Application of the new EFSA Guidance on assessment of metabolites for dietary risk assessment for new submissions

An industry perspective

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The new EFSA guidance

GUIDANCE

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Guidance on the establishment of the residue definition for dietary risk assessment

EFSA Panel on Plant Protection Products and their Residues (PPR)

→ First draft in March 2016, final document published in December 2016

→ Takes into account both toxicity and dietary exposure of metabolites

→ Not yet officially in force

The new EFSA Guidance - Structure

Module 1: Assessment of genotoxicity

Needed for all identified metabolites ***at any level***

→ no trigger values

Module 2: Assessment of general toxicity

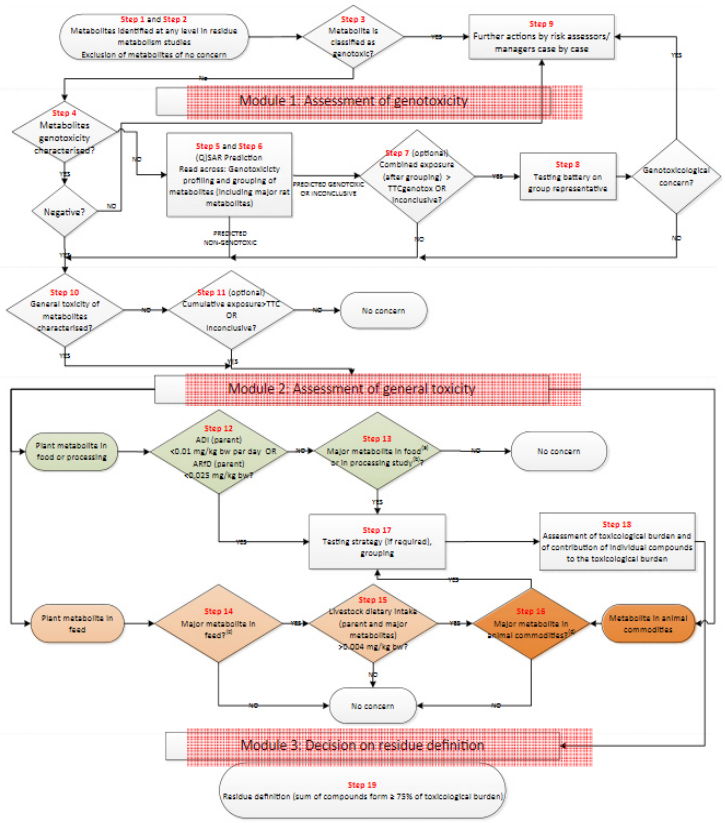
Needed for all „major“ metabolites in ***food and feed***

