WG Guidance on Residue Definition for Dietary Risk

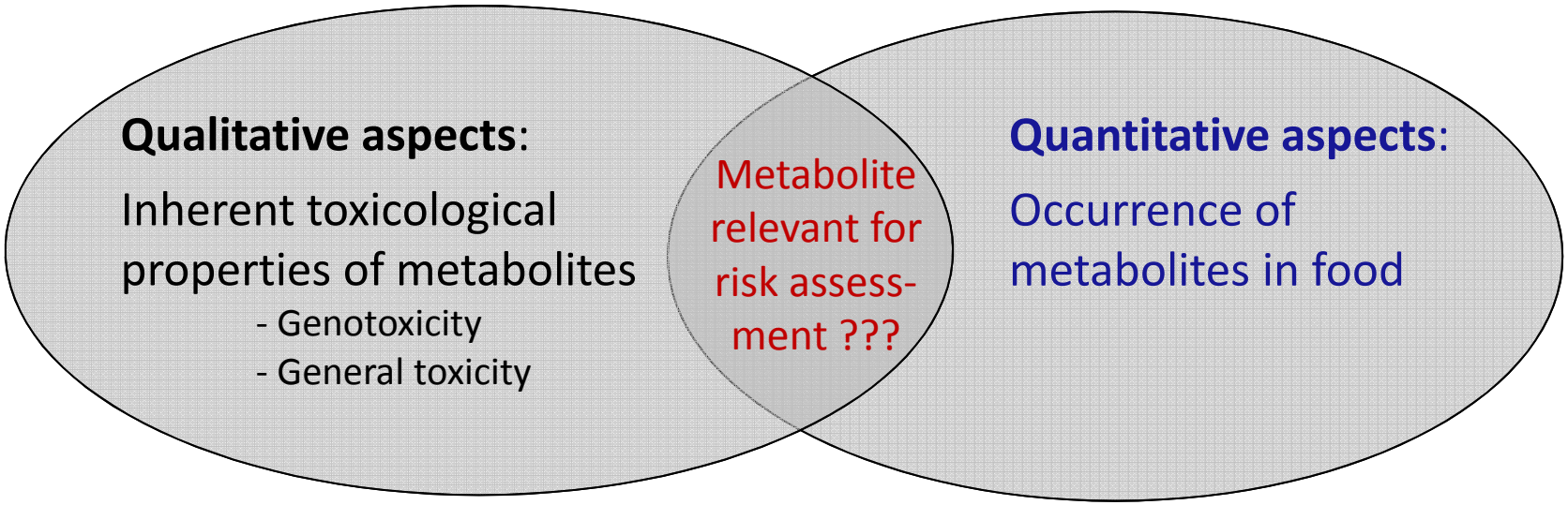
Prospective exposure estimates in the relevance assessment of metabolites

Thomas Kuhl

European Food Safety Authority

www.efsa.europa.eu

Relevance assessments for metabolites



Exclusion of metabolites by exposure estimates

Requirements

- insensitive to changes in authorisation situation
- reliable (uncertainties)
- worst case oral consumption

Relevance assessments for metabolites

Absolute quantities (mg/kg → mg/kg bw)

+	−
Correlate to toxicological reference values	Exposure snapshot (limited view on exposure) Fixed boundary conditions New use – new review

Livestock burden and **TTC/refinement**

Absolute quantity (mg/kg)

Livestock dietary burden (mandatory):

- Used to decide on the requirement for livestock metabolism studies
- No change to current evaluation practice
- No impact on metabolites relevance for residue definition

TTC/refinement (facultative):

- Used to exclude potential genotoxicants from testing (TTC)
- Used to exclude metabolites from general tox assessment (TTC, refinement by higher tier studies)

