QSAR, Threshold of Toxicological Concern & Other Computational Approaches under REACH

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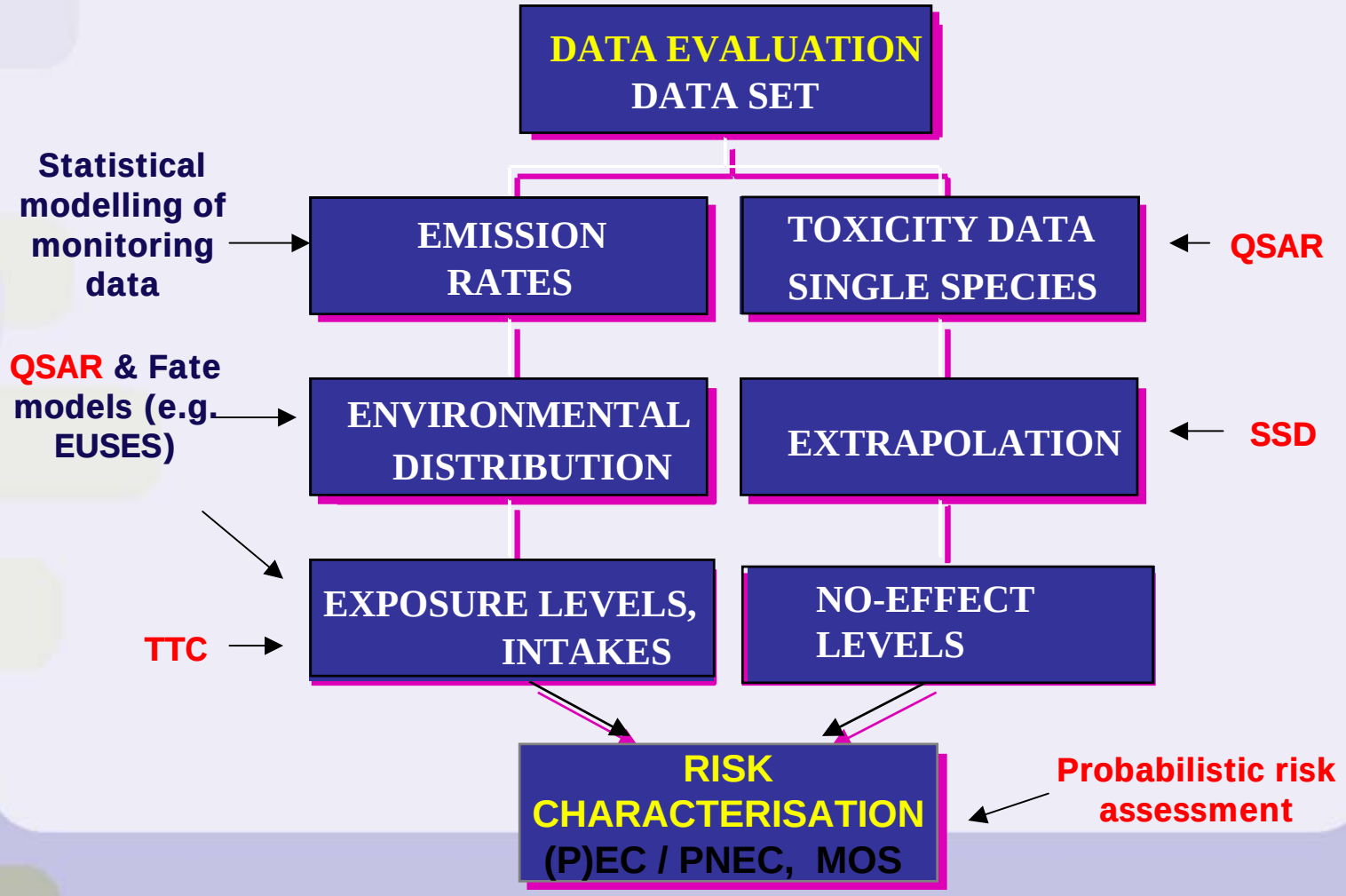
Overview

- When are computational approaches useful?
- REACH guidance on computational approaches
- Selected computational approaches
  - QSARs
  - TTC
  - SSDs
  - Probabilistic modelling (uncertainty analysis)
- Conclusions
  - Data waiving
  - Other benefits

When can computational approaches be used?



REACH Guidance on computational approaches

- Quantitative Structure Activity Relationships: Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals.
- Threshold of Toxicological Concern: No REACH guidance, but SCHENIR draft opinion of November 2008.
- SSDs: REACH Guidance on information requirements and chemical safety assessment Chapter R.10:Characterisation of dose [concentration]-response for environment.
- Probabilistic Risk Assessment: REACH Guidance on information requirements and chemical safety assessment Chapter R.19: Uncertainty analysis.