→ above low trigger values

Module 3: Decision on residue definition

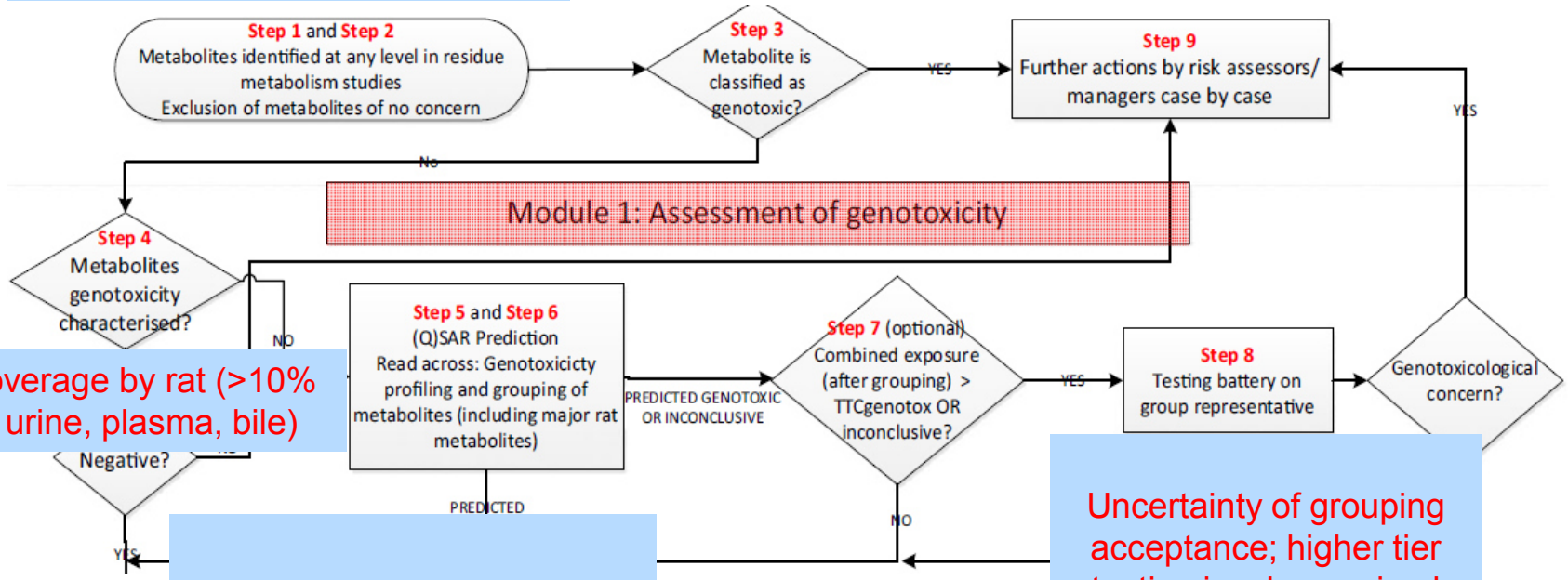
New ***toxburden concept*** leads to

→ complex residue definitions



EFSA guidance – Module 1

no exclusion of metabolites possible



Coverage by rat (>10% in urine, plasma, bile)