Threshold of toxicological concern

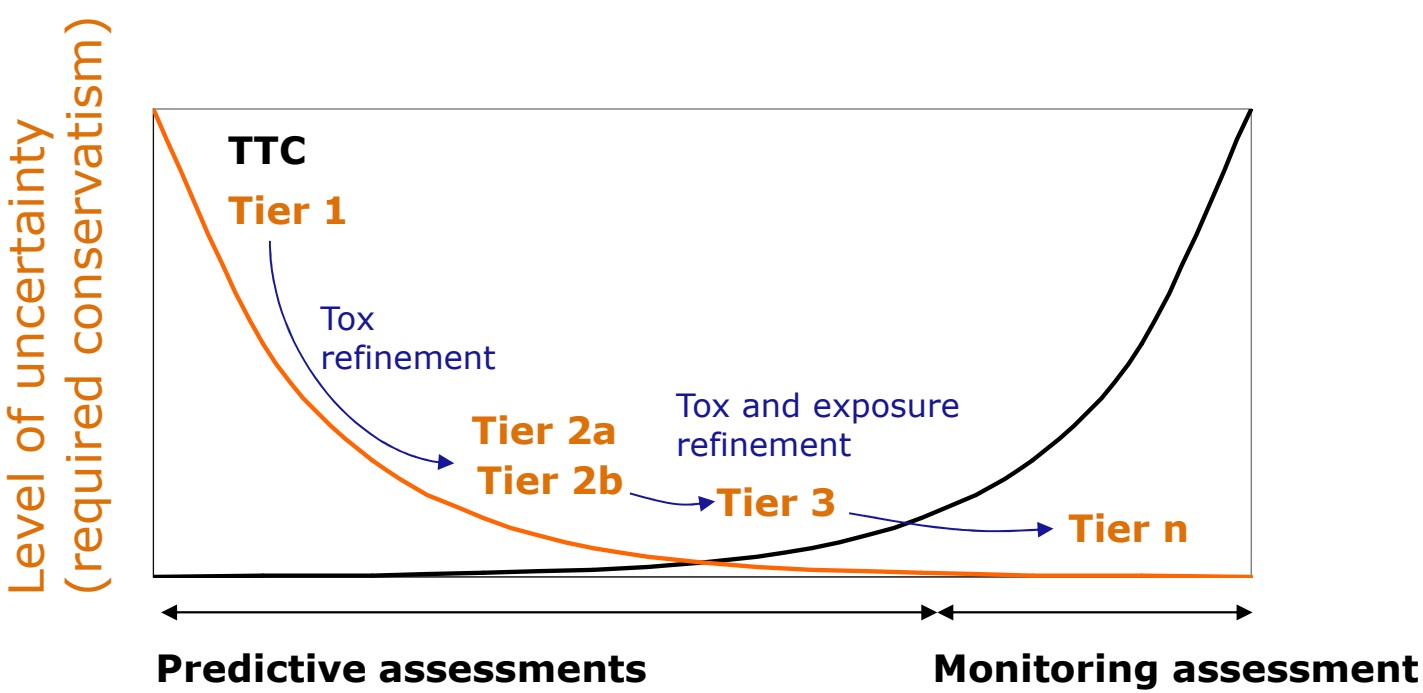
Assume a genotoxic (neurotoxic etc.) effect for a toxicologically uncharacterised metabolite and screen, whether the risk of developing this effect is acceptable from a regulatory view

