ECPA input

Initial Experience of applicants with the Draft Guidance Document (March, 2016)

Stephanie Melching-Kollmuss, BASF SE

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Outline of presentation

- Conduct of the ECPA impact assessment
- Overview of our observations
- Example case study 1 - increased tox efforts
- Example case study 2 - increased exposure efforts
- ECPA's key findings from the assessment
- Questions and discussion topics

ECPA impact assessment

- **14 active substances were taken through the assessment**
  - Anonymized datasets of:
    - 6 fungicides/4 insecticides/4 herbicides
- **Who did the work?**
  - 6 companies evaluated 2 – 3 compounds (different regulatory stages)
  - Limited experience and different approaches/understanding
- **Stepwise approach**
  - Taking account of all reliably identified metabolites
  - Module by module
  - Comparison between existing and newly proposed approaches
  - Potent/non-potent AI / DART alert

ECPA impact assessment

Active Substance Code e.g. STT-11 I - insecticide F - fungicide H - herbicide	Plant Metabolism Studies (primary, CRC, HTH) total number of major metabolites in **food** ≥10% and ≥0.01 mg/kg **OR** ≥0.05 mg/kg	Plant Metabolism Studies (primary, CRC, HTH) total number of major metabolites in **feed** ≥10% **and** ≥0.01 mg/kg	Plant Metabolism Studies (primary, CRC, HTH) total number of minor metabolites ≤10% or ≤0.01 mg/kg (currently the GD is requesting 'every identified metabolite' needing genotox assessment)	Animal Metabolism Studies (hen, goat) total number of metabolites ≥10% **OR** ≥0.01 mg/kg	Animal Metabolism (hen, goat) total number of metabolites ≤10% or ≤0.01 mg/kg (currently the GD is requesting 'every identified metabolite' needing genotox assessment)	Residue data available for how many of these metabolites?	Comments
AS 1	15	15	5	6	3	Crop: 5 Animal: 3	Please specify whether your active will be considered as potent

- **Using the data from the available metabolism studies**
  - Plant metabolism studies – how many major/minor metabolites in food?
  - Plant metabolism studies – how many major/minor metabolites in feed?
  - Livestock studies – how many major/minor metabolites?
- **Residue data available for how many of these metabolites?**
- **Rat metabolism**
  - How many of the metabolites are considered covered?

Modules in overview

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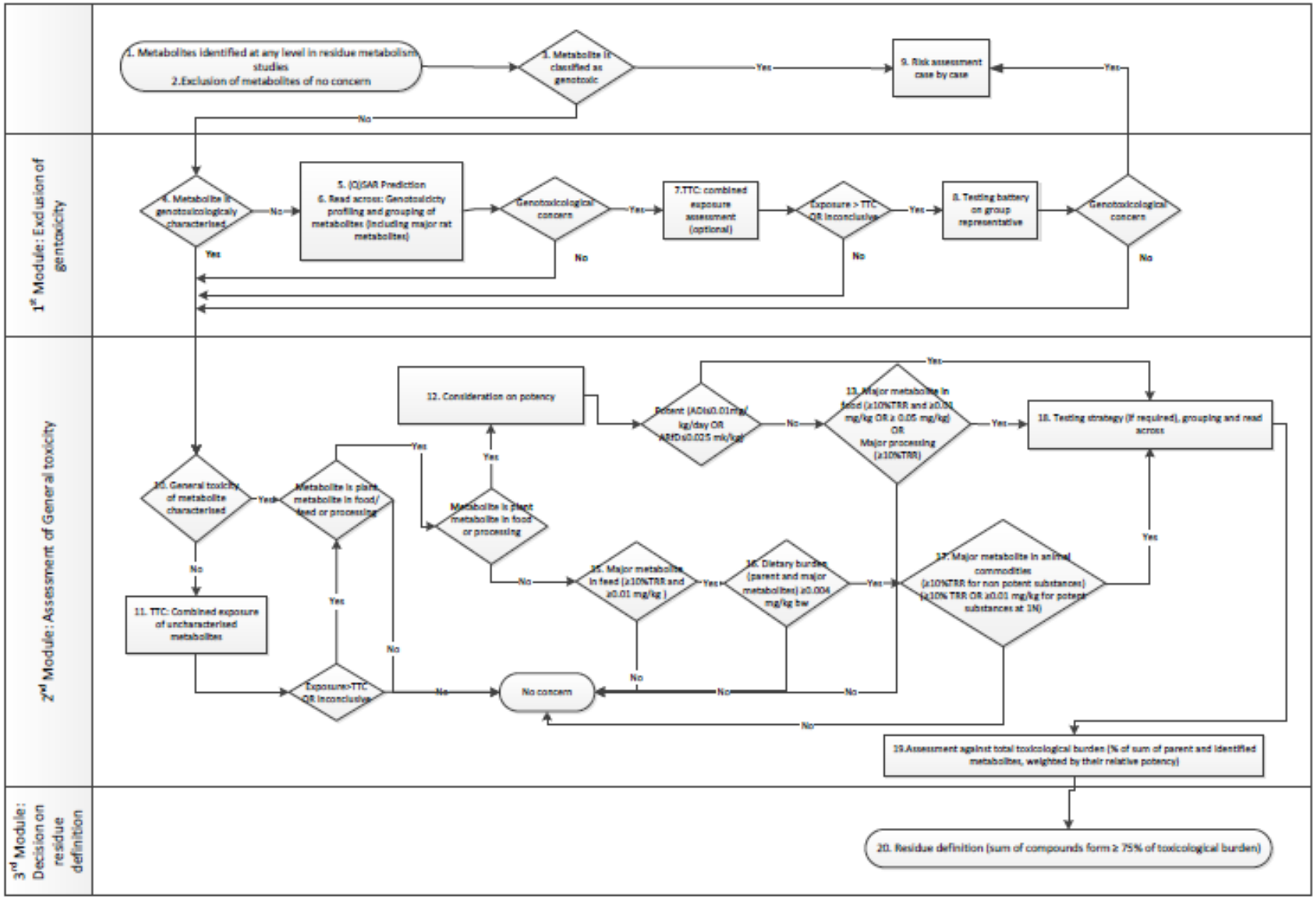

ECPA impact assessment

Stepwise approach, capturing….