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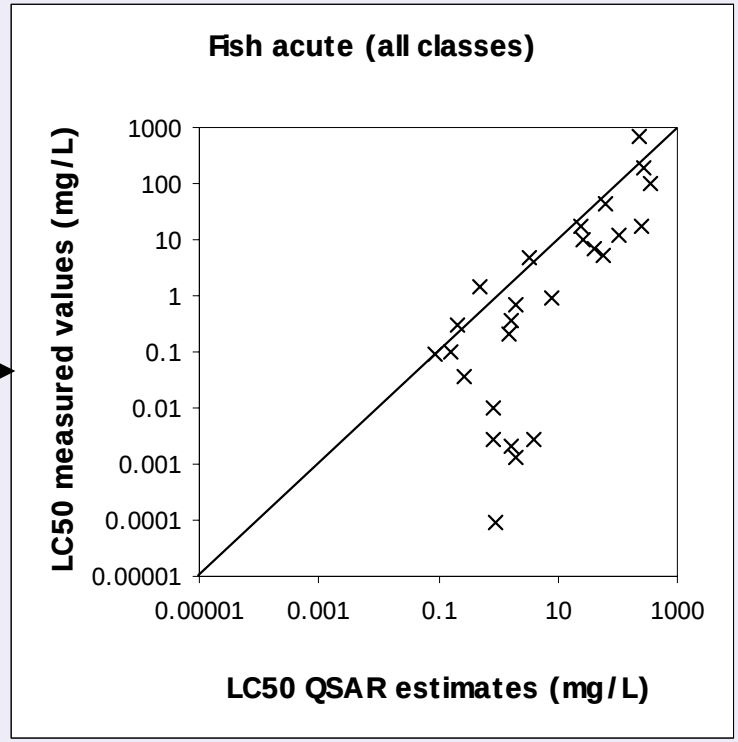
Quantitative Structure Activity Relationships

When can QSARs be used?

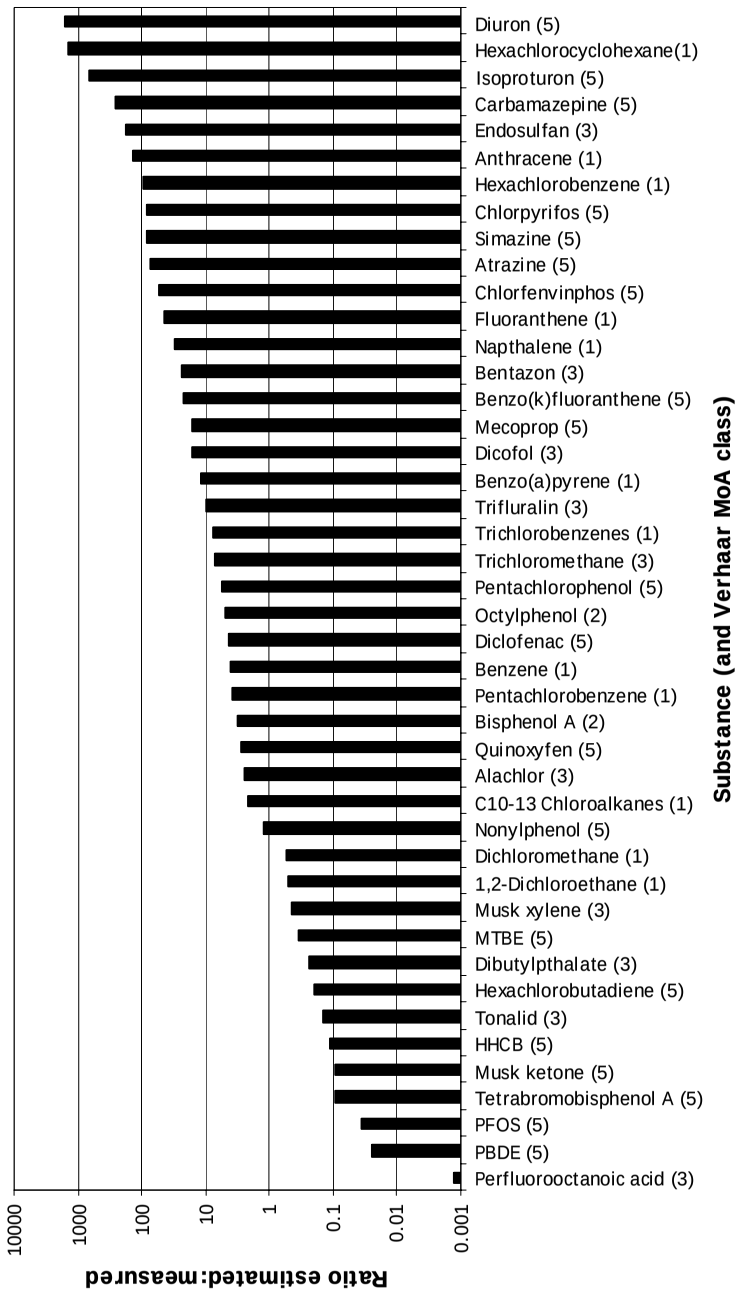
- Under REACH data from QSARs instead of experimental data can be used if four conditions are fulfilled:
  - The model used is shown to be scientifically valid.
  - It is applicable to the chemical of interest.
  - The prediction is relevant for the regulatory purpose.
  - Appropriate documentation on the method and result is given (e.g., by using the QSAR Model Reporting Format recommended by the European Commission).

