Scientific Guidance Document of the PPR Panel on the establishment of the residue definition to be used for dietary risk assessment (EFSA-Q-2013-01001)

EFSA Info Session Pesticides
26/27 September 2016

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EFSA Pesticides Unit (Residues team)

BACKGROUND

- Follow-up activity on 2012 PPR Panel opinion **Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment**

- Terms of reference: stepwise method, based on **factual information** (toxicology & metabolism data), **non-testing methods** & **by weight of evidence** to:
  - conclude for which residues a hazard identification and characterisation is needed;
  - perform such a hazard identification and characterisation
  - define the compounds to be included in the residue definition for risk assessment

TIMELINE

Aug /Sep 2016 prepare publication Guidance & Technical report

June /July 2016 — **PPR Plenary adoption**

May & June 2016 — WG addressed comments; PSN consultation

Mar & Apr 2016 — Public consultation

Feb 2016 — PPR Panel endorsement of Draft

Jan 2016 — Finalisation of Draft

Feb 2014 — WG starts working

Dec 2013 — Acceptance of Mandate by PPR Panel

GUIDANCE

EFSA Journal

ADOPTED: 22 July 2016

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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)

Abstract

The European Food Safety Authority (EFSA) has asked the Panel on Plant Protection Products and their Residues to prepare guidance on the establishment of the residue definition for dietary risk assessment. The residue definition for risk assessment is used by risk assessors to evaluat potential risk of dietary intake of residues resulting from the application of a pesticide. This do guides the complex process of identifying the pertinent residue components that should be co for dietary risk assessments of chemical active substances. Specifically, the document

WORKING GROUP COMPOSITION

- **PPR Panel members:**

  Chair: Thomas Kuhl (BfR)

  Susanne Hougaard (Danish EPA);
  Gerrit Wolterink (RIVM) – as from Oct 2015

  former members (until mid 2015): B. Ossendorp (RIVM), A. Mantovani (ISS) & M. Filipič (NIB)

- **PRAS staff:**

  Secretariat: Andrea Terron & Anja Friel

  Scientific support: Juan Parra Morte, Rositsa Serafimova

- **External hearing experts:**

  Andrew Worth (JRC); Bruno Urbain (EMA's CVMP)

GUIDANCE OBJECTIVES

- Practical instrument to adopt residue definition for risk assessment
  - stepwise, based on decision tree
  - use data & scientific tools in combination
  - illustrated by selection of case studies

- create a sequence for a process that OECD acknowledged as *'far from being straight forward'*
- complement, not replicate OECD Guidance

REGULATORY CONTEXT

(EC) No **1107/2009** of EP & Council concerning the placing of PPP on the market

(EU) No **283/2013** setting out data requirements for a.s.

COM Communication **2013/C 95/01** providing list of test methods and guidance documents for the implementation of (EU) No 283/2013

OECD Test Guidelines Sections 4, 5 & pertinent Guidance documents

ELEMENTS TO BE CONSIDERED

Reg (EU) 283/2013. Residue definition

- the toxicological significance of the compounds,
- the amounts likely to be present, […]

OECD no. 63. Guidance Document on the Definition of Residues.

- significantly contribute to the dietary risk considering
  - potential for exposure in the diet
  - relative toxicity to the parent

Residue definition RA should be representative of actual "toxicological burden"