- **Module 1:**
  - number of metabolites needing assessment
- **Module 2:**
  - number of genotox assessments (QSAR) and tests (*in vitro*/*in vivo*)
  - associated efforts (time, synthesis)
  - number of metabolites requiring toxicological testing
  - associated efforts (time, synthesis)
  - additional residue work (e.g. field trials, feeding studies, analytical methods, storage stability), triggering of any other studies

Difficult to capture the underlying uncertainties

- Assessment was conducted using the **DRAFT GD**
- Grouping/s
- Selection of group representative
- Read-across
- Further work needed depending on outcome

- **Module 3:**
  - Number of metabolites ending up in the residue definition for plant/animal
  - Number of different residue definitions derived by toxicological burden approach

Overview of observations

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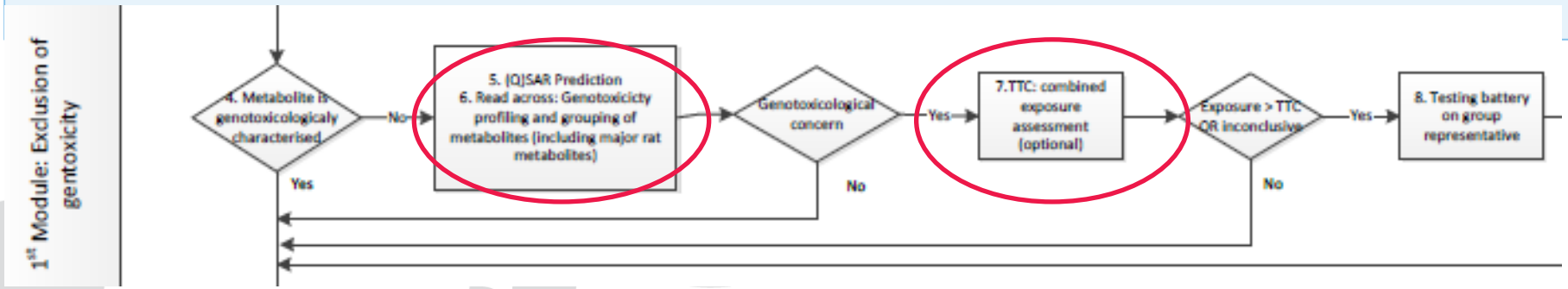
Module 1: Exclusion of genotoxicity: stepwise approach

- QSAR assessment (VEGA, OECD Toolbox, OASIS-Times, DEREK,…)
  - Most structures are “out of domain”
  - Use of structural alert information for grouping
  - Applicability domains need to be enhanced
- Robustness/acceptance of read-across
- Step 7: TTC genotox trigger applicable for subgroups/individual compounds?



Module 1 – main areas of concern/uncertainties

- Suitability of QSAR tools and expertise needed
- Acceptance of read-across approaches
- Reliability of structural alert information
- Huge number of additional genotox assessment/testing
  - >180 metabolites across the 14 ASs
  - Synthesis
  - Testing and potential follow-up testing

Overview of observations

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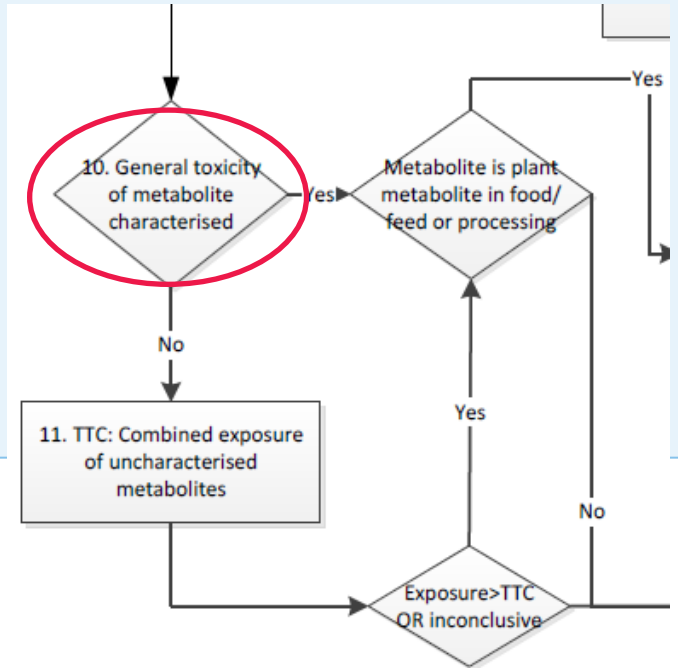
Module 2: Assessment of general toxicity

- Large number of metabolites have to be taken through assessment in Module 2
- Step 10: Which metabolites are covered by rat metabolism?
  - Occurrence in bile/feces
  - %administered dose vs %absorbed dose
  - Take into account dosages administered in toxicological studies
  - Combined occurrence of metabolites in a pathway



Overview of observations

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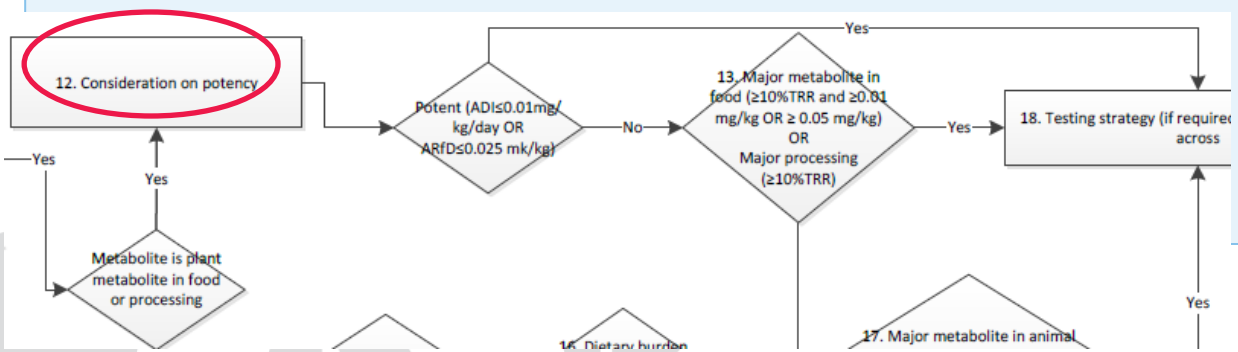
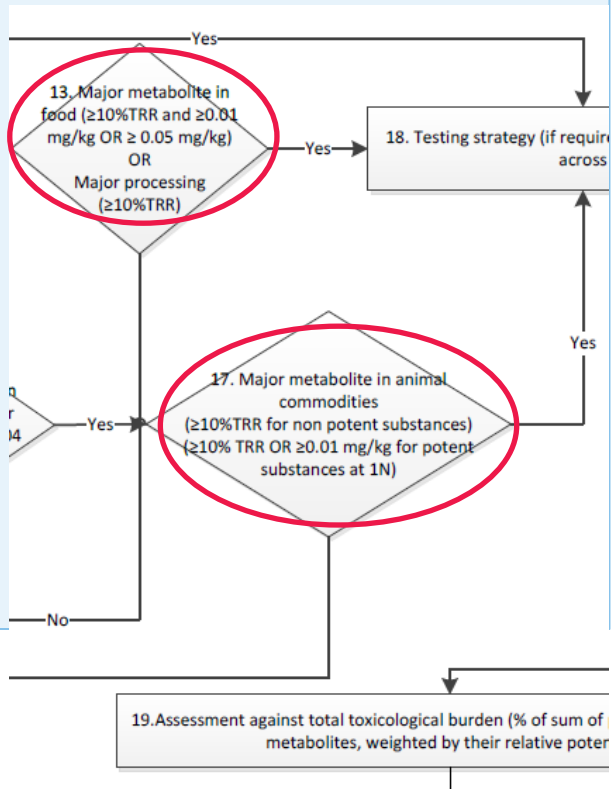
Module 2: Assessment of general toxicity