Effective use of QSARs

- Use of one standard QSAR package (e.g. ECOSAR in EPIWIN) for all substances is inappropriate
- Likely to require specific QSARs for substance groups with different MoAs
- Requires expertise



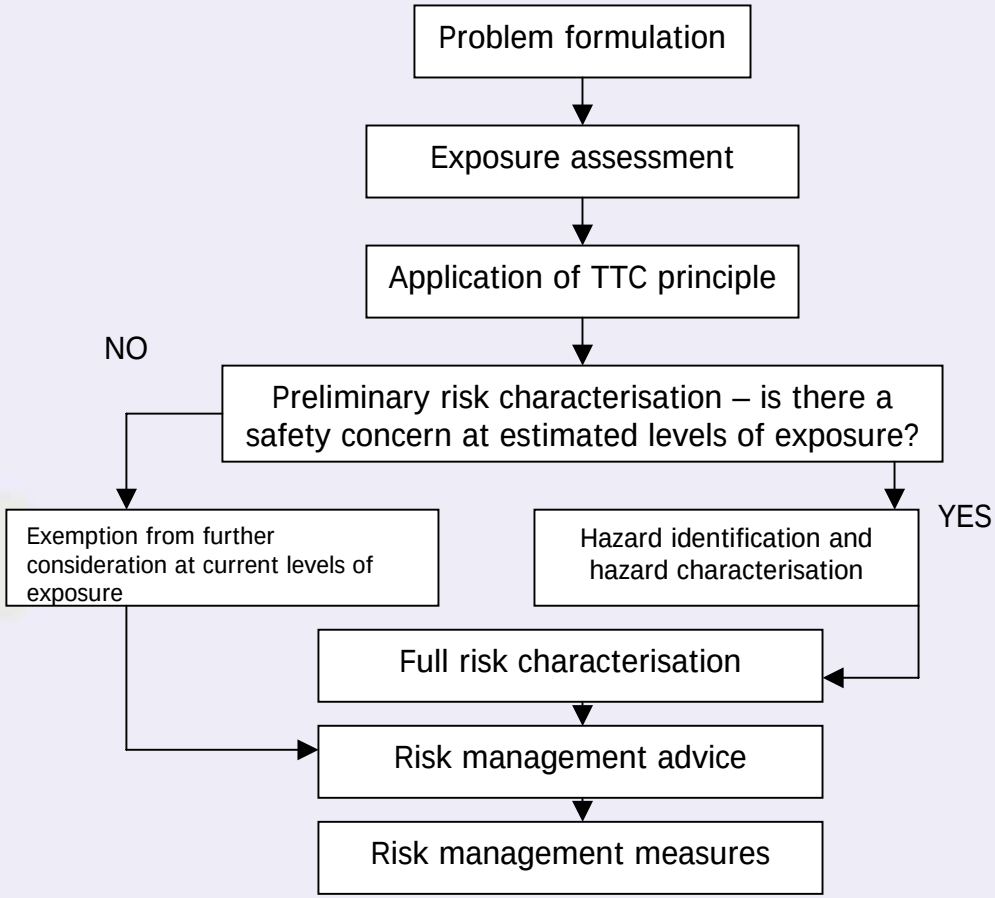
Crane M, Watts C, Daginnus K, Worth A. 2008. Possible application of non-testing methods in setting environmental quality standards (EQS). JRC Scientific and Technical Report EUR 23758 EN, European Commission Joint Research Centre, Ispra, Italy.


Diuron (5)
Hexachlorocyclohexane(1)
Isoproturon (5)
Carbamazepine (5)
Endosulfan (3)
Anthracene (1)
Hexachlorobenzene (1)
Chlorpyrifos (5)
Simazine (5)
Atrazine (5)
Chlorfenvinphos (5)
Fluoranthene (1)
Napthalene (1)
Bentazon (3)
Benzo(k)fluoranthene (5)
Mecoprop (5)
Dicofol (3)
Benzo(a)pyrene (1)
Trifluralin (3)
Trichlorobenzenes (1)
Trichloromethane (3)
Pentachlorophenol (5)
Octylphenol (2)
Diclofenac (5)
Benzene (1)
Pentachlorobenzene (1)
Bisphenol A (2)
Quinoxyfen (5)
Alachlor (3)
C10-13 Chloroalkanes (1)
Nonylphenol (5)
Dichloromethane (1)
1,2-Dichloroethane (1)
Musk xylene (3)
MTBE (5)
Dibutylpthalate (3)
Hexachlorobutadiene (5)
Tonalid (3)
HHCB (5)
Musk ketone (5)
Tetrabromobisphenol A (5)
PFOS (5)
PBDE (5)
Perfluorooctanoic acid (3)
Substance (and Verhaar MoA class)
10000
1000
100
10
1
0.1
0.01
0.001
Ratio estimated:measured

Threshold of Toxicological Concern (TTC)

What is a TTC?