Exposure < Trigger

Exposure > Trigger

→ Risk is not acceptable (tier 1); further actions required

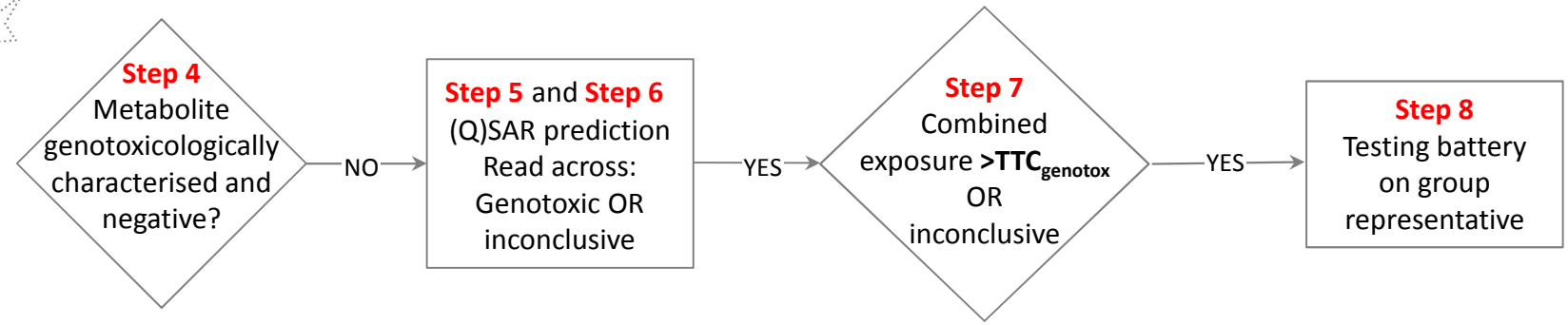
Facultative TTC assessments



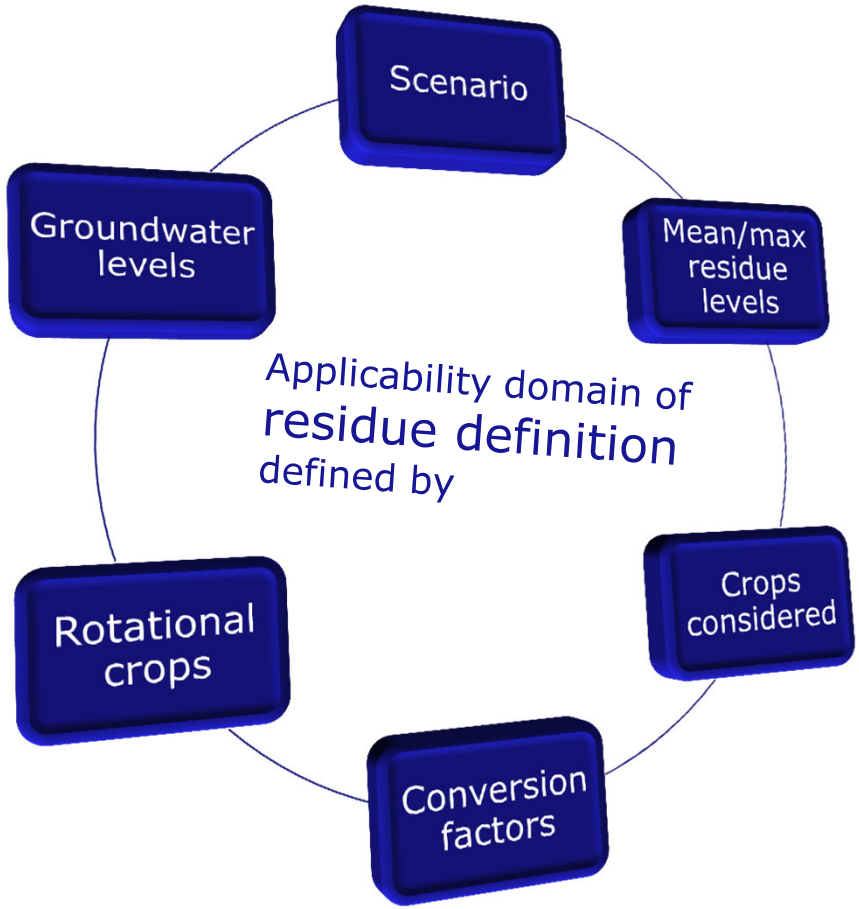
Tox evaluation or reference values
Additional exposure info

Preliminary considerations on TTC

- dietary exposure calculations for sum of all metabolites in a group (cumulative), reflecting mixture toxicity (dose addition)
- unrefined TTC assessment has little prospect of success
- refined assessment is ressource intensive
- high uncertainty of exposure scenario; acceptance by authorities is not pre-defined
- TTC for genotoxicity is recommended in combination with **QSAR** and **read-across**



Facultative TTC exposure estimates



→ **no extrapolation of the residue definition beyond what was evaluated**!

Boundary conditions for TTC exposure estimates

- Grouping of metabolites for TTC genotoxicity and general toxicity assessment
- Acute and chronic exposure estimates
- Expression of metabolites
- Consideration of groundwater residue levels

Boundary conditions for TTC exposure estimates

(1) Grouping of metabolites for TTC genotoxicity assessment

- QSAR/RA: **molecular initiating event** (interaction with DNA and/or proteins)
- No genotox alert = no TTC required
- Organic functional group profilers = indicators for electronic and structural influence to the structural alerts
- Same MIE = same effect
- Different MIE = independence of effects
- TTC for groups of metabolites without endpoint information
- Restricted to cases, where assessment comprises the likely total exposure:
  - No additional uses apart of what is assessed
  - No additional sources of exposure
  - No indirect exposure via livestock

Boundary conditions for TTC exposure estimates

(2) Grouping of metabolites for TTC general toxicity assessment

- Group all toxicologically uncharacterised metabolites
- Restricted to cases, where assessment comprises the likely total exposure (see genotoxicity assessment)

Boundary conditions for TTC exposure estimates

(3) Acute and chronic exposure estimates for TTC assessment

TTC **genotoxicity** assessment

Acute:	Non-thresholded genotoxicity
Chronic:	TTC derived from chronic data

TTC **general toxicity** assessment

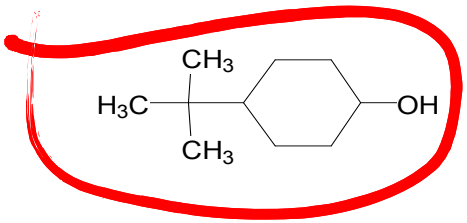
Acute:	Pesticide specific *ad hoc* acute TTC´s
Chronic:	TTC derived from chronic data