- Large number of metabolites selected as major
  - in plant up to 15 metabolites (in 10 of the 14 cases more than 5 metabolites)
  - in animal up to 18 metabolites (in 12 of the 14 cases more than 5 metabolites)

- Step 12: Consideration of potency
  - For potent compounds all food metabolites need further assessment/testing
  - In the candidate for substitution document the 5th percentile instead of the 25th percentile is used





Overview of observations

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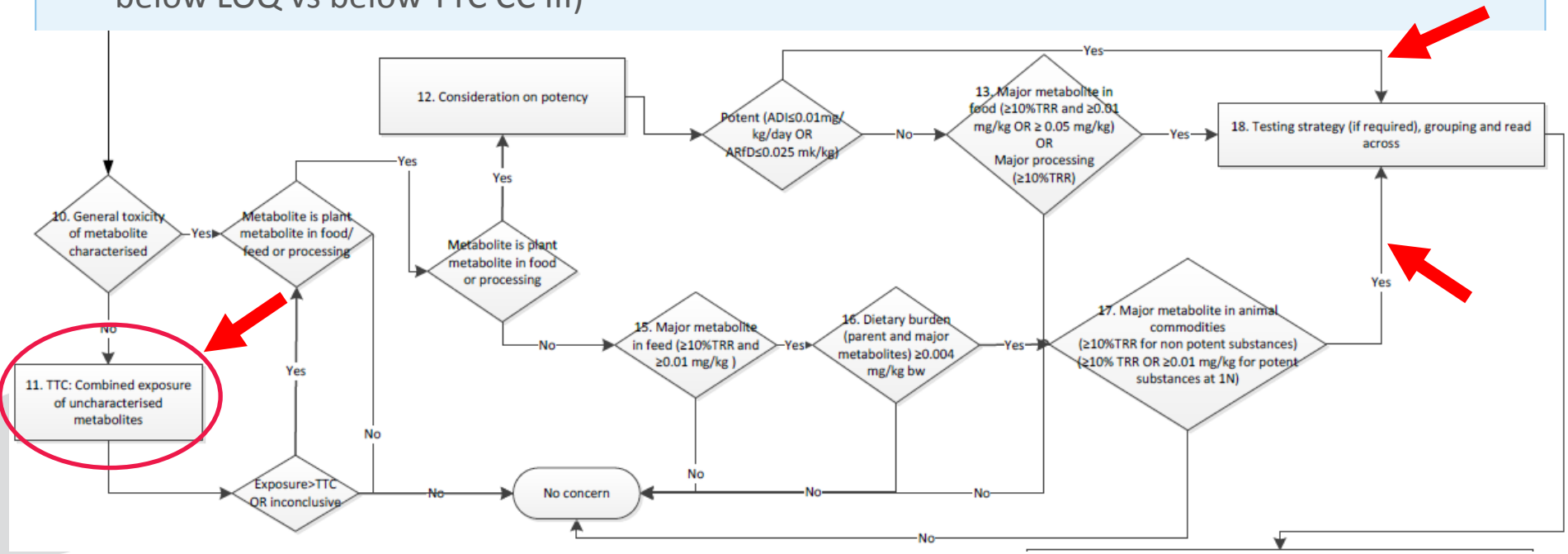
Module 2: Assessment of general toxicity

- Step 11 (**combined** exposure assessment against TTC Cramer thresholds): Unclear if only a rough screening or if it could lead to prioritized testing
- Should be applied for subgroups not for **all** uncharacterized metabolites
  - Consider to use molar TTC thresholds
- Exposure assessment considerations before testing defines efforts for tox testing (values below LOQ vs below TTC CC III)



Overview of observations

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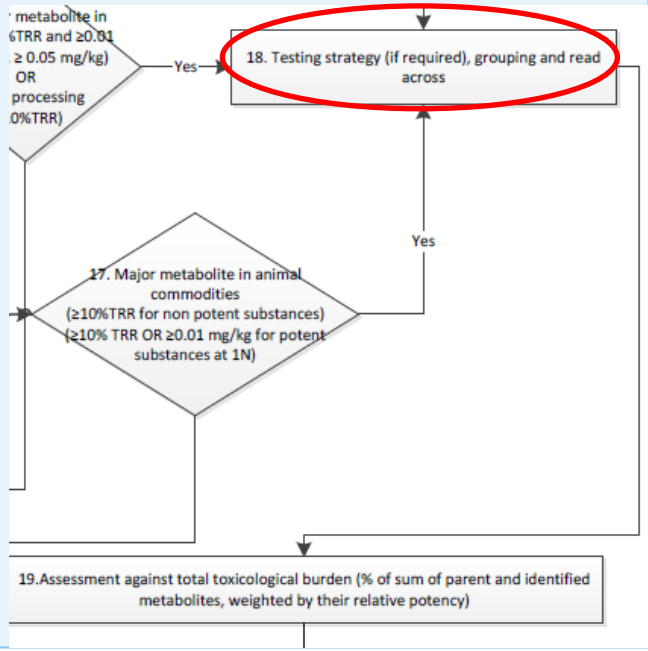
Module 2: Assessment of general toxicity

- Step 18: Testing strategy

- Further toxicological testing necessary in 8 out of 14 cases (max. 10 further metabolite testings) => **More animal testing**
- Huge uncertainties
  - Grouping and representative (accepted?)
  - What is considered similar toxicity?
  - DART alerts (in OECD toolbox)
  - Reproduction toxicity testing needed?
  - Uncertainty factors (extrapolation from subacute subchronic studies)

- Step 19: Accurate relative potency derivations require:
  - More animals tests
  - Mechanistic in vitro studies (robustness?)