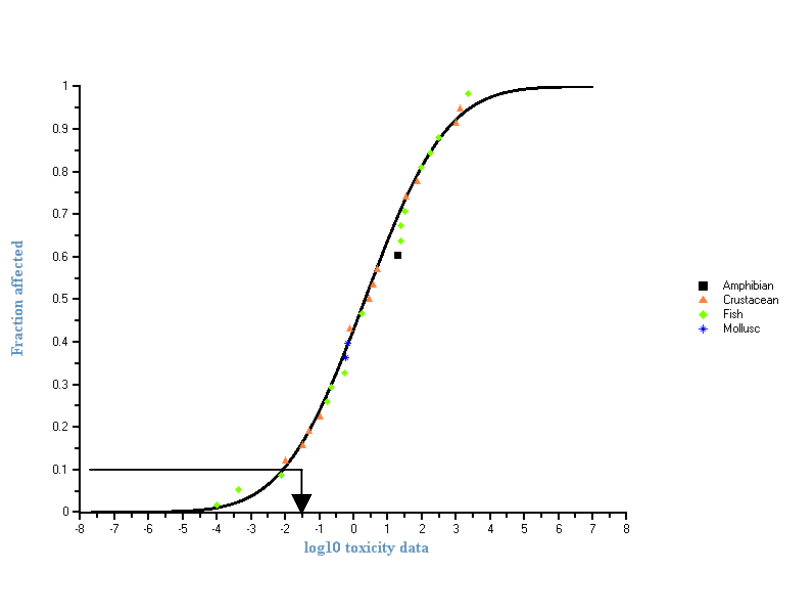
- TTC approach emerged in recent years from human health risk assessment approaches.
- Used to establish a human exposure threshold value for chemicals (or groups of chemicals) below which there is no significant risk to human health.
- Proposes that a *de minimis* value can be identified for chemicals, including those of unknown toxicity, by taking the chemical's structure or Mode of Action (MOA) into consideration.
- Concept forms the scientific basis of the US Food and Drug Administration (FDA) 1995 Threshold of Regulation for indirect food additives. Also been adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its evaluations of flavouring substances.



Kroes et al. (2005)

Environmental TTC example

- **Most sensitive taxon per chemical**
- 29 chemicals included, 29 NOECs
- Accepted by all goodness of fit tests at all significance levels.
- LLHC5 = 0.0001420
- HC5 = 0.001666
- UL HC5 = 0.01017



But.....

SCHENIR opinion (November 2008)

- Principle of the TTC approach in itself is scientifically acceptable.
- However, application in chemical risk assessment depends on quality, quantity, and relevance of the underlying toxicity database, and reliable estimation of exposure to the chemical in the respective field of application.
- Several classes of chemicals have been identified, for which the TTC concept can not be applied:
  - heavy metals and polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans and polyhalogenated biphenyls, or any other compound known to accumulate in the body
  - endocrine disrupting chemicals, including steroids
  - high molecular weight chemicals, such as polymers
  - organophosphates
  - proteins Also for certain endpoints, like allergic reactions,
- Approach cannot be used for certain endpoints (e.g. allergic reactions, intolerance, local effects and pharmacological effects) and exposure routes (inhalation and dermal).
- Appropriate exposure assessment is essential for TTC – this is OK for genotoxic contaminants in pharmaceuticals, and food flavourings, where TTC is already in use, but limited knowledge for other areas, e.g. for consumer products, where large diversity of products and complex exposure scenarios have to be considered, including multiple exposure routes.

Use of TTC

- Not likely to be usful under REACH except for low tonnage substances.
- Likely to be many substances excluded.
- Reliable monitoring data likely to be vital to estimate exposure.....but may be much more expensive to obtain than simply performing Annex VII tests.

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More (data) = less (conservatism)?