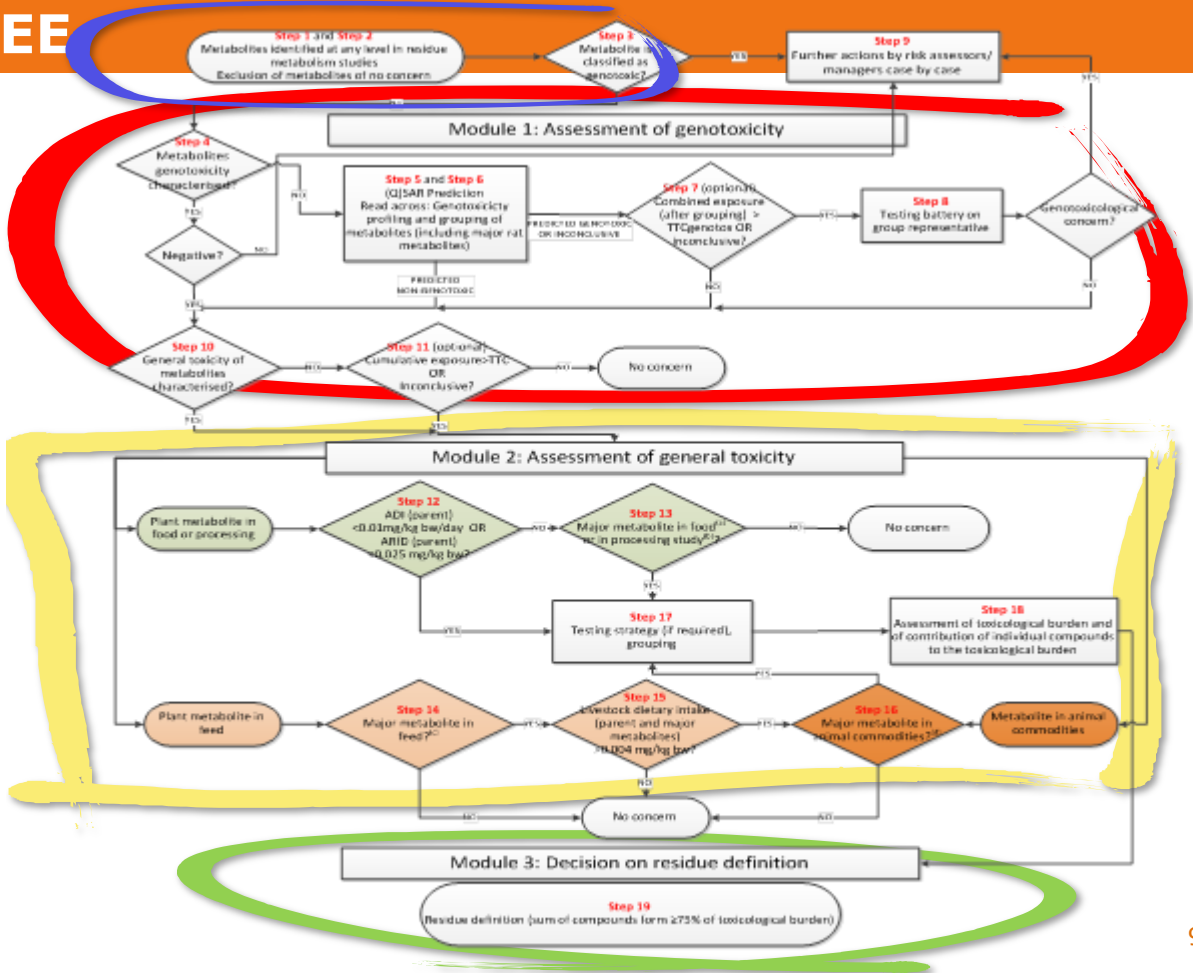
BASIC STRUCTURE

3 assessment modules building on each other,

supplemented by considerations on **dietary exposure**

- **Module 1: Genotoxicity** Assessment
- **Module 2: General Toxicity** Assessment
- **Module 3: Decision** making for residue definition

DECISION TREE



Depicting reality

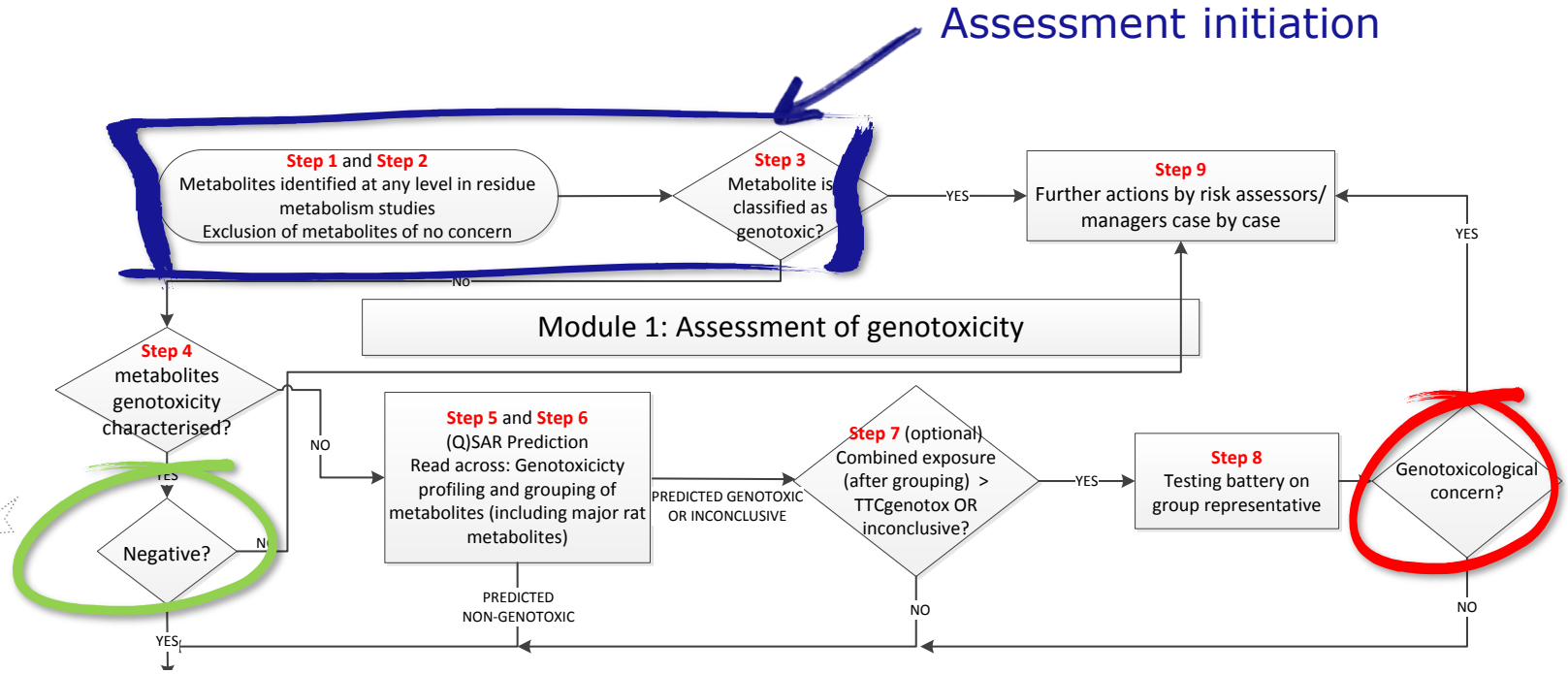
the simple, the complicated and the complex …