Module 2 – Main areas of concern/uncertainties

- **TTC thresholds should be used for prioritization**
  - Combined exposure of subgroups
  - Inclusion at a later stage to reduce animal testing
- **What is considered covered by rat metabolism**
  - Bile/feces, 10% in plasma, administered doses, combine compartments, combine pathways, consider doses
- **Efforts and uncertainties in tox testing (~30 metabolites)**
- **Triggers for “major metabolites” (≥ 10%TRR + ≥ 0.01 mg/kg) without considering the exposure contribution are causing a high workload**
- **Concept of (relative) potency needs experience and further thoughts**

Overview of observations

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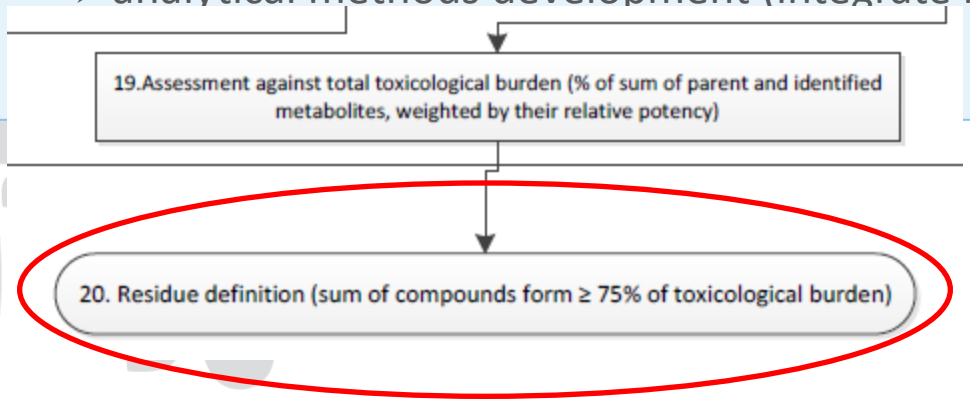
Module 3: Decision on residue definition (RD)

- Uncertainties in interpretation of toxicological burden approach:
  - strict interpretation (*inclusion of all major metabolites ≥ 75% toxicological burden*) leads to different RDs for each crop, livestock matrix (even if metabolism is qualitatively similar)
  - difficulties to derive a general residue definition for plant in these cases

- Increased number of metabolites in residue definition triggers high workload:
  - new residue trial programs
  - repetition of livestock feeding studies (?)
  - analytical methods development (integrate many metabolites into one method!)



Module 3 – Main areas of concern/uncertainties

- **More flexibility is needed in the 75% trigger of toxicological burden**
  - More realistic consumer exposure estimates needs to be taken into account before residue definition is finalized
- **Requirement of various residue definitions increases complexity of risk assessment**
- **Increased efforts for residue data generation (e.g. additional residue trials, feeding studies)**

Example case study 1

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Fungicide

- **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

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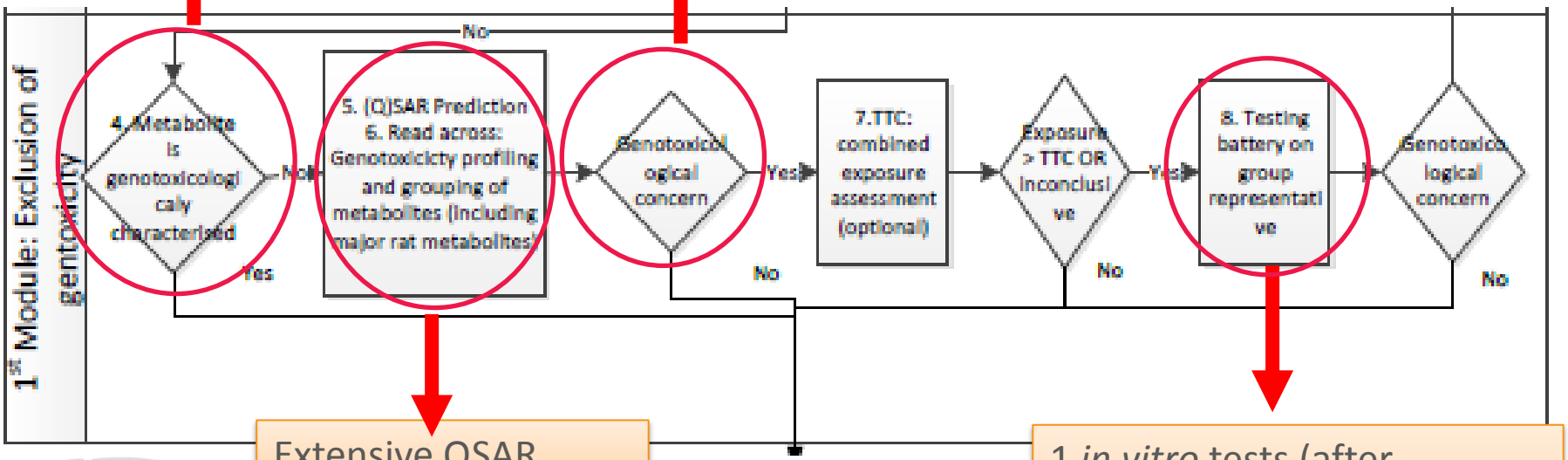
Efforts for module 1

Assessment needed for 23 metabolites

QSAR not reliable/sufficient: many structures out of domain

Grouping approach: uncertain, whether accepted (structural alerts, two ring systems, hydroxylations, further oxidations)