Other potentially useful computational approaches

Species Sensitivity Distributions

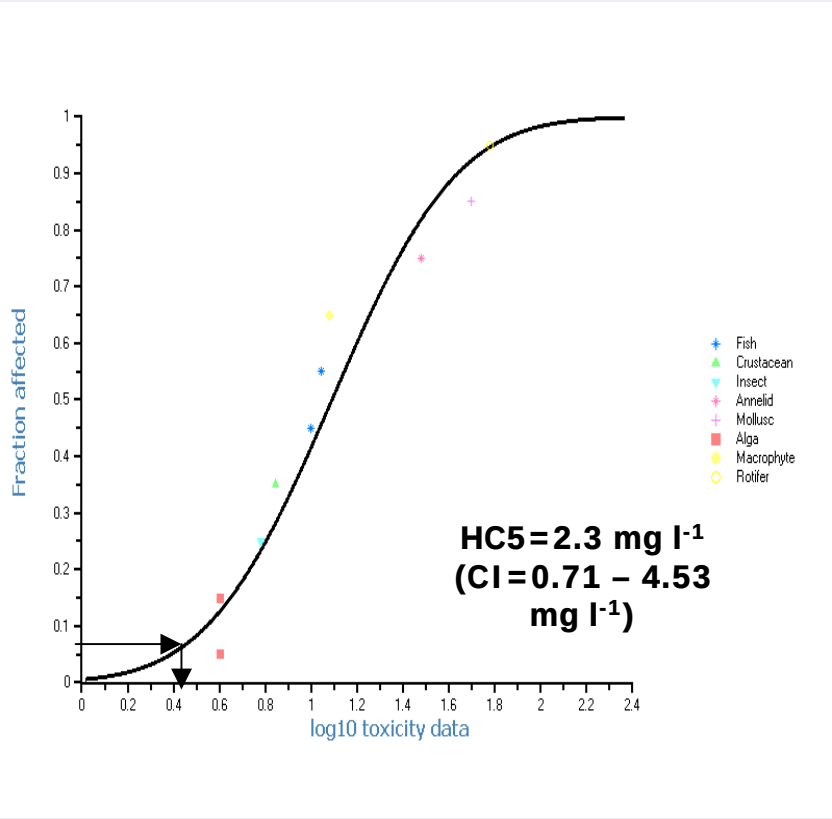
Species Sensitivity Distributions

- Statistical approach to model (eco)toxicity data.
- A low value, the HC5, is theoretically protective of 95% of organisms.
- An assessment factor of 1-5 (usually 3-5) is applied to the HC5 to calculate a PNEC.
- [An analogous approach can be used for human effect data - the dose-response relationship for the most critical endpoint(s) is used to derive the DNEL uncertainty]

- At least 10 NOECs from at least 8 taxonomic groups:
  - fish
  - second family in the phylum Chordata (fish, amphibian, etc.)
  - crustacean
  - insect
  - family in phylum other than Arthropoda or Chordata (e.g. Rotifera, Annelida, Mollusca, etc.)
  - family in any order of insect or any phylum not already represented
  - algae
  - higher plants

Example of SSD

- Following NOECs (mg l^{-1}) available:
  - Fish sp 1: 10
  - Fish sp 2: 11
  - Crustacean: 7
  - Insect: 4
  - Rotifer: 100
  - Annelid: 30
  - Mollusc: 50
  - Alga sp 1: 5
  - Alga sp 2: 4
  - Higher plant: 12



What is the advantage of an SSD?

- Assume long term NOECs (mg l^{-1}) from previous slide of
  - Fish sp 1: 10
  - Crustacean: 7
  - Alga sp 2: 4
- PNEC = lowest value (4)/10 = 0.4 mg l^{-1}.
- HC5 from SSD with these data and other spp = 2.3 mg l^{-1}.
- The "worst" PNEC = 2.3/5 = 0.46 mg l^{-1}.
- But it *could* be 2.3/4 = 0.58, or 2.3/3 = 0.77 mg l^{-1}.
- The value of an SSD depends on how close the PNEC is likely to be to the PEC and what AF is applied to the HC5.

Probabilistic Risk Assessment (uncertainty analysis)

Sources of uncertainty in chemical risk assessment

- Scenario uncertainty
- Model uncertainty
- Parameter uncertainty
- Uncertainty vs variability

Uncertainty

- **Uncertain** model components are those that
  - Arise from incomplete knowledge
  - Are theoretically reducible through increased empirical effort
- Examples:
  - Limited sample size
  - Possible biases in sampling design
  - Use of surrogate data

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Variability

- **Variable** model components are those that
  - Arise from natural stochasticity
  - Are not reducible through increased empirical effort (but can be better understood)
- Examples:
  - Spatial distribution of chemical concentrations
  - Temporal fluctuations in precipitation
  - Size differences amongst individuals

When to perform uncertainty analysis under REACH

- Uncertainty analysis recommended when:
  - RCR >1. Uncertainty assessment can help registrant identify and target main sources of uncertainty in the chemical safety assessment for subsequent refinement in higher tier approaches. Additionally, the assessment can be used to improve the characterisation of risk.
  - When non-standard, non-guideline approaches have been used - registrant might include uncertainty analysis to justify use and applicability of non-standard risk characterisation method.
  - Where RCR is < but close to 1 and standard approaches have been used - registrant might choose to carry out qualitative uncertainty analysis to help satisfy themselves that their chemical safety assessment is robust and adequate [this seems rather unlikely!].