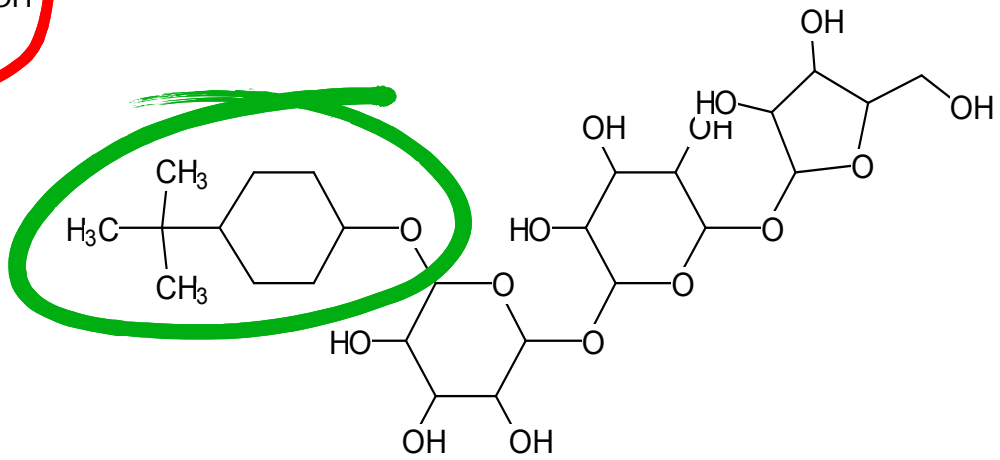
Boundary conditions for TTC exposure estimates

(4) Expression of metabolites as parent equivalents

Different molecular weights have influence on exposure calculations (e.g. conjugates, cleavage products)

Where no specific reference values are available for metabolites, values for the parent are the basis for assessments (rat metabolites; comparative tox assessment)





Boundary conditions for TTC exposure estimates

(5) Consideration of groundwater residue levels for TTC

Calculation of PEC_{gw} values:

- Assume 26 yrs of continuous use
- 6 yrs equilibration phase + 20 yrs leaching
- 20 yrs: spatial and time-dependent **80. Percentile**
- values are representative for different local scenarios (EFSA 2012)

Example for possible refinement:

1. tier: Apply maximum values from the List of Endpoints and combine it with worst case diet
2. tier: Combine national diets with representative groundwater levels

[3. tier: Calculate 50. Percentile GW levels during 20 yrs → **not recommended**; re-assessment by fate specialists required]

Specific conditions for TTC exposure estimates

(I) Pre-harvest intervals for combinations of metabolites

(II) How to derive suitable residue input values by use of

i. Field data

ii. Field AND metabolism data (conversion factors)