Extensive QSAR analysis

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

Example case study 1

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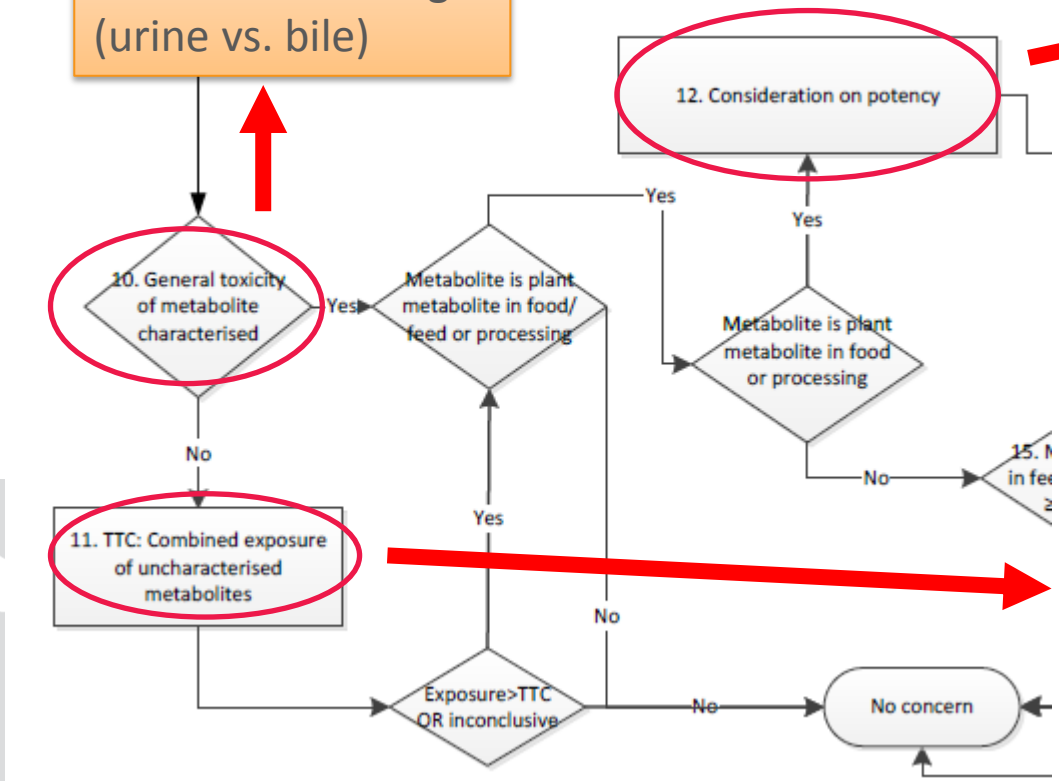
Efforts for module 2

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



AI is considered potent: Different criteria used (e.g. candidate for substitution 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

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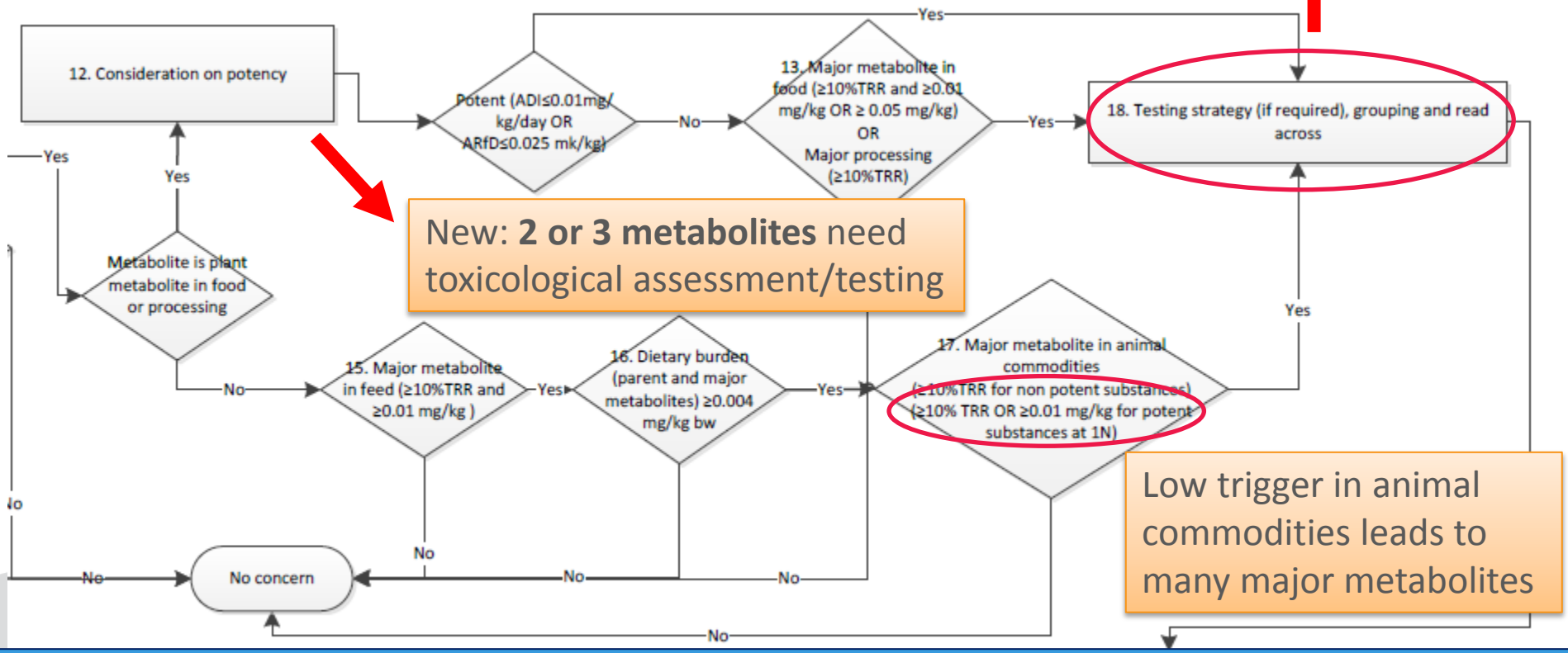
- Efforts for module 2

Based on outcome of 28-day studies further repro studies might be needed (UF)



New: **2 or 3 metabolites** need toxicological assessment/testing

Low trigger in animal commodities leads to many major metabolites

Major impact: Increased animal testing!