When not to perform uncertainty analysis under REACH

- It should follow a tiered & proportionate approach
  - *"It would not add much practical value to a chemical safety assessment to provide a detailed probabilistic uncertainty analysis for a substance which has a full data set, few dangerous properties, minimal exposure and a risk characterisation ratio (RCR) which is significantly less than 1."*

What does a probabilistic RA/UA look like?

- Best developed & most widely used for higher tier pesticide risk assessment (e.g. Crane et al. 2003. Evaluation of probabilistic risk assessment of pesticides in the UK: Chlorpyrifos use on top fruit. *Pest Man Sci* 59:512-526)
- ...But also used increasingly in other areas of chemical RA (e.g. Crane et al. 2004. Risk characterisation in Direct Toxicity Assessment of the River Esk and the Tees Estuary. *Ecotoxicology* 13:463-474).

Example

Skylark (*Alauda arvensis*) - focal species of interest in UK (& other European countries)
  - Breeds in cereal fields
  - Small
  - Omnivorous
  - Forages extensively
- Exposure to pesticides sprayed on cereal crops potentially high through ingestion of contaminated food items

What do Skylarks Eat?

- Insects
- Mature Seeds
- Immature Seeds
- Grasses
- Broad-leaved plants
- .....Each is eaten in different quantities by birds, has different moisture and energy content, and different assimilation efficiency

Conceptual Model of Skylark Pesticide Exposure

$$ETE = \frac{DEE}{BW} \times \frac{\sum_i C_i \times PD_i}{\sum_i PD_i \times (1 - M_i) \times GE_i \times AE_i} \times AV \times PT$$

For each food type, where

ETE = Estimated Theoretical Exposure (mg/kg/d)

i = Subscript for different food types (small insects, cereal seeds, weed seeds, etc.)

DEE = Daily energy expenditure (kJ) = 2.41*BW + 20.2

BW = Body weight (g)

Ci = Concentration (mg pesticide/kg wt) of pesticide residue on food type *i* (= application rate x *RUDi*)

RUDi = Residue per unit dose on food type *i* (mg pesticide/kg/kg/ha)

PDi = Proportion (fresh wt) of diet made up by food type *i* (0-1)

Mi = Proportion of moisture in fresh food of type *i*

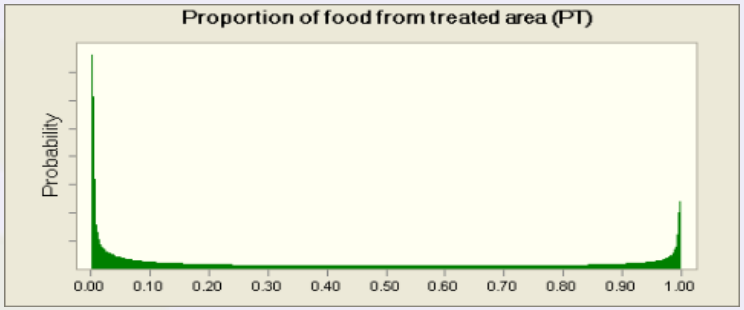
GEi = Gross energy (KJ/g dry wt) provided by food type *i*

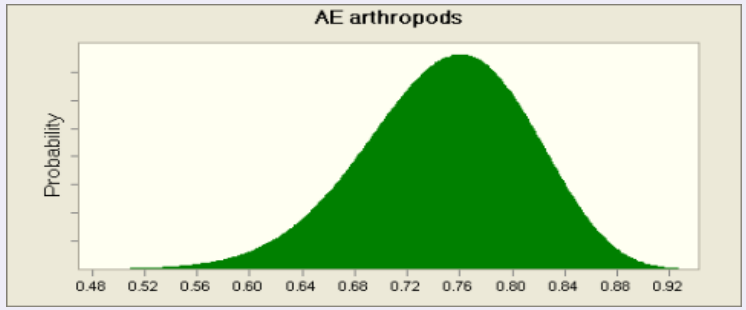
AEi = Assimilation efficiency of food type *i* (0-1)