- Isoproturon (1 use, 16 metabolite)
- Spiroxamine (4 uses, 43 metabolites)
- Epoxiconazole (3 uses, 46 metabolites, metabolites with specific reference values, isomer analysis)

NEW FEATURES

- all identified metabolites screened for genotoxicity potential
- routine use of (Q)SAR, Grouping & Read Across
- TTC for combined exposure
- consideration of potency before exclusion of minor residue compounds
- guided strategy for selection of metabolites for testing
- alternative / mechanistic methods for testing
- uncertainty factor for developmental and reproductive toxicology (DART)
- assessment of relative potency factors (RPFs) where relevant
- 75% of consumer toxicological burden covered in RA

MODULE 1: GENOTOXICITY ASSESSMENT



SCREENING FOR GENOTOXICITY

- metabolites with genotoxic potential are a fact - not fiction
- minor /very minor metabolites but levels high enough to cause a concern
- genotoxic potential discovered by data triggered in areas other than residues & consumer RA
- increase credibility of consumer safety assessments
- systematic screening for genotox potential of metabolites in residue core studies
  - 1) non-testing methods (Q)SAR, grouping, read across, TTC
  - 2) clarify suspicion by testing of representative
- approach discussed and agreed with WG genotoxicity of EFSA Scientific Committee

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TTC CONCEPT

- application possible & optional in Module 1 & Module 2
- Requirements for application:
  - Chemical structure is known ✓
  - Compound is not covered by any exclusion criteria (e.g. potential for bioaccumulation) ✓
  - Exposure levels are known or can be reliably estimated ?
- mixture toxicity stipulation: dose addition for compounds that produce common adverse outcomes (assumption for related non-characterised metabolites)
- combined exposure of metabolites is compared to specific TTC

TTC CONCEPT

- ‚clearance' of any metabolite based on exposure estimates is restricted to exposure scenarios assessed
- requires assessment of very complex exposure patterns
- list of uses + 28 MS diets + exposure from other sources + cumulative ((EU)283/2013 Sec. 6.9)
- acknowledge TTC concept is useful in other assessment contexts but **not a cure-all** in mixture context (simultaneous presence of multiple metabolites)