Example case study 1

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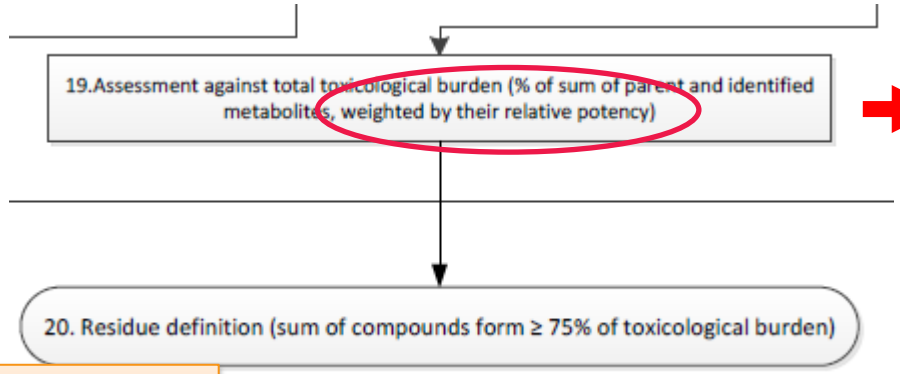
Efforts for module 3



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 (to cover primary and rotational crops)
Parent + up to 4 metabolites

Example case study 2

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Herbicide

- Potent (*according to definition in the draft EFSA guidance*)
- Broad registration: EU approval in 25 crops from 5 crop categories (cereals, pulses/oilseeds, root crops, fruit crops, leafy crops)
- Available metabolism studies:
  - plants: in 5 crops covering 3 crop groups (cereals, pulses/oilseeds, root crops) =>common metabolic pathway, studies cover all other crop groups as well
  - livestock: goat and hen metabolism with main feed metabolites => low residues (<0.01 mg/kg) at 1N feed burden, no need to consider animal metabolites
- Available residue data: common moiety
- 10 major plant metabolites, 12 minor plant metabolites

Example case study 2

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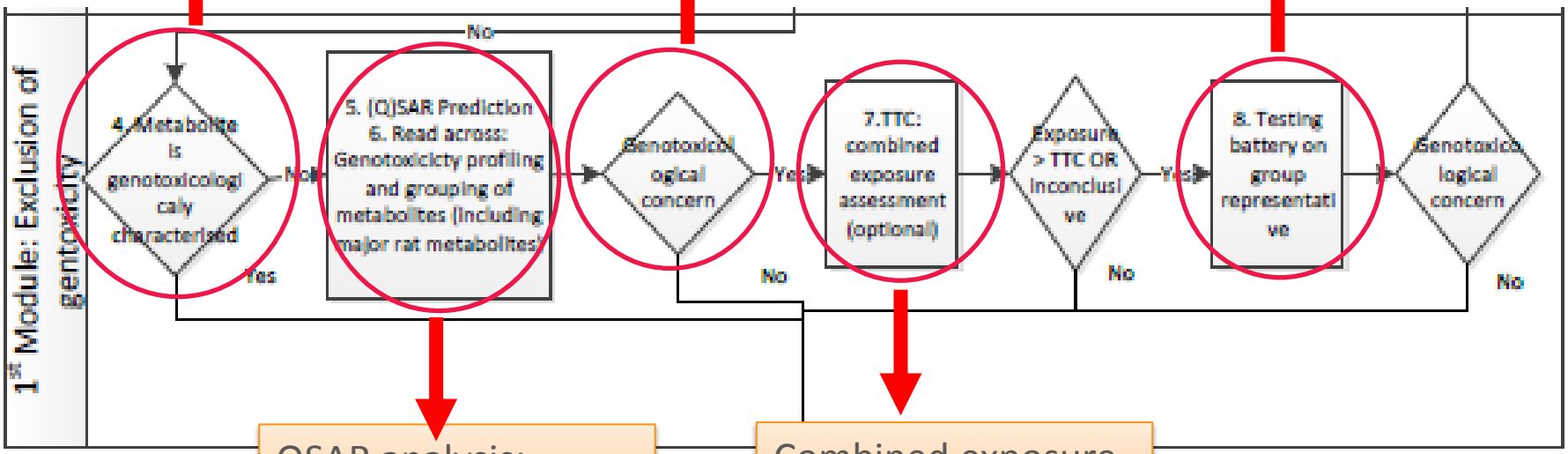
Efforts for module 1

Assessment needed for additional 10 metabolites

QSAR not reliable/sufficient: many structures out of domain

At least 13 *in vitro* tests (after grouping); *in vivo follow up?*



QSAR analysis: time extensive

Combined exposure > gentox TTC

Example case study 2

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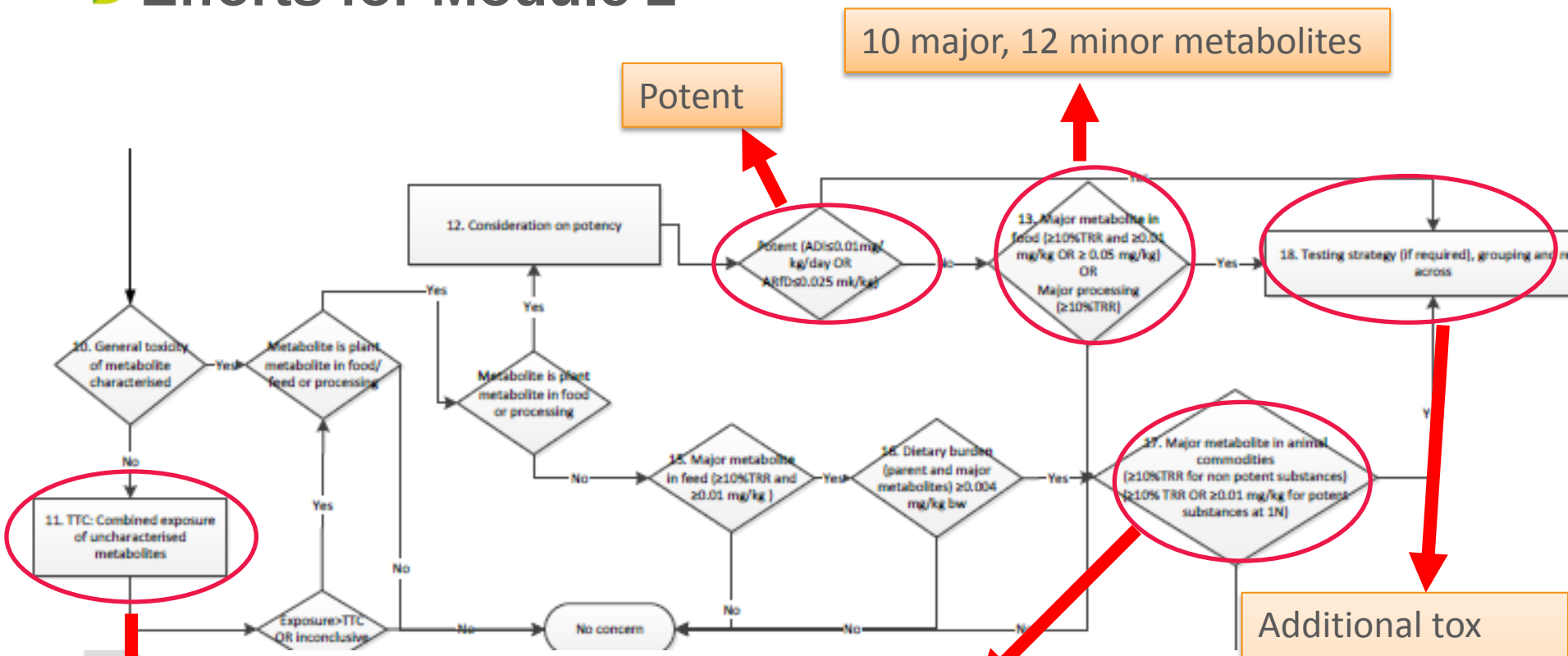
Efforts for Module 2