QSAR models/read across/interpretations not ready-to-use

Uncertainty of grouping acceptance; higher tier testing involves animal studies

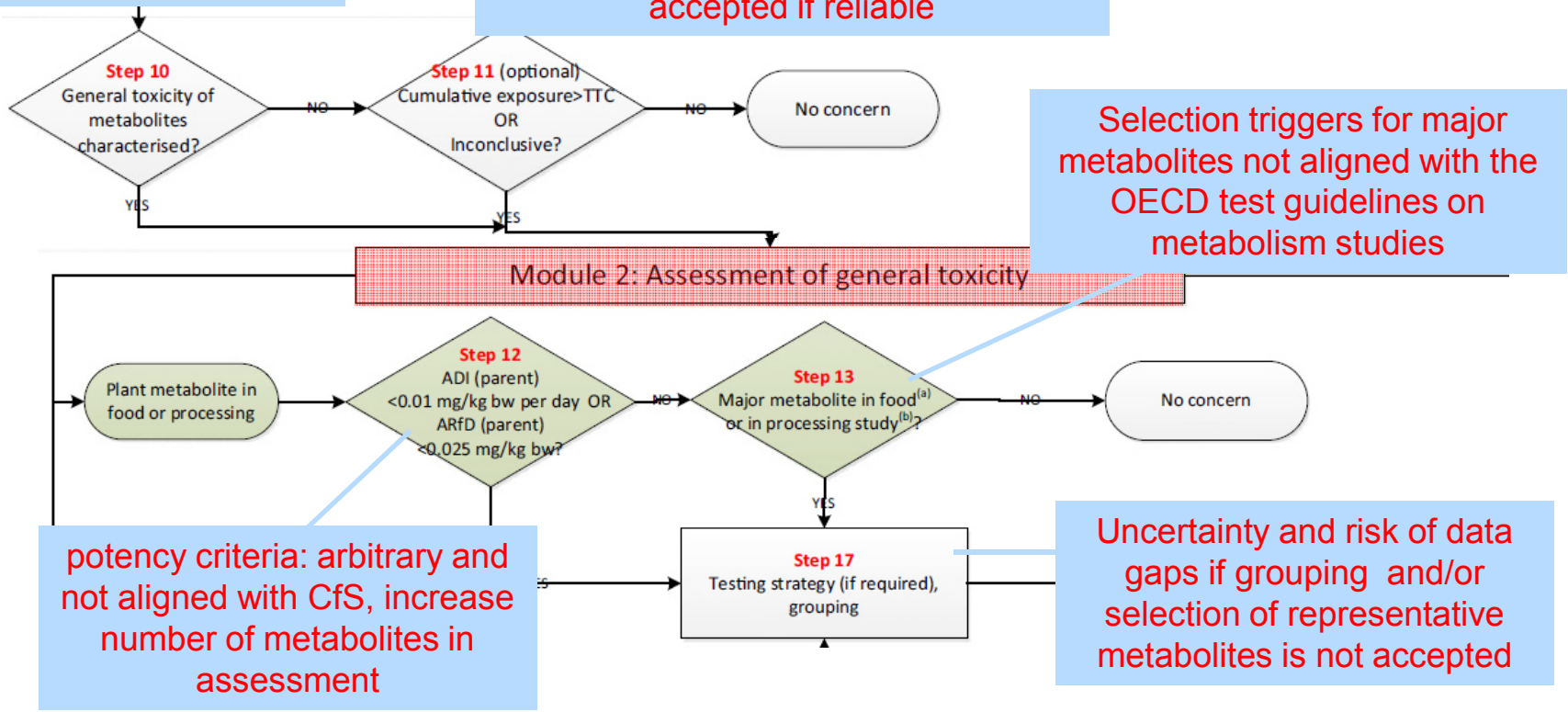
Module 1 – Feedback

- No exclusion of metabolites possible (e.g. with no human exposure)
- QSAR models/interpretations not ready–to-use (chosen models have to be trained for agrochemicals)
- Acceptance of read-across unclear (models? training?)
- Huge uncertainty in acceptance of grouping
- Genotox assessment/testing
  - Synthesis
  - In vitro testing and potential higher tier in vivo testing (additional animal studies)

EFSA guidance – Module 2

Assessment of rat metabolism accepted? Source of uncertainty

Combined exposure of all uncharacterized metabolites; only accepted if reliable



Selection triggers for major metabolites not aligned with the OECD test guidelines on metabolism studies

