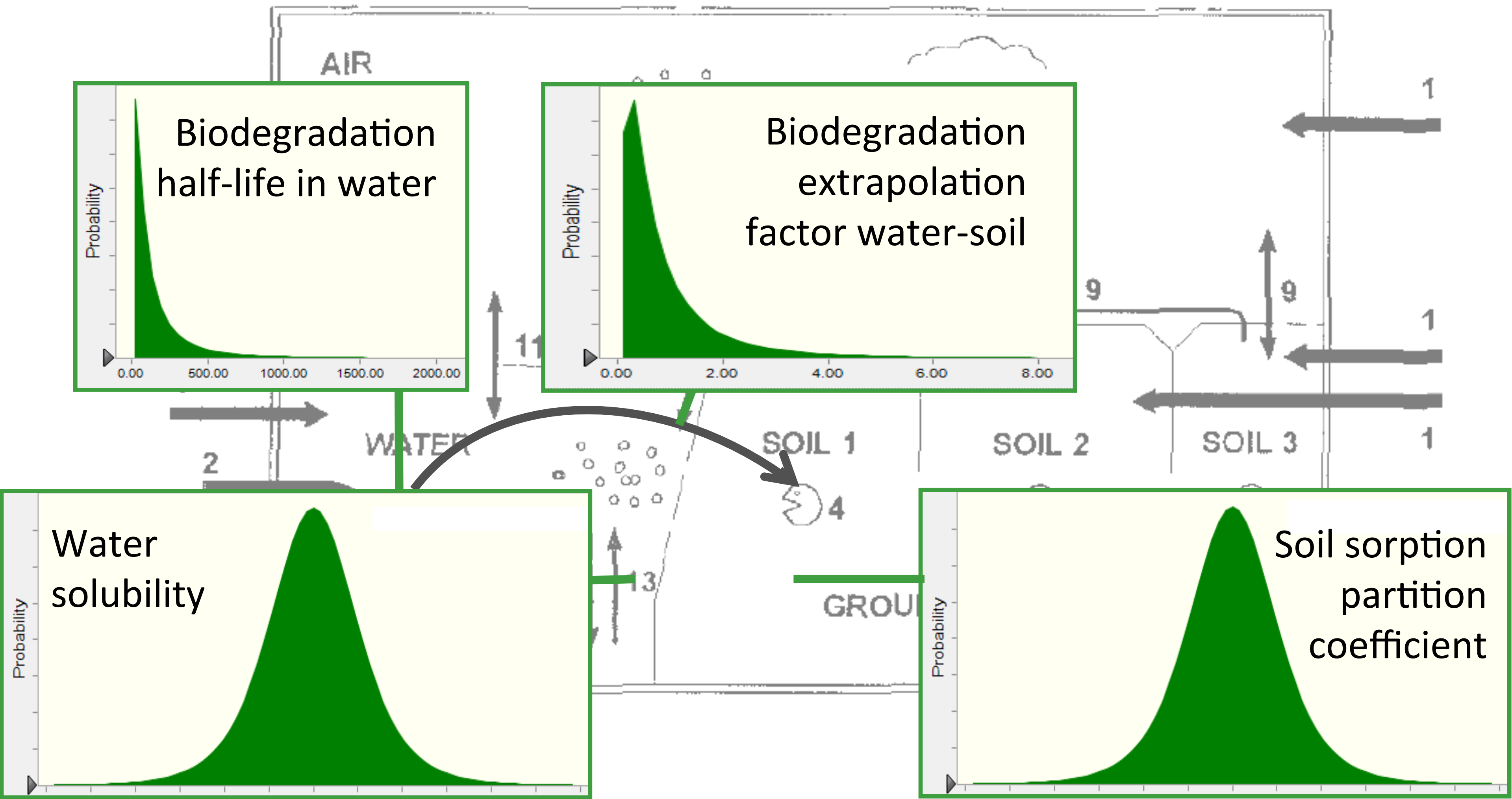
Uncertainty in Biodegradation

Log-normal distribution *D. Aronson et al. / Chemosphere 63 (2006) 1953–1960*

EPI Suite™ Biowin3	median (days)	95% CI
days-weeks	4.65	(0.7 – 29.9)
weeks	8.35	(0.4 – 163.4)
weeks-months	14.9	(0.3 – 763.7)
months	85	(7.3 – 996.2)
recalcitrant	88	(7.7 – 1001.4)
recalcitrant	281	(13.3 – 5948.9)