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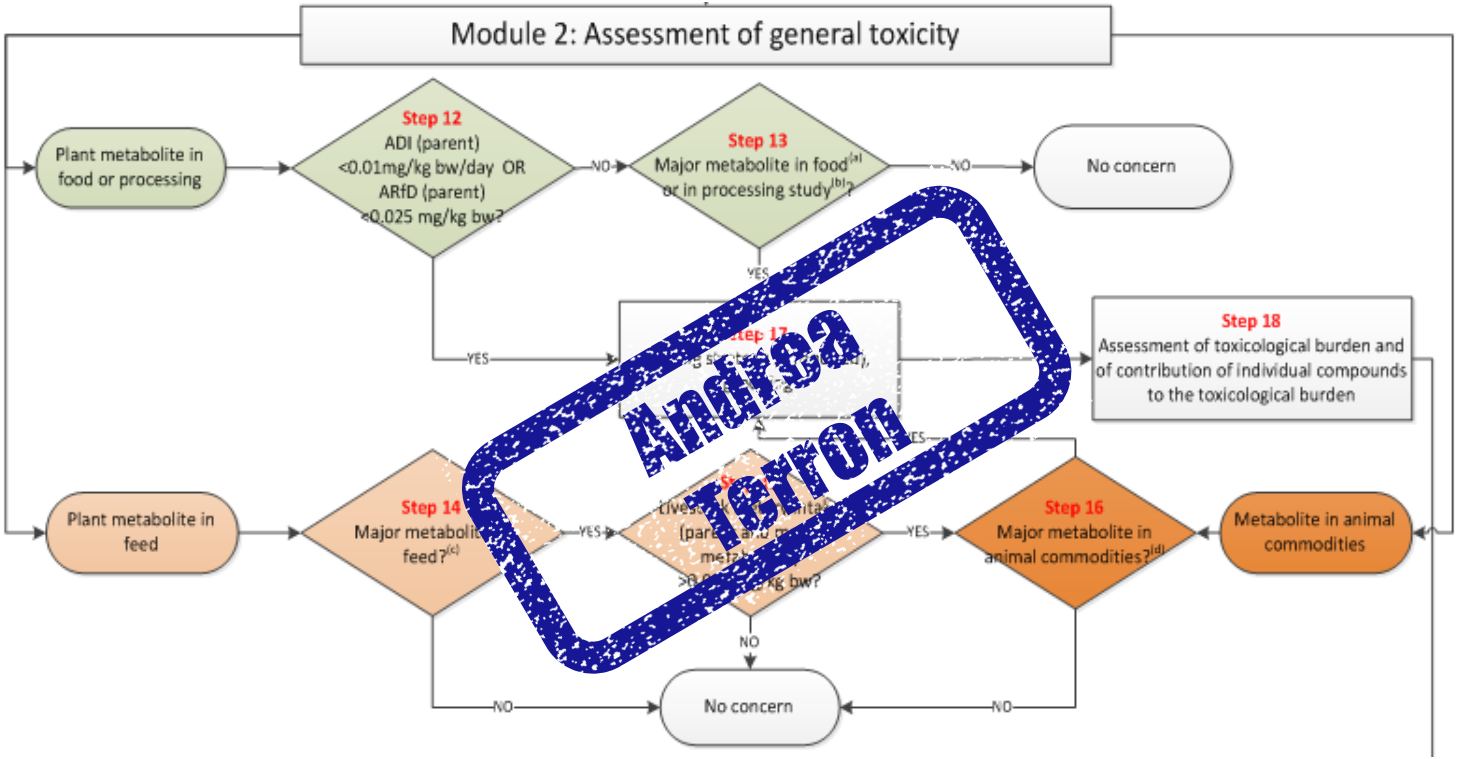
MODULE 2: GENERAL TOXICITY ASSESSMENT



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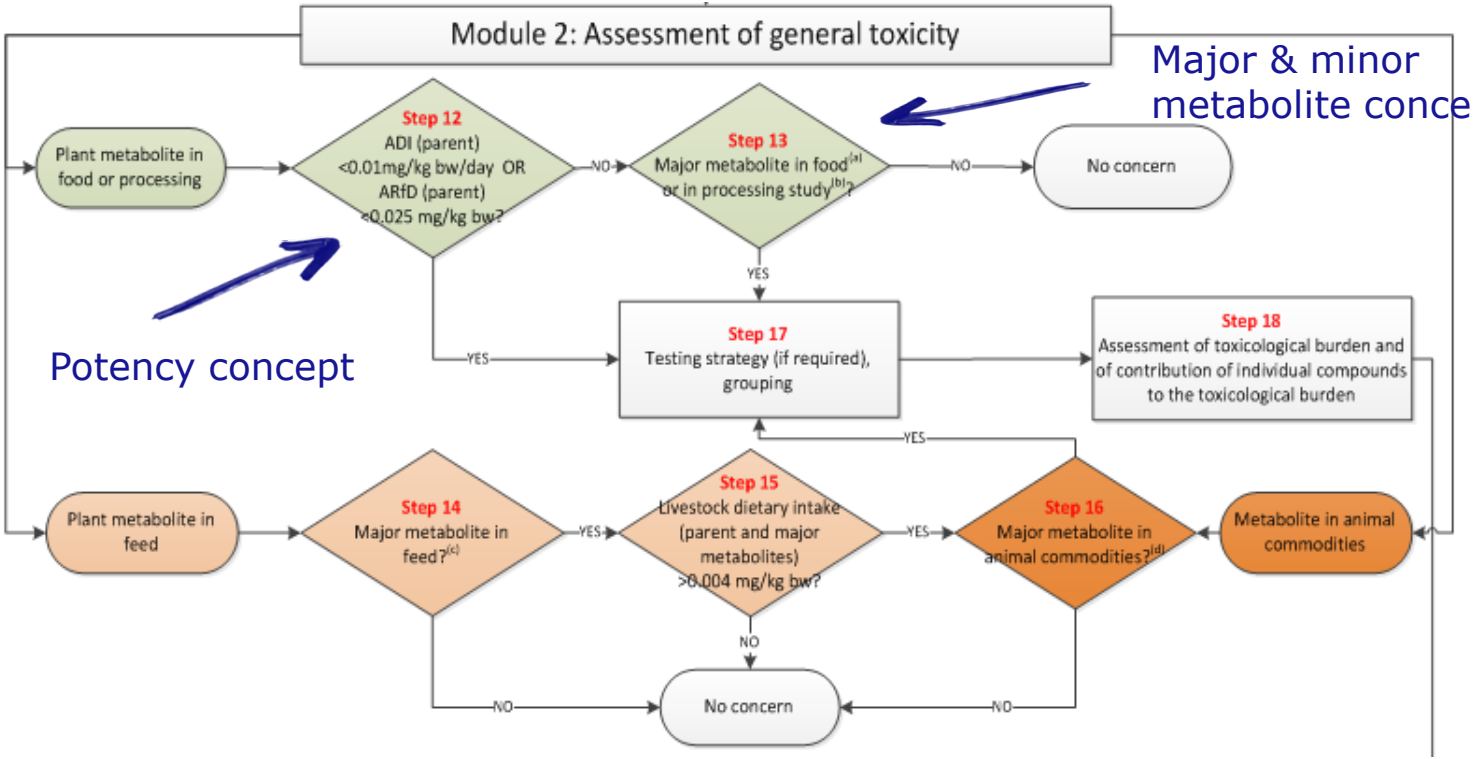