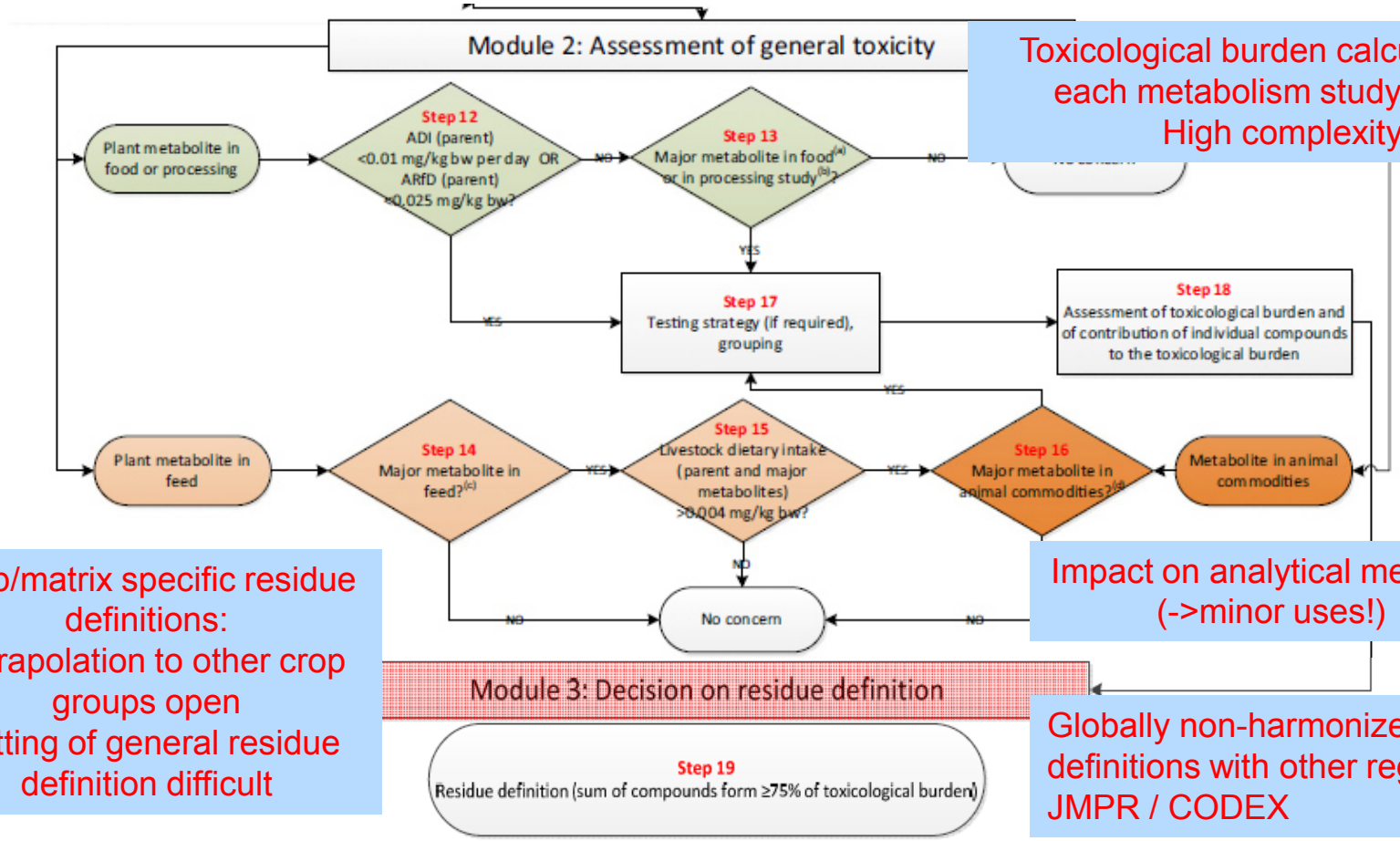
potency criteria: arbitrary and not aligned with CfS, increase number of metabolites in assessment

Uncertainty and risk of data gaps if grouping and/or selection of representative metabolites is not accepted

Module 2 – Feedback

- Individual or subgroup TTC assessments are not foreseen
  - Risk assessments fail in Module 2 (esp. for Ais with low reference values)
- Metabolite coverage by rat metabolism: only >10% dose on single metabolite basis, no down-stream metabolites
- Triggers for “major metabolites” (≥ 10%TRR + ≥ 0.01 mg/kg) without considering the exposure contribution
- Potency criteria: arbitrary and not aligned with CfS, increase number of metabolites in assessment
- Acceptance of grouping and/or selection of representative metabolites: source of uncertainty and risk of data gaps
- Expected strongly increased demand for toxicity testing

EFSA guidance – Module 3



Toxicological burden calculation for each metabolism study / label: High complexity

Crop/matrix specific residue definitions: Extrapolation to other crop groups open Setting of general residue definition difficult

Impact on analytical methods (->minor uses!)

Globally non-harmonized residue definitions with other regions or JMPR / CODEX

Module 3 – Feedback

- Toxicological burden calculation for each metabolism study / label: High complexity
- Crop/matrix specific residue definitions: Setting of general residue definition difficult, extrapolation to other crop groups open
- Impact on analytical methods (->minor uses!)
- Globally non-harmonized residue definitions with other regions (e.g. US/CA) or JMPR / CODEX

Example case study

- Potent (according to definition in the draft EFSA guidance)
- Classified Repr. 2
- Limited registration: 4 crops in 2 crop categories
- Available metabolism studies:
  - plants: in cereals and pulses/oilseeds
  - livestock: goat and hen
  - rat: extensive metabolism; 2 metabolites were found >20% in bile
  - Similar metabolic profile
- Available residue data: only for parent
- 7 plant metabolites, 6 minor plant feed metabolites, 8 major livestock metabolites, 6 minor livestock metabolites