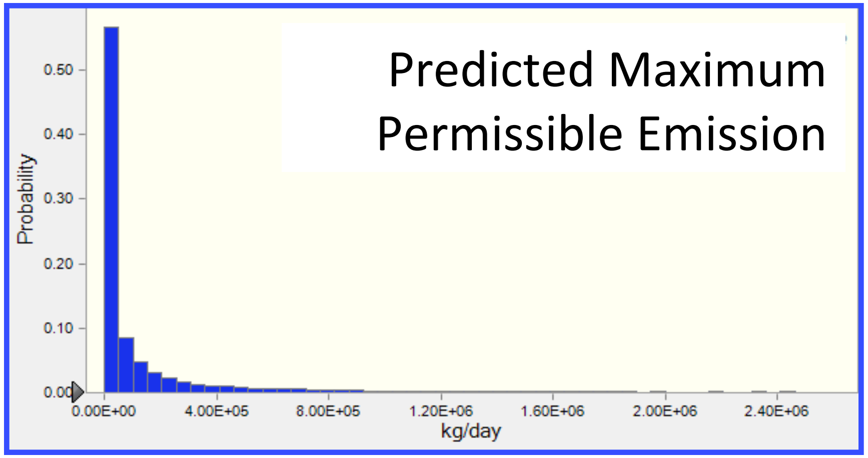
Extrapolation factor to soil and sediment followed a log-normal distribution with 95% CI (0.1 – 4.5)

