Grouping principles, assessment and testing of metabolites for the approval and re-approval of active substances - An authority perspective

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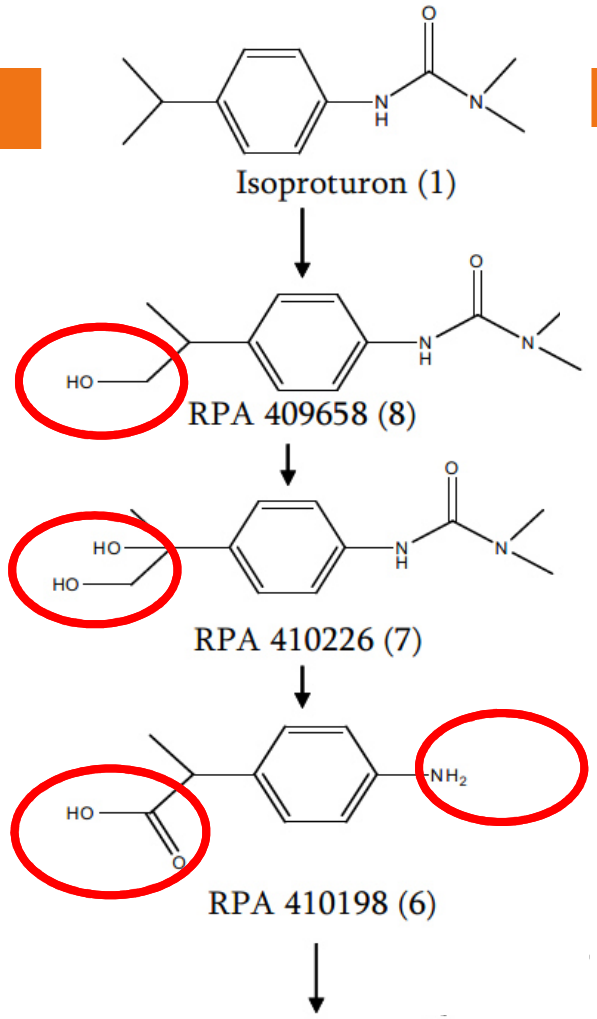
efsa
European Food Safety Authority

1. WHAT?


Isoproturon (1)
HO
RPA 409658 (8)
HO
HO
RPA 410226 (7)
HO
NH2
O
RPA 410198 (6)

2. WHERE?

Complementary routes and assessments

- Metabolites in treated crops
- Metabolites in succeeding crops (translocation from soil)
- Metabolites in livestock
- Metabolites in processed commodities
- Metabolites in drinking water following purification

- Metabolites in soil
- Metabolites in water
- Metabolites in air

- Metabolites in exposed humans and animals

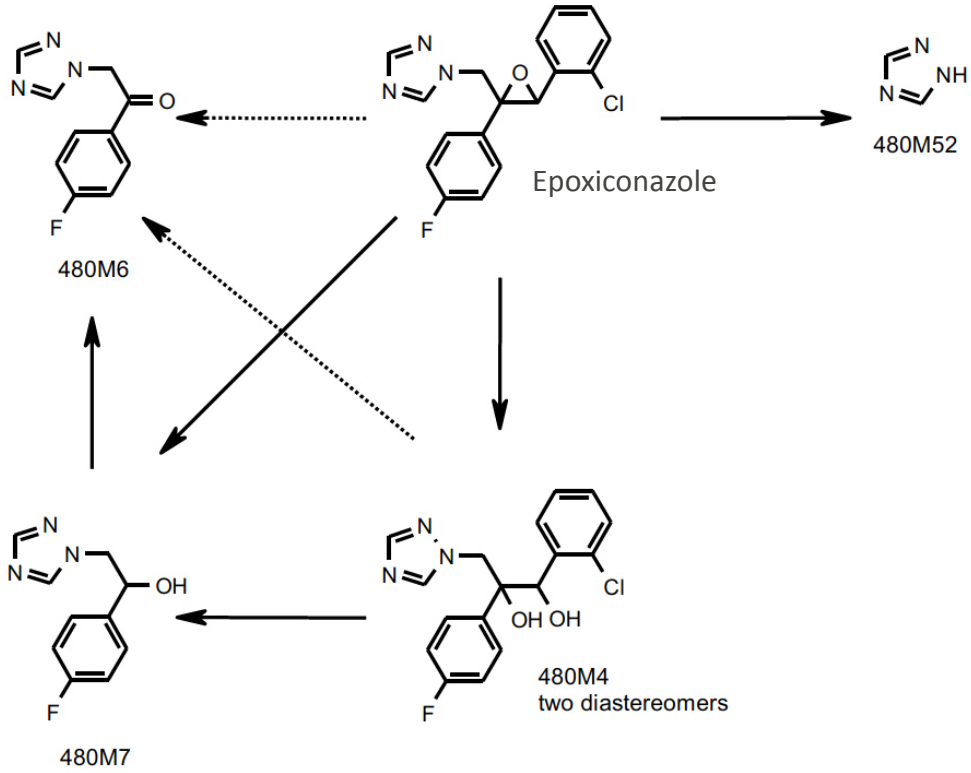
3. IDENTIFICATION

- Metabolisms studies (radiolabelled material)
  - Metabolisms in primary and rotational crops
  - Metabolisms in livestock
  - Metabolisms in experimental animals
    - In vitro metabolism studies in humans
  - Soil degradation
  - Water degradation
- Other sources
  - Reactivity: effects of drinking water purification