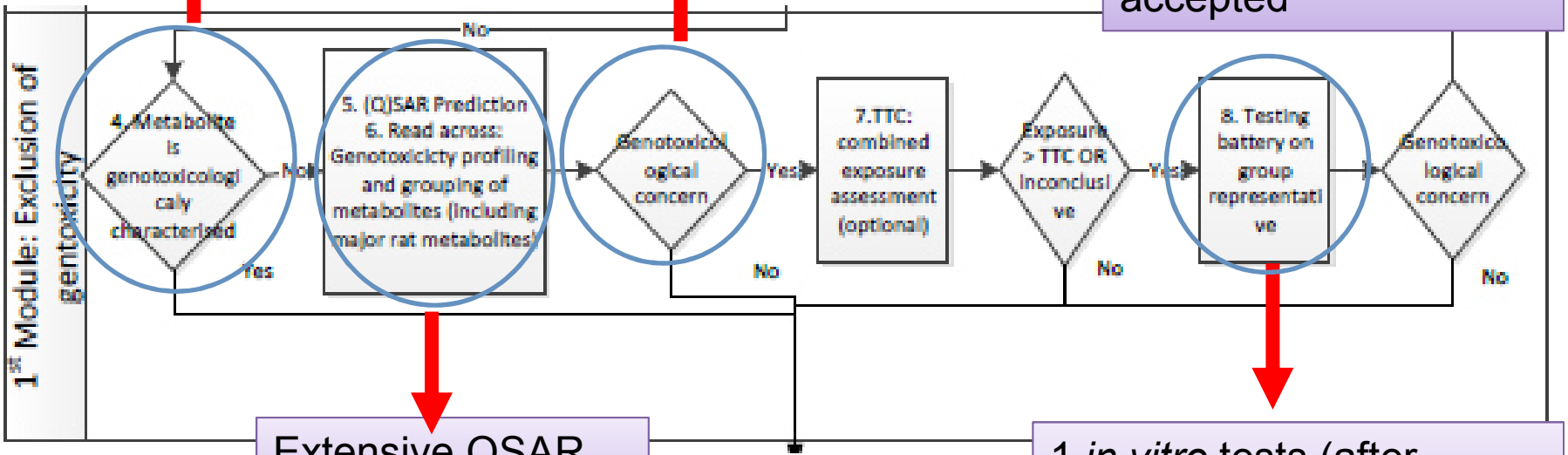
Example case study 1

Efforts for module 1

Assessment needed for 23 metabolites

QSAR not reliable/sufficient: many structures out of domain

Grouping approach: uncertain, whether accepted



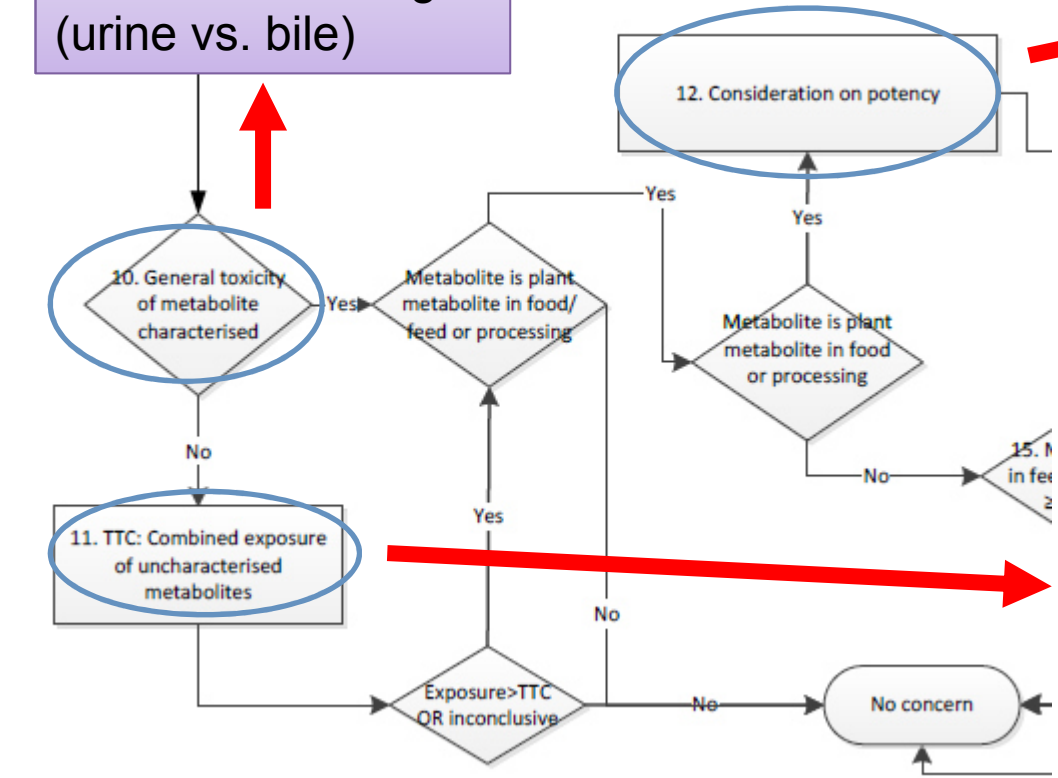
Extensive QSAR analysis

1 *in vitro* tests (after grouping); *in vivo follow up?* → depends on acceptance of grouping

Example case study 1

Efforts for module 2

Extensive metabolism in rats → limited coverage (urine vs. bile)

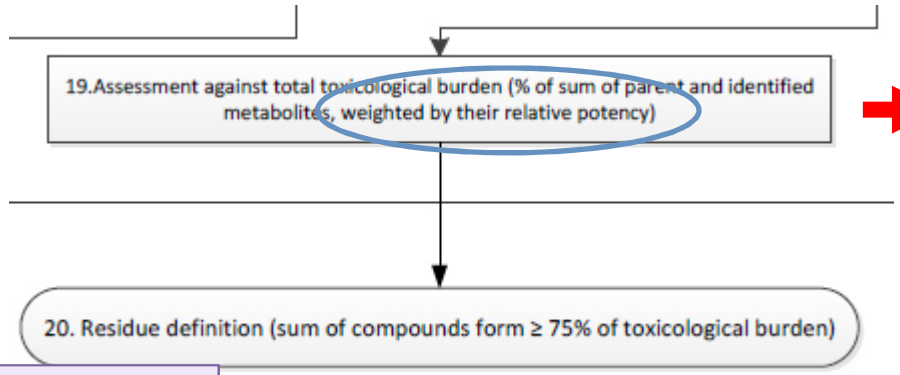


AI is considered potent: criteria used differ from CfS document)

Previously: Each metabolite < 1.5 µg/kg bw → no health concern
Now: Combined exposure > 1.5 µg/kg bw → Each metabolite needs tox assessment/testing

Example case study 1

Efforts for module 3



Concept of relative potency only relevant if metabolites are considered similar

Inclusion of all metabolites in the RD does not necessarily increase consumer safety, but increases efforts and complicates risk assessment.

Existing residue definition (RD):
Parent + 1 metabolite
New RD:
3 RDs (primary and rotational crops)
Parent + up to 4 metabolites

Current experiences at EU level

RMS partially apply guidance (genotox module) for ongoing assessments

Guidance not yet implemented

BUT

changes in residue definitions (inclusion of metabolites, restriction to crop groups)

Full application of guidance for upcoming submissions requested?

EFSA conclusions show partial application of the guidance (genotox and general tox module):
->many data gaps
-> non-finalized residue definitions and risk assessments!

challenged metabolite strategy (grouping)

Take home messages

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A scientific toolkit with suitable and reliable QSAR tools/databases is necessary including the relevant training and development of expertise

The subjective grouping approach/interpretation of what is considered a similar metabolite vs parent is leading to huge uncertainties with the risk of being assessed an incomplete data package.

TTC assessment against all uncharacterized metabolites but not for single metabolites/distinct groups → animal testing ↑

The complexity of the evaluation scheme/application of the toxicological burden approach requires training and development of expertise at MS level and Industry

A multiple residue definition approach can lead to increased complexity of risk assessments without necessarily increasing consumer safety

A lack of consistency with national/international review systems resulting in an impact on global harmonisation of RDs, MRLs, ITs and trade

Thank you