MAJOR & MINOR METABOLITE CONCEPT

Food of plant origin

- *OECD no. 63: Major metabolites contribute at any point in time to **≥10% TRR** in metabolism studies (plants, rotational crops)*
  - —> major ≥10% TRR
- *OECD no. 501: Metabolite is of minimal (minor) importance due to its **low absolute level** (<0.05 mg/kg) or %TRRs (<10% TRRs)*
  - —> minor <10% TRR or <0.05 mg/kg
  - —> major ≥10% TRR or ≥ 0.05 mg/kg
- *OECD no. 63: Residues which are major in terms of %TRR, but present at **very low absolute levels** (mg/kg) have lower exposure potential.*
  - —> non-significant major ≥10% TRR but <0.01 mg/kg

MAJOR & MINOR METABOLITE CONCEPT

Feed

- *OECD no. 63: Major metabolites found in commodities which are human **foods - as opposed to animal feeds** have a higher exposure potential*
  - —> distinction between triggers for food and feed metabolites

Animal commodities

- *OECD no. 63: Major metabolites contribute at any point in time to **>10% TRR** in metabolism studies (livestock)*
  - —> major ≥10% TRR
  - (+ refinement option)

Note

- *OECD no. 501 & 503: trigger values [...]may not apply to situations where a metabolite is suspected to be of particular **toxicological concern***
  - —> distinction made, taking into account toxicity
  - —> Concept not applicable to potent substances !

POTENCY CONCEPT

- *OECD no. 63: „ questions typically considered to define residue for risk assessment*
  - *How toxic is the parent compound and what are relevant endpoints?*
  - *[if] toxicity data are not available for metabolites,[..] they are assumed to possess the same toxicity as the parent.*
  - *the more toxic the parent compound the greater the need to ensure all relevant metabolites/degradates are included in the assessment. “*