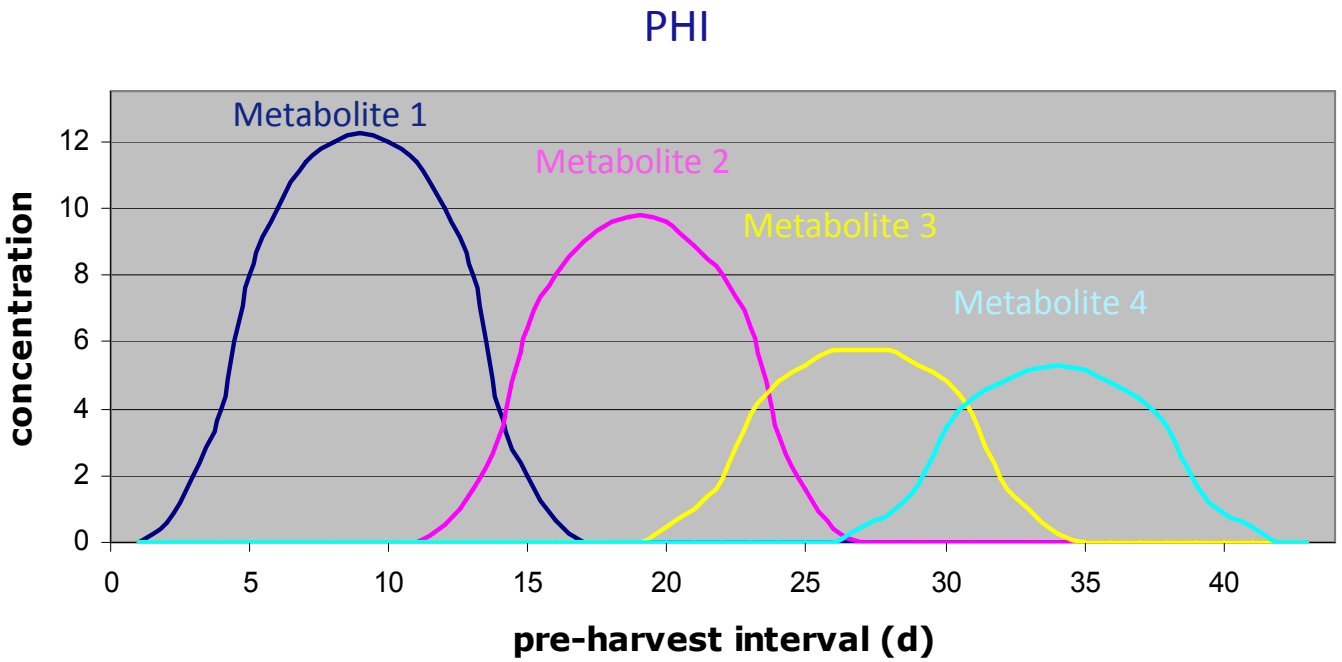
iii. Metabolism data

iv. Normalisation to 1N rate

(III) Accumulation in rotational crops

(I) Pre-harvest intervals for combination of metabolites

- Assessment (default) at target PHI
- Suspected genotoxicity → maximum occurrence of metabolites at the target PHI or later
- No combination of different PBIs



(II) How to derive suitable residue input values

i. Measured GAP field data

If non-GAP data, transform to realistic conditions according to the recommendations of the WHO proportionality approach:

- linear extra- or intrapolation to GAP rate
- 0.3 – 4N rate
- no ±25% rule
- restriction to minimum 50% GAP trials may not always be necessary pre-setting the residue definition

(II) How to derive suitable residue input values

ii. Conversion factors (1)

derived from metabolism (CF = $metabolite_{met}/indicator_{met}$)
and applied to the set of field data (CF x $indicator_{field}$)

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ii. Conversion factors (1)

derived from metabolism (CF = $metabolite_{met}/indicator_{met}$) and applied to the set of field data (CF x $indicator_{field}$)

a. Targeted data better than averaged data

b. Mean CFs should be derived in case of more than one study (multi label; multi crops within one crop group)

c. CFs can be based on intermediate or non-food/non-feed samples (note: increasing uncertainty with increasing distance from target design)

(II) How to derive suitable residue input values

ii. Conversion factors (2)

d. Provide justification for the choice of data

- type of application, e.g. soil or foliar
- role of the number of applications, interval and sampling stage regarding metabolisation rate
- matrix type
- active substance properties, e.g. systemic behaviour
- differences metabolism-metabolism and metabolism-field studies, e.g. reduced or enhanced metabolisation in field compared to metabolism studies

e. Not applicable, where indicator (parent) levels in field studies are <LOQ.

(II) How to derive suitable residue input values

iii. Metabolism study data

Single or a set of residue values (median/highest, mg/kg) from metabolism studies can be used, where indicator levels in field studies are <LOQ

- normalise metabolite levels to 1N GAP conditions
- take this value derived for one (or more) model crops in metabolism studies and extrapolate to all intended crops for exposure assessment
- provide justification and explain uncertainties

Residues in rotational crops

For non-accumulating metabolites: **-**

For accumulating metabolites: **Do uncertainties allow conclusions**?

The same principles for exposure assessments apply to primary and rotational crops:

- conversion factors
- selection of indicator compound
- preference of field data over metabolism data
- normalisation and extrapolation of crops

Refinement by evidence of reduced bioavailability (“aging”)

Conclusions

1. Exposure estimates within TTC can be facultatively used to exclude metabolites from further assessment and probably from *in vitro* or *in vivo* animal testing
2. The frame for acceptance of exposure estimates is given by the uncertainties connected with the calculation
3. Case-specific justifications and uncertainty considerations need to be made for all key parameters
4. Regulatory decisions based on TTC are restricted to the residue situation assessed, i.e. no extrapolation without re-calculation
5. TTC should be used (and accepted) only where significant future changes in the residue situation are unlikely (e.g. complete residue data package available; very limited field of uses)