4. ASSESSMENT APPROACHES

- Metabolites covered by testing the parent
- Metabolites covered by specific studies
- Metabolites to be screened using non-testing methods
  - Metabolites of no concern
  - Metabolites to be assessed with the parent
    - Confirmed or assumed equivalent hazard than parent
    - Risk based on combined exposure
  - Metabolites requiring specific assessment

4. ASSESSMENT (CONT.)



5. AVAILABLE GUIDANCE

- Dietary assessment via food
  - Test battery for the identification
  - Detailed assessment: **EFSA Guidance on Residue Definition**

- Environmental assessment
  - Test battery for the identification
  - Assessment included in the specific non-target group guidance

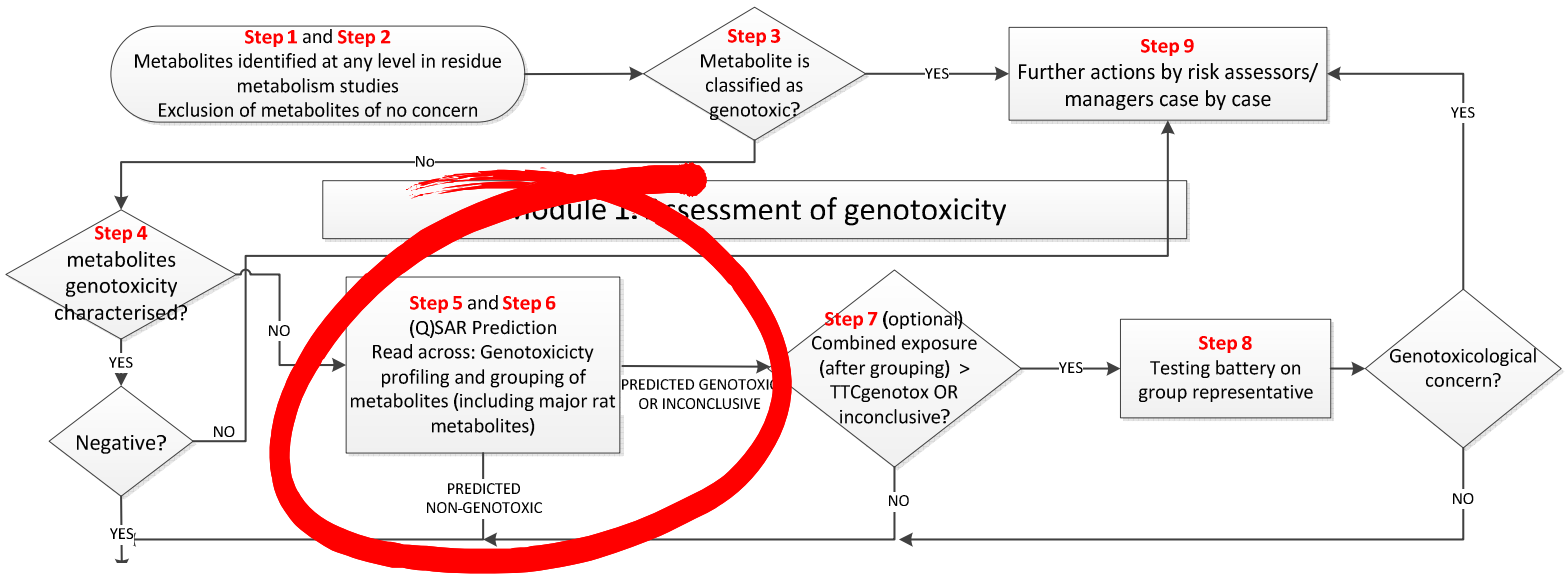
EFSA GUIDANCE ON RESIDUE DEFINITION

3 assessment modules building on each other,

supplemented by considerations on **dietary exposure** in each of the modules

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

MODULE 1: GENOTOXICITY ASSESSMENT



STEPS 5 & 6: (Q)SAR PREDICTION AND READ ACROSS

- no new methodologies were developed
- (Q)SAR models - adapted from ECHA (2008), and OECD (2007) guidance.
- Read across - adapted from ECHA (2008; 2013; 2015) and OECD (2014)

ECHA, 2008. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R6. ECHA, Helsinki, Finland. 134pp.
ECHA, 2013. Grouping of substances and read across approach, Part1. ECHA, Helsinki, Finland.
ECHA, 2015. Read across Assessment Framework, ECHA, Helsinki, Finland.
OECD, 2014, Series on testing & assessment No 194. Guidance on grouping of Chemicals. Second edition.
OECD, 2007. Guidance Document on the Validation of (Quantitative) Structure Activity Relationship ((Q)SAR) Models. OECD Series on Testing and Assessment No. 69.ENV/JM/MONO(2007)2.