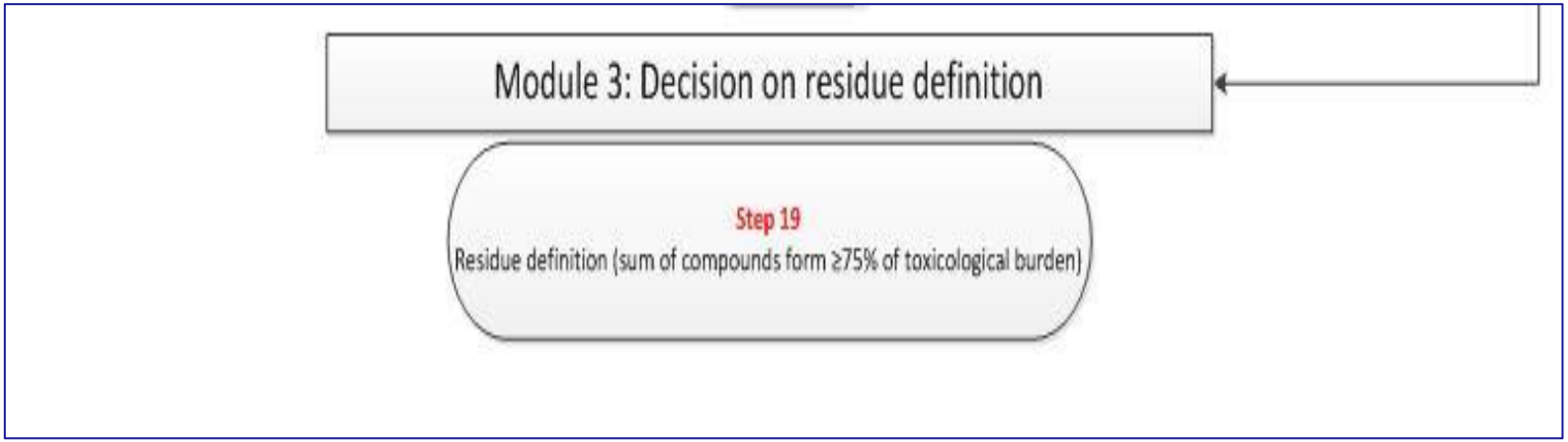
POTENCY CONCEPT

Definition of potent compounds

- WG proposed **ADI <0.01 mg/kg/bw**, or **ARfD <0.025 mg/kg/bw**
- applicable to ADI / ARfD of metabolites when available
- consistent with the lowest 25th percentile for ADI and ARfD distribution for 270 and 195 a.s. respectively
- covered by proposal:
  - ADI: approx. 67% a.s. for that neurotoxic effects are relevant,
  - ARfD: approx. 50% a.s. inducing acute clinical signs and/or neurotoxic effects

→ minor metabolites of a potent a.s. not subject to exclusion rule by default

MODULE 3: DECISION ON RD



TOXICOLOGICAL BURDEN CONCEPT

Definition of toxicological burden

- sum of identified residue compounds, not previously excluded from the assessment (as of no concern, insignificant exposure), weighted by relative potency
  - % toxicological burden ≠ % TRR

- criterium for ‚*significant contribution*‘ of compounds to toxicological consumer burden
- WG proposal upon consultation with PSN members:
  - compounds included for RA should cover at least **75%** of toxicological burden
  - flexibility possible