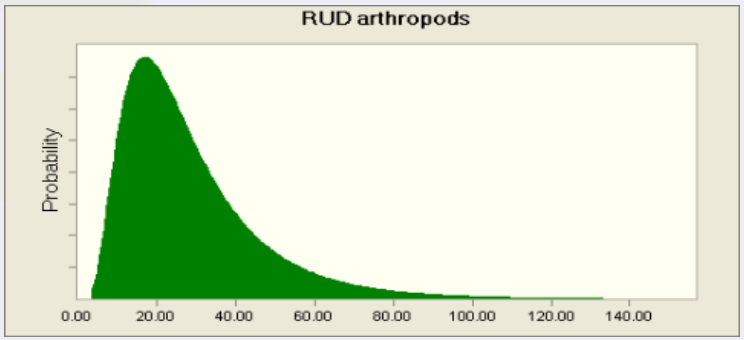
PT = Proportion of food eaten that is from the treated area (0-1)

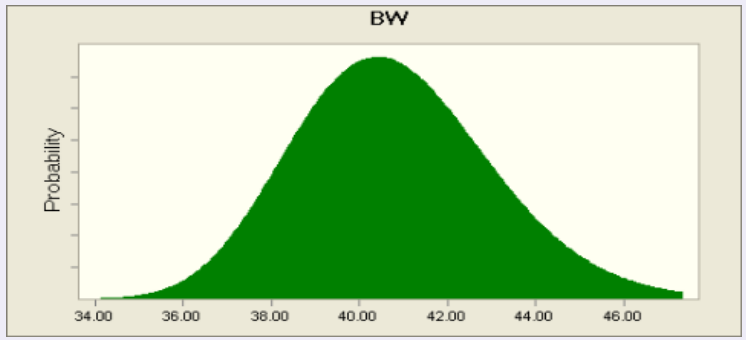
AV = Avoidance of treated food (0 = wholly avoided; 1 = not avoided)