Combined exposure > TTC CC III

No major animal metabolites

Additional tox testing for 1 metabolite (after grouping): duration 6-12 months

Example case study 2

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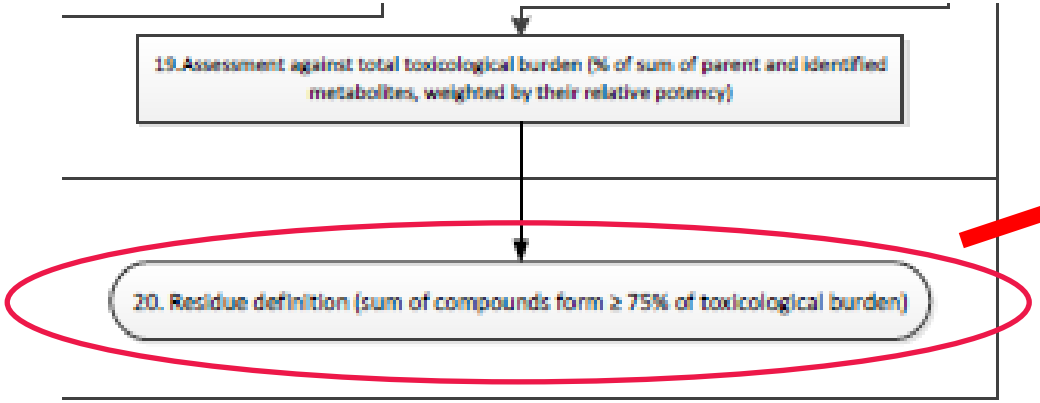
Efforts for Module 3



5 different residue definitions in plants, including up to 9 different metabolites

Analytical methods for plants

Storage stability for all metabolites

Residue trial program for up to 13 crops (limited extrapolation of metabolite levels beyond crop categories covered by metabolism studies)

ECPA's key findings

- Increased upskilling necessary in scientific tools (QSAR, read-across) in industry and Regulatory Authorities
- More toxicological testing will be necessary (increased animal testing, big impact in terms of time and uncertainty)
- Significantly increased efforts for metabolite synthesis and analytical method development necessary
- New studies triggered e.g. toxicological studies, feeding studies, crop residue trials, storage stability

ECPA's key findings

- Increased number of metabolites in the residue definition; may lead to exceedances of ADI/ARfD
- Entire approach is very complex (especially modules 2 and 3): inconsistent interpretation among companies → how will Member States do the assessment consistently?
- Low trigger values for selecting metabolites as "major" without consideration of absolute dietary exposure leads to high workload
- Strict application of 75% tox burden per crop and livestock commodity approach leads to complex residue definitions, increased complexity of risk assessments, and lack of consistency with other national and international review systems

Questions and discussion topics

- It is suggested to conduct the combined TTC risk assessment (step 11) at least on subgroups
- Single compound assessment against TTC could be a prioritization step
- If metabolite toxicity is not similar to parent, additional safety factors or reproductive studies (with eventual follow-up) have to be considered
- Future experience to be gained on what is considered robust and reliable exposure estimates (e.g. needed for Step 11)

Questions and discussion topics

- Clarity on "coverage by parent“:
  - >10% absorbed vs administered dose
  - Combination of percentages in different biofluids
  - Inclusion of metabolites in a pathway
- Application of the toxicological burden concept for deriving the residue definition:
  - ≥75% target to be handled more flexible
  - Included metabolites to be checked for relevance to the consumer (exposure assessment)
- Guidance needed on deriving one residue definition for all crop commodities in case residue definitions differ for crop groups covered by plant metabolism (clearer from 26th September discussion)

New final Draft GD (July 2016)

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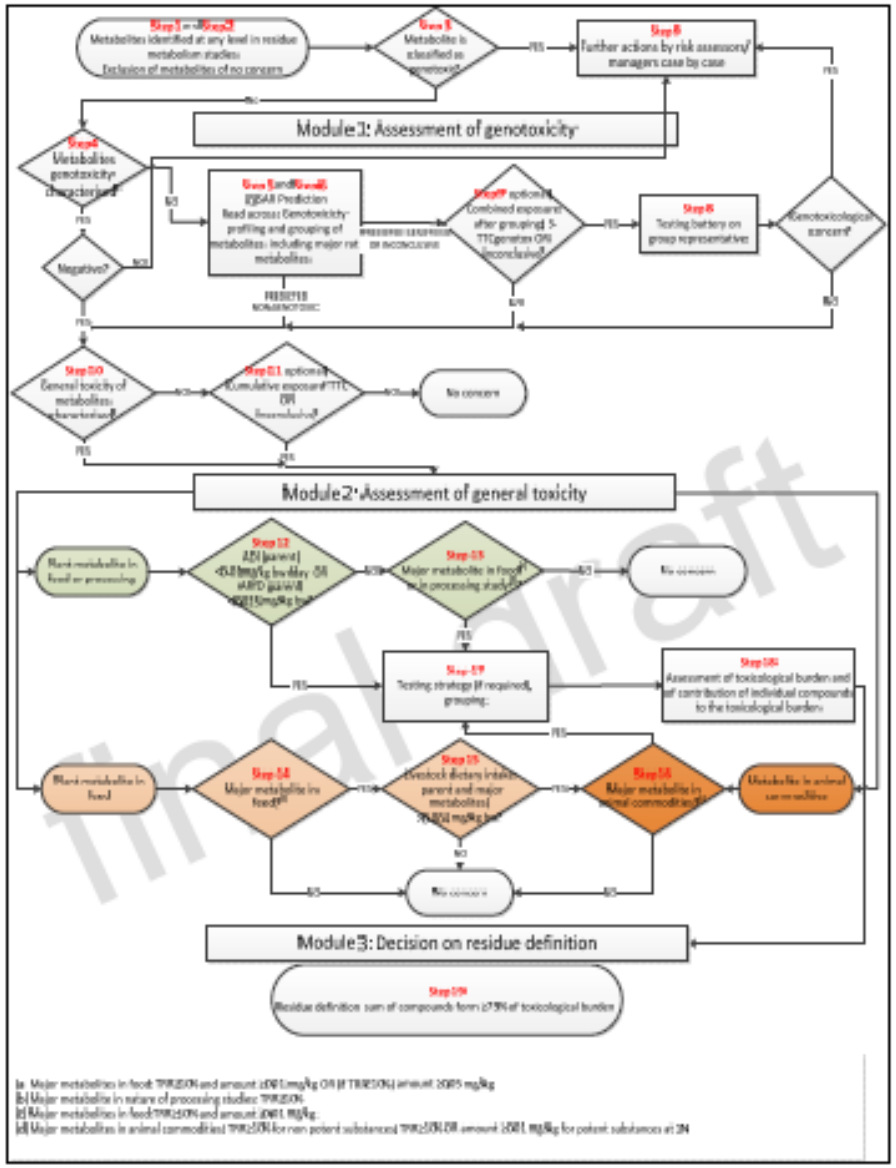