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STAKEHOLDER CONSULTATIONS

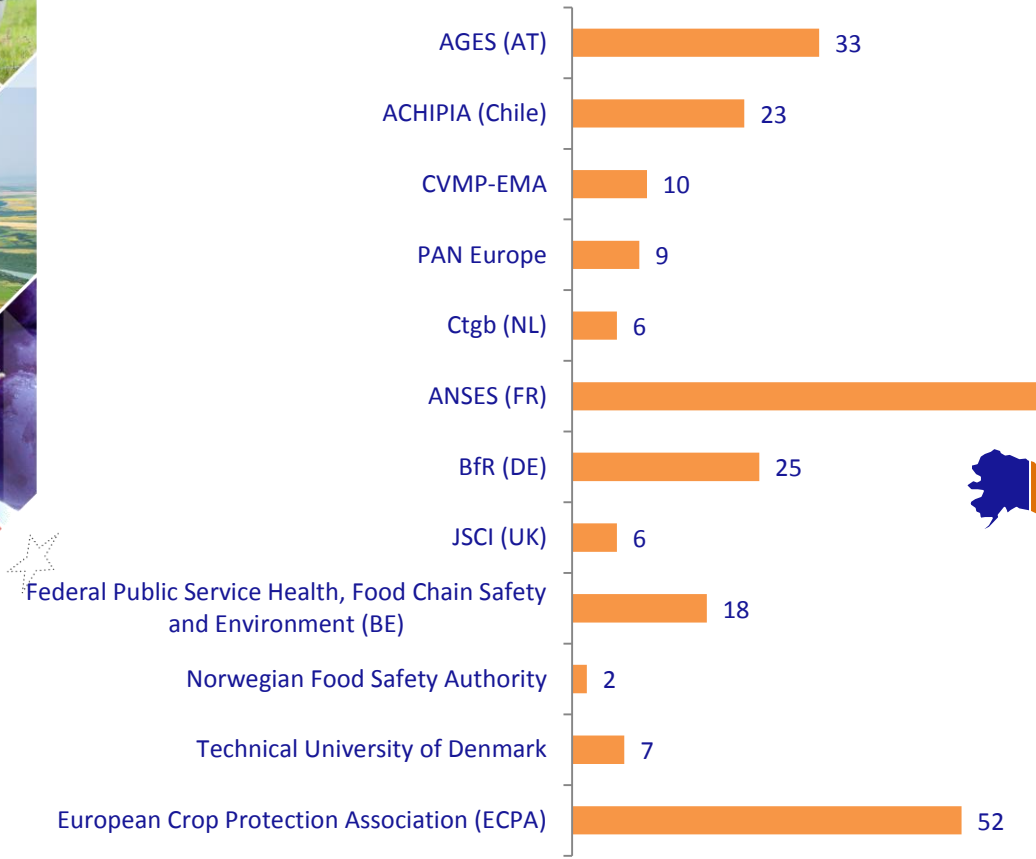
Public consultation

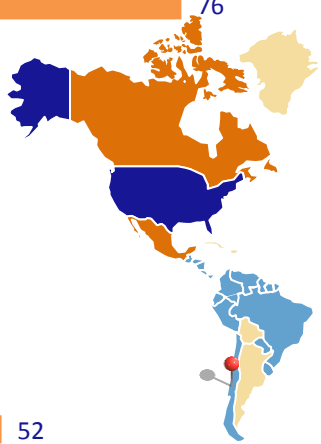
- public consultation was opened from 7 March to 2 May 2016
- a total of 267 comments from 12 interested parties received

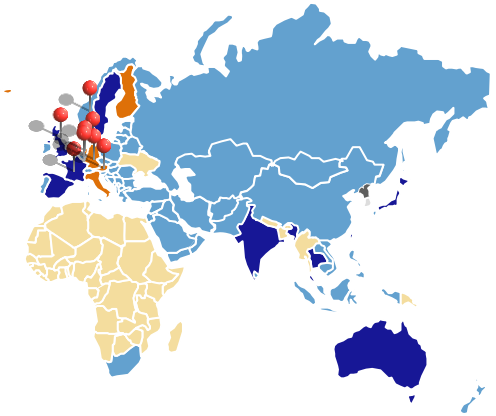
PSN consultation

- commenting period from 23 March to 22 April 2016
- Web conference on 25 May 2016
- a total of 38 comments from 5 Member states received