Exposure input parameters are distributions...not point estimates

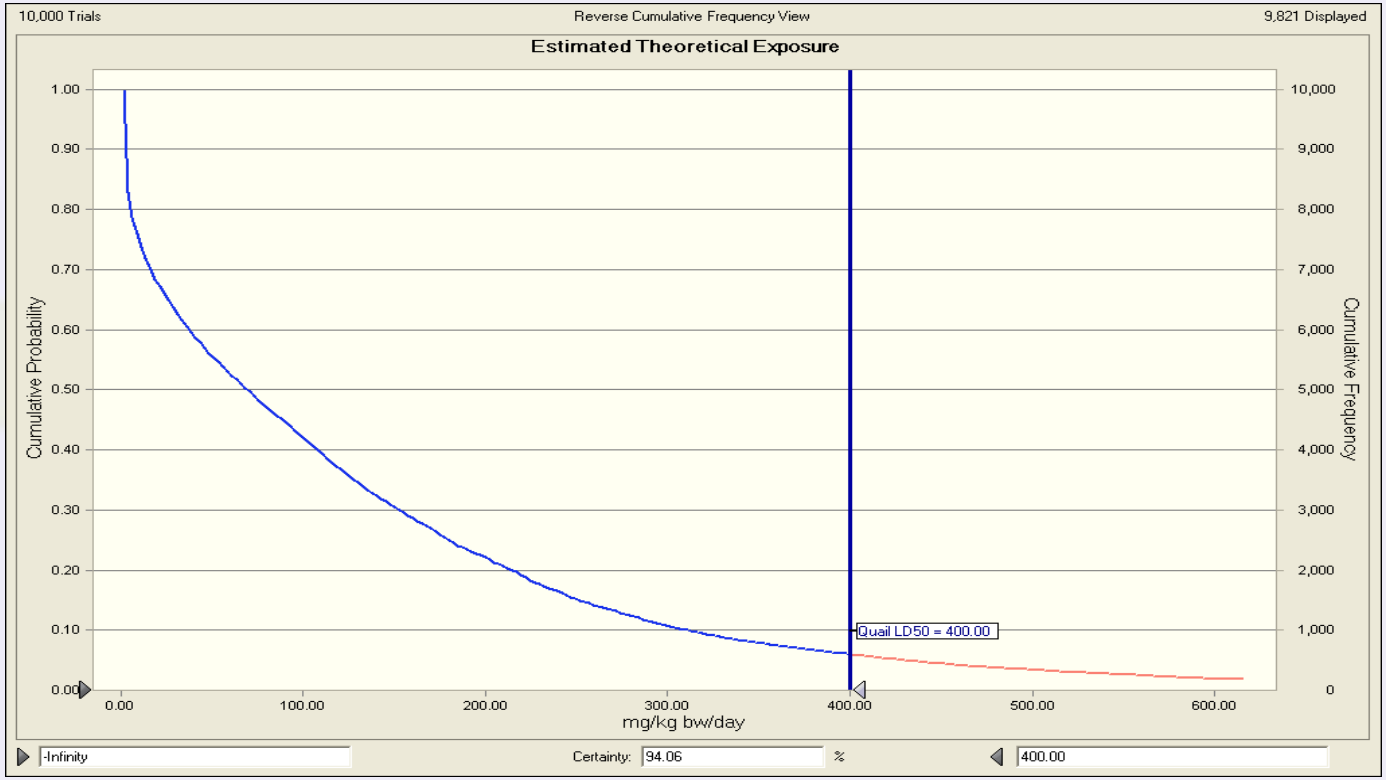




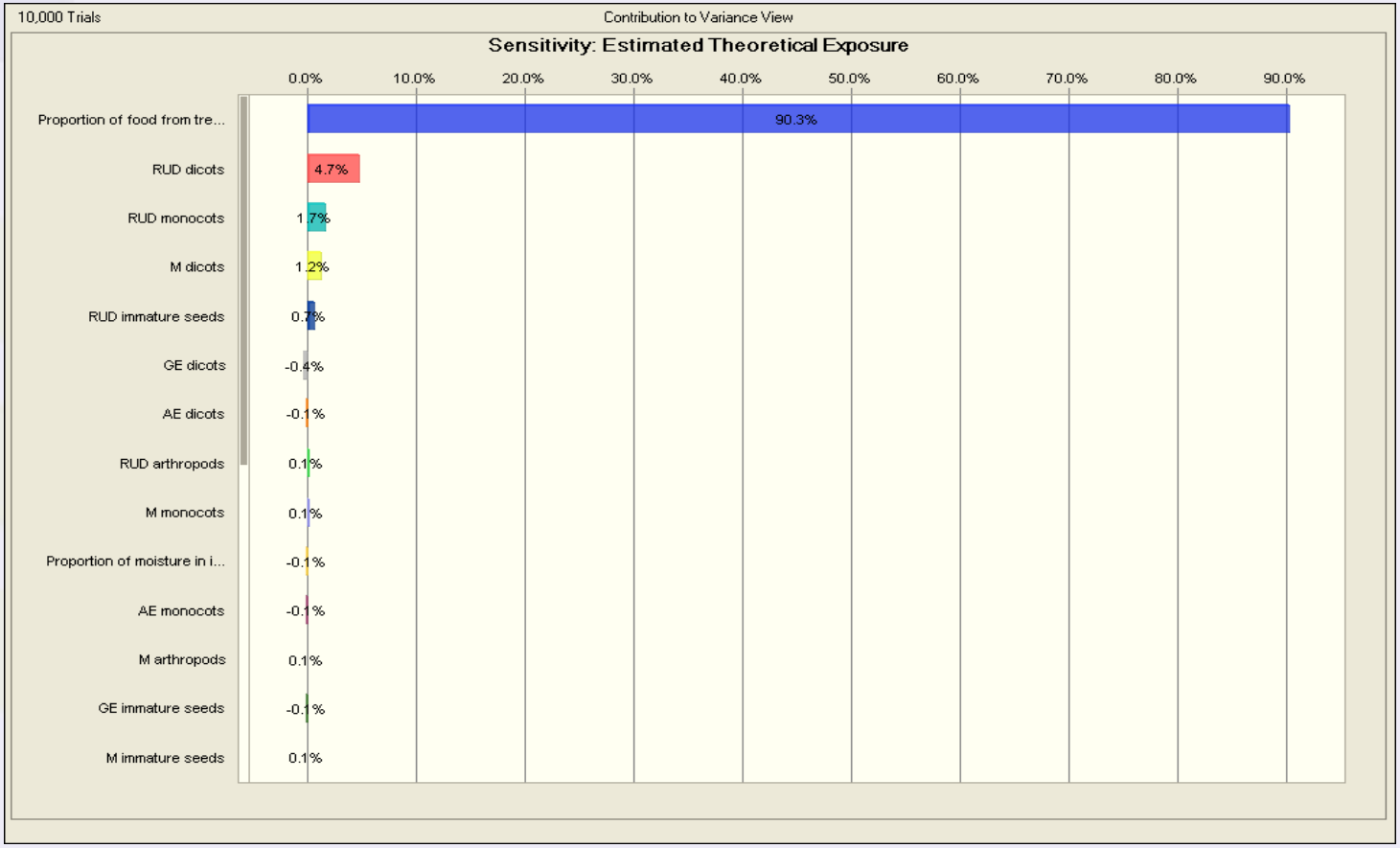




1D Monte Carlo Simulation of Risks from GX - Exceedance Curve



Sensitivity Analysis of 1D Simulation



Conclusions

Conclusions: data waiving

- Data waiving through use of QSARs will require expert application of valid, applicable and relevant models in the required reporting format – adequate models are available for some, but not all, substance groups.
- Data waiving through use of the TTC is unlikely for most substances.

Conclusions: other benefits of computational approaches

- Use of an SSD can lead to a less conservative PNEC (or DNEL using analogous approach), but this is likely to be useful only if an AF approach leads to a RCR just a little over 1.
- PRA – as for SSDs (which are likely to be an important component of most PRAs), this approach will be of most use in refining RCRs that are just a little over 1.

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