Propagation of Uncertainty



Propagation of Uncertainty

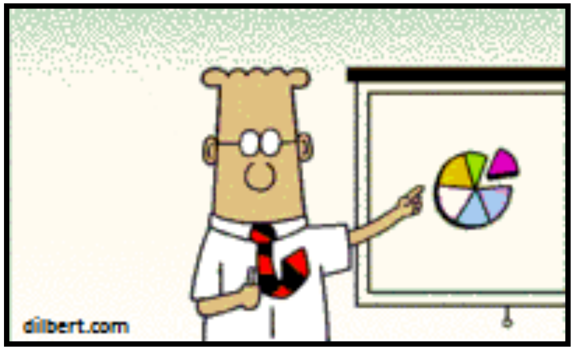
ORACLE
CRYSTAL BALL



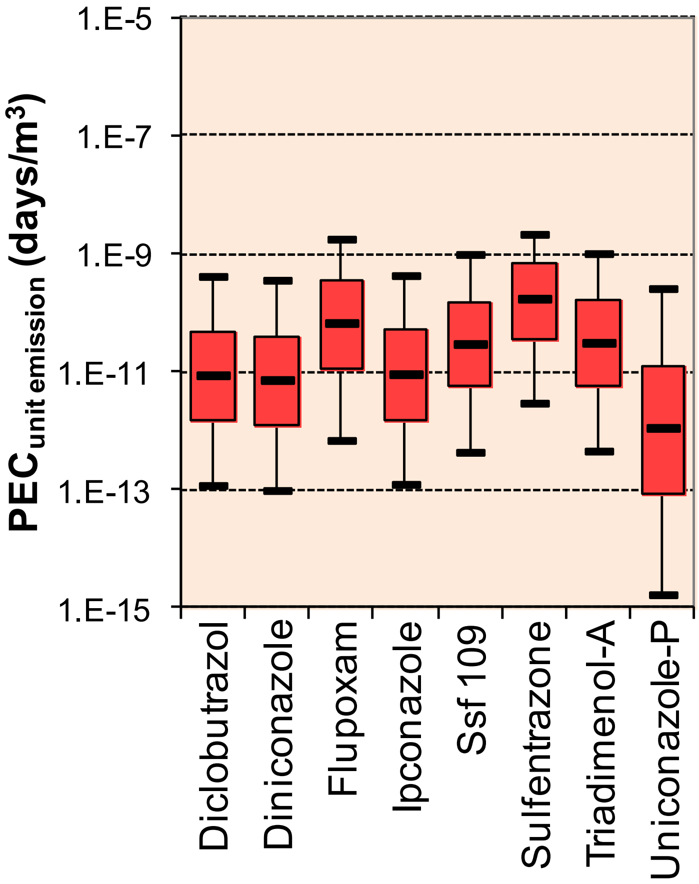
Analysis of Variance

Crystal Ball:

- Spearman's rank correlation coefficients between each input parameter and the outcome variable
- Rank correlation coefficients were squared and normalized to 100 %
- Contribution to variance

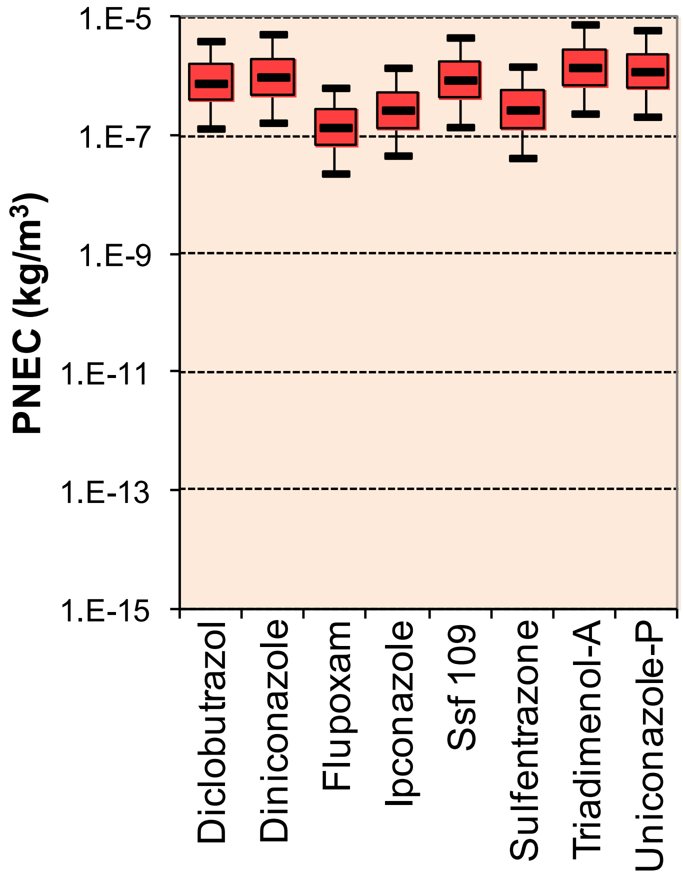


PEC



1.E-5
1.E-7
1.E-9
1.E-11
1.E-13
1.E-15
PEC unit emission (days/m3)
Diclobutrazol
Diniconazole
Flupoxam
Ipconazole
Ssf 109
Sulfentrazone
Triadimenol-A
Uniconazole-P