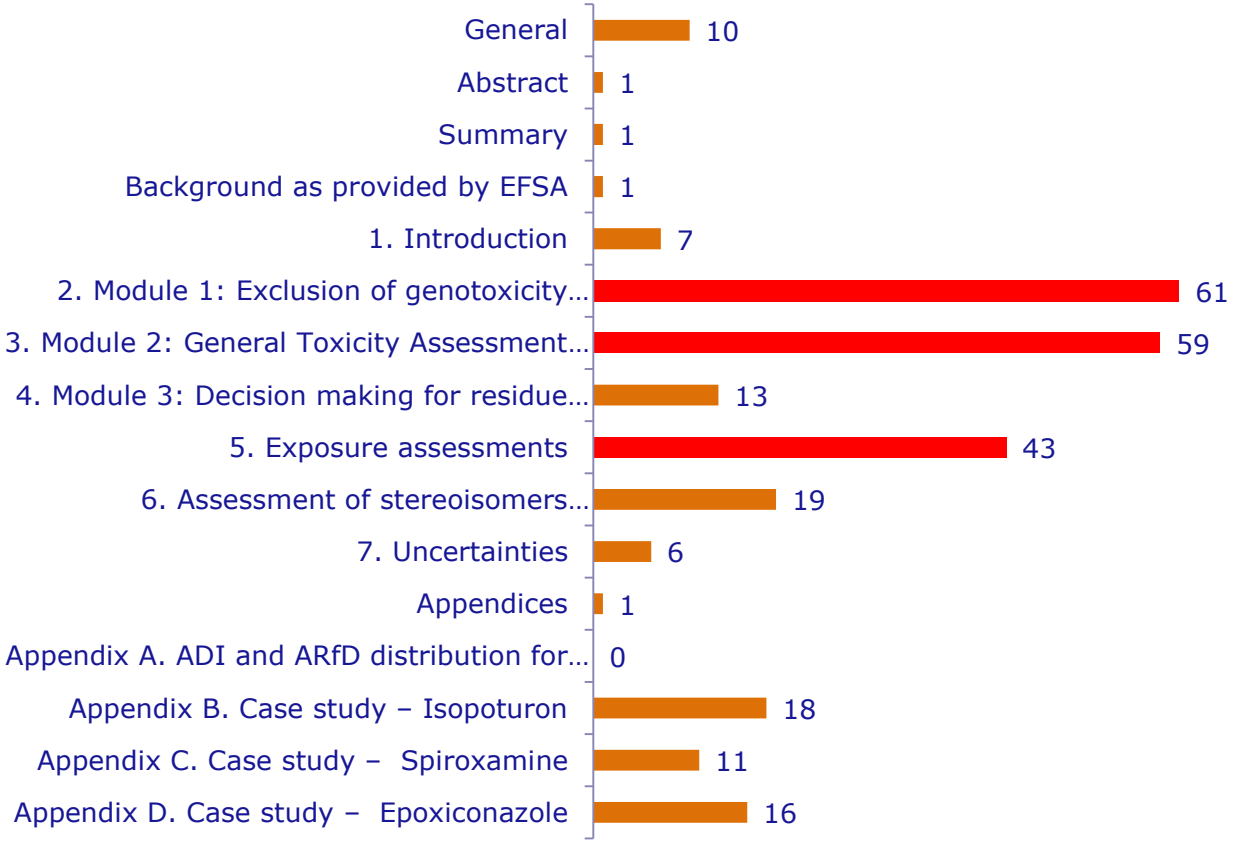
PUBLIC CONSULTATION - COMMENTS BY ORGANISATIONS





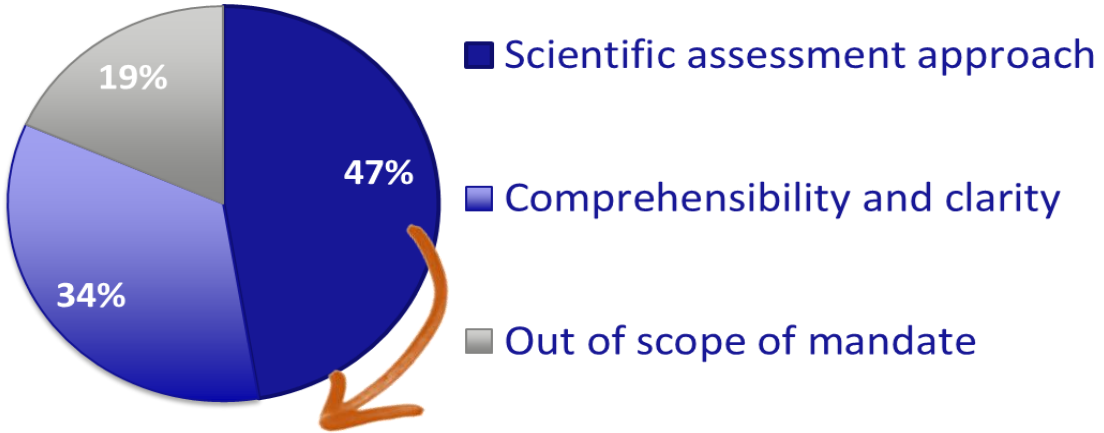


PUBLIC CONSULTATION - COMMENTS BY SECTIONS



PSN CONSULTATION

- Expert nominations: AT, DE, IE, NL, NO, UK & comments sent by AT, FR, IE, NL, UK



- TTC and complexity of proposed approach
- Potency / toxicity considerations & vertebrate studies
- % toxicological burden covered by RA residue definition

Amendment following stakeholder consultations:

- metabolite characterisation by toxicological studies (bile & plasma, top dose, limited absorption ...)
- MTD approach eliminated
- use of uncertainty factor clarified
- use of toxicological burden approach and RPF clarified
- ...

METHODOLOGIGAL EXPECTATIONS

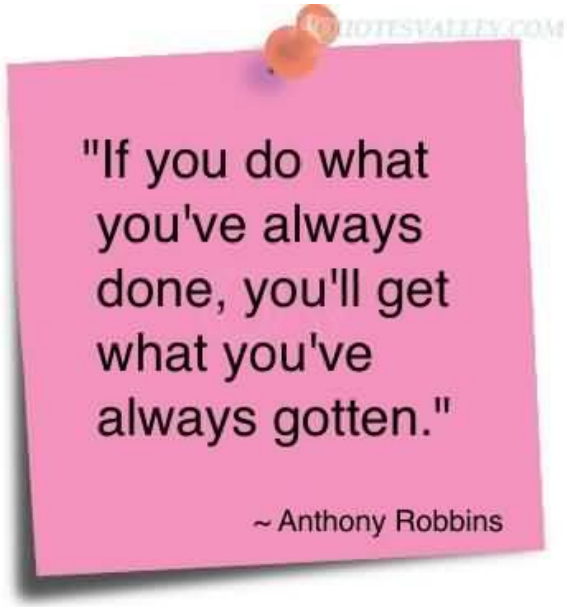
Challenges

- application of new tools and approaches never used systematically before in pesticide regulatory assessments
- resources & training required to enable assessors to be up to the job

Gains

- current empirical approach on metabolites assessment becoming more consistent and transparent
- long-term gains in knowledge regarding metabolites

THANK YOU!


"If you do what you've always done, you'll get what you've always gotten."
~ Anthony Robbins