Comparison between March and July Draft

- Bile and plasma are included as to be considered absorbed
- Clearer description, which metabolites in a metabolic pathway can be considered together
- MTD testing no longer required (rather the concept of side-by-side testing proposed)
- Flow chart improved (e.g. separation between food and feed metabolites)

Comparison between March and July Draft

- **Exposure step included before toxicological testing**
  - Major metabolites can be qualified non-significant (if below LOQ in field trials) → no testing required

  → Why not using TTC CC III trigger?
- **Concept of toxicological burden is better described**
  - Applicability is still open to interpretation
- **Use of field residue data can be used to exclude metabolites from residue definition (→ wording in the final guidance needs clarification for livestock)**

Impact on key stakeholders

- **General**
  - Increased animal usage
  - How can the dialogue between applicant, RMS and EFSA work in practice?
  - Clear Guidance vs. a living document
- **Industry**
  - Increased cost (money and staff days) and duration for AI development
  - Application of a new Guidance document to old datasets
- **Member States/Regulatory Authorities**
  - Increased time and different expertise needed for evaluation
  - How will a consistent approach be achieved?

Impact on key stakeholders

- **Minor Use Associations**
  - Challenges of increased number of metabolites in residue definition and associated data generation will make it difficult for this community

This was a real team effort

- James Booth, Syngenta
- Monika Bross, BASF SE
- Leo-Waldemar Bürkle, Bayer Crop Science
- Dee Clarke, Syngenta
- Anja Hüser, Bayer Crop Science
- Frank Laporte, Bayer Crop Science
- Heike Lohmann, Adama
- Tina Mehta, Dow Agrosciences
- Janet Ruhl, DuPont Crop Protection
- Michaela Seiferlein, BASF SE

Many thanks

European
Crop Protection

Thank you for your attention

Example case study 1b

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Fungicide

- Not potent, **20** major metabolites, **14** minor metabolites ***(BASF F1)***

- **Efforts for Module 1:**
  - Assessment needed for 30 metabolites
  - In-silico/read-across assessments (240 working hours)
  - At least 3 metabolites for *in vitro/in vivo* testing (12 – 18 months)

- **Efforts for Module 2:**
  - Tox testing for up to 4 metabolites (18 - 36 months)
  - Synthesis, new analytical methods and storage stability studies
  - New residue trials for one crop group
  - New field rotational crop study
  - New cow feeding study (13 cows)

- **Efforts for Module 3:**
  - 5 different residue definitions to cover primary crops (2). rotated crops, livestock
  - Up to 7 additional metabolites in the RDs compared to current RDs

Example case study 1c

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Fungicide

- Not potent, **14** major metabolites, **10** minor metabolites ***(SYT 1)***

- **Efforts for Module 1:**
  - Assessment needed for 24 metabolites
  - In-silico/read-across assessments (160 working hours)
  - At least 13 metabolites for *in vitro testing and 5 estimated for in vivo* testing (12 – 18 months)

- **Efforts for Module 2:**
  - Tox testing for up to 2 metabolites (18 - 36 months)
  - Synthesis, new analytical methods and storage stability studies
  - New crop residue trials

- **Efforts for Module 3:**
  - Potential change to crop RD

Example case study 2a

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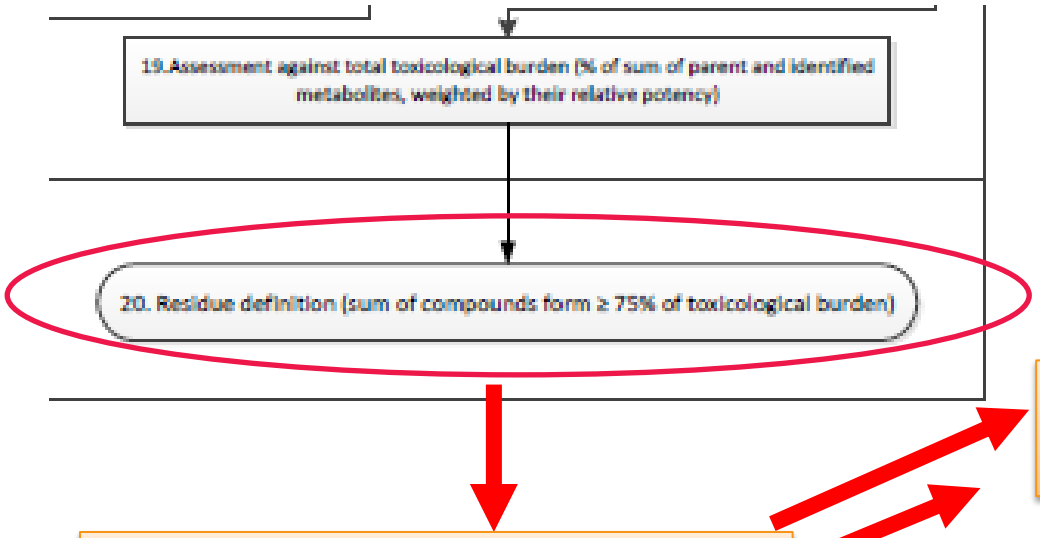
Efforts for Module 3 for supporting example



≥ 2 Analytical methods (plant, livestock)

Storage stability for all included metabolites

Residue trial program for 12 crop groups , processing studies

Number of residue definitions:
Plants: 4 (up to 7 metabolites)
Livestock: 4 (up to 6 metabolites)
Total no of different metabolites: 9

→ **Strict tox burden approach: different residue definitions -> considerable residue work and complex risk assessment**