PNEC



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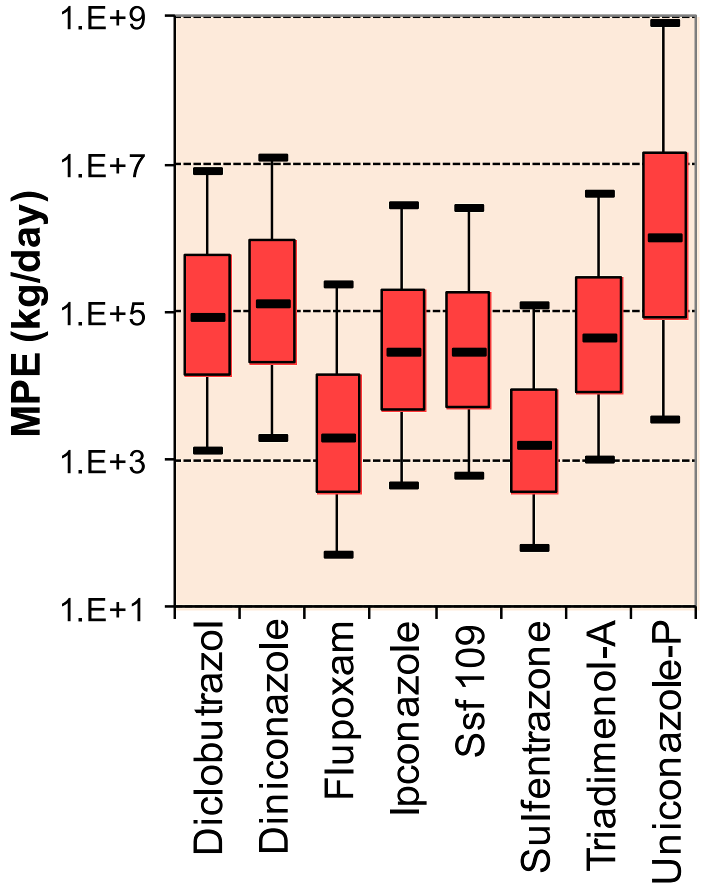
Maximum Permissible Emissions



Analysis of Variance

Parameter	Diclobutrazol	Sulfentrazone	Uniconazole-P
Soil sorption partition coefficient	37.8%	23.5%	14.6%
Biodegradation in water	36.1%	43.9%	72.6%
Biodegradation extrapolation factor water-soil	14.5%	14.7%	7.5%
LC50 O. Mykiss	9.2%	5.3%	4.1%
EC50 P. Subcapitata	2.3%	12.5%	1.1%

Contributions of aqueous solubility, melting point, vapor pressure, hydroxyl radical reaction, biodegradation extrapolation factor water-sediment, and EC50 D. Magna were **≤ 0.1 %**

Limitations : Predictions outside the AD

- A QSAR's reliability is restrained by its Applicability Domain (AD), which is depending on
  - the number of training chemicals
  - the number of model variables

- Almost all QSAR predictions were within the AD

Limitations: Predictions outside the AD

- k_{OH} of Flupoxam and Sulfentrazone
  - no key property
- K_{oc} of Flupoxam
  - important property: movement and leaching from the soil
  - prediction (and uncertainty) similar to other predictions
- EC50 of *P. Subcapitata* of Flupoxam
  - prediction (and uncertainty) similar to other predictions

Warning for model applicability,
but not a final decision on prediction quality
(Nikolova and Jaworska 2003)

Limitations: General or Specific QSAR

- K_{oc} prediction with 'general' QSAR
  - Triazoles represented less than 2% of the training set chemicals
  - Therefore, little structural and experimental information on triazoles was included
  - Suggestion for further research: comparison between uncertainties in predictions calculated by 'general' or 'specific' QSARs → quantify impact on MPEs

Limitations: Predictions of Biodegradation

- Biodegradation half-lives in water were predicted with EPI Suite & Aronson et al.
  - important contributor to overall uncertainty!
- Biodegradation in soil and sediment were extrapolated from water
  - equal rates with uncertain extrapolation factor
- But… current guidance indicates that the half live in soil is 2 x as long as in water
  - If degradation is indeed slower, the MPEs are overestimated

Limitations: PNEC

- PNEC was based on assessment factor method

- 3 species only!

  Are *O. Mykiss, D. Magna, and P. Subcapitata* a representative sample?

- Alternative: statistical extrapolation

  In that case sample size is highly relevant

Conclusion

The main sources of uncertainty in the triazoles' MPE were:

- the uncertainty in the biodegradation rate in water
- the uncertainty in the extrapolation factor used to predict biodegradation in soil from biodegradation in water
- the uncertainty in the QSAR for soil sorption partitioning

Discussion

The reliability of the MPE predictions for triazoles can be improved particularly by including experimental data for <u>biodegradation</u> and <u>sorption to soil</u>

Thank you for your attention!

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