ANNEX WITH CASE STUDIES

Depicting reality

the simple, the complicated and the complex …

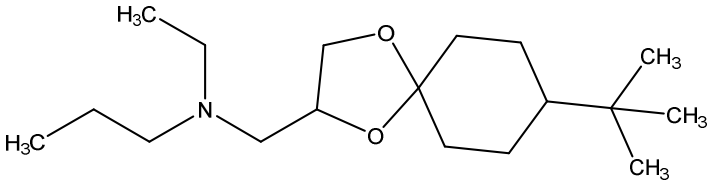
- Isoproturon (1 use, 16 metabolite)
- **Spiroxamine (4 uses, 43 metabolites)**
- Epoxiconazole (3 uses, 46 metabolites, metabolites with specific reference values, isomer analysis)

STEP 5: (Q)SAR PREDICTION OF GENOTOXICITY

		CAESAR prediction of gene mutation (Applicability Domain)	OASIS prediction of gene mutation (Applicability Domain)	Rule based model for prediction of in vivo CA (Toxtree) (no Applicability Domain evaluation is available)	OASIS prediction of CA (Applicability Domain)
M01	Desethyl	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M02	Despropyl	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M04	N-formyl-desethyl	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M05	Hydroxyl	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M07	Hydroxy acid	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M08	8-hydroxy acid	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M09	Hydroxy-despropyl	Positive (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M10	Hydroxy-N-oxide	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M11	Desethyl acid	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M12	Despropyl acid	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M13	Cyclohexanol	Negative (In)	Negative (In)	Negative	Negative (out)
M14	Diol	Negative (In)	Negative (In)	Negative	Negative (In)
M15	Ketone	Negative (Could be out)	Negative (In)	Negative	Negative (out)
M16	Hydroxy-ketone	Negative (In)	Negative (In)	Negative	Negative (out)
M25	Sulfate	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M26	Desethyl-sulfate	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M27	Despropyl-sulfate	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M28	Aminodiol	Negative (In)	Negative (In)	Positive alert for CA	Negative (In)
M29	Aminodiol-N-oxide	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)
M30	Desethyl-aminodiol	Negative (Could be out)	Negative (In)	Positive alert for CA	Negative (out)
M31	Despropyl-aminodiol	Negative (In)	Negative (In)	Positive alert for CA	Negative (out)
M35	Docosanoic acid ester	Negative (Could be out)	Negative (In)	Negative	Negative (out)
M36	Tetracosanoic acid ester	Negative (Could be out)	Negative (In)	Negative	Negative (out)
M37	Cyclohexenol	Negative (In)	Negative (out)	Negative	Positive (In)
M38	N-formyl-despropyl	Negative (Could be out)	Negative (out)	Positive alert for CA	Negative (out)
M41	Hydroxy-desethyl	Negative (Out)	Negative (out)	Positive alert for CA	Negative (out)

STEP 6: READ ACROSS GENOTOXICITY

Spiroxamine



		DNA binding by OECD	in vivo mutagenicity (MN) by ISS	Protein binding by OECD
		SN1: Iminium Ion Formation, Aliphatic tertiary amines	Hacceptor-spath3-Haccepter	
Parent*	Spiroxamine	x	x	
M01	desacetyl		x	
M02	despropyl		x	
M03	N-oxide		x	
M04	N-formyl-desethyl	x	x	
M05	hydroxyl	x	x	
M06*	acid	x	x	
M07	hydroxy acid	x	x	
M08	N-acetyl acid	x	x	
M09	hydroxy-despropyl		x	
M10	hydroxy-N-oxide		x	
M11	desethyl acid		x	
M12	despropyl acid		x	
M13	cyclohexanol			
M14	diol			
M15	ketone			
M16	hydroxy-ketone			
M25	sulfate	x	x	
M26	desethyl-sulfate		x	
M27	despropyl-sulfate		x	
M28	aminodiol	x	x	
M29	aminodiol-N-oxide		x	
M30	desethyl-aminodiol		x	
M31	despropyl-aminodiol		x	
M35	docosanoic acid ester		x	x
M36	tetracosanoic acid ester		x	x
M37	cyclohexenol			
M38	N-formyl-despropyl	x	x	
M41	hydroxy-desethyl		x	

Group 4

Group 3

Group 2

Group 1

STEP 6: READ ACROSS

New alert

Group 1

NO alerts

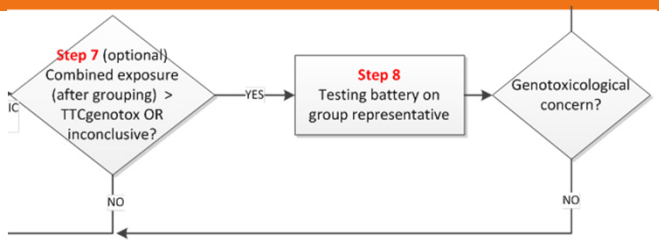
Group 2

All parent's alerts

Group 3

One parent's alert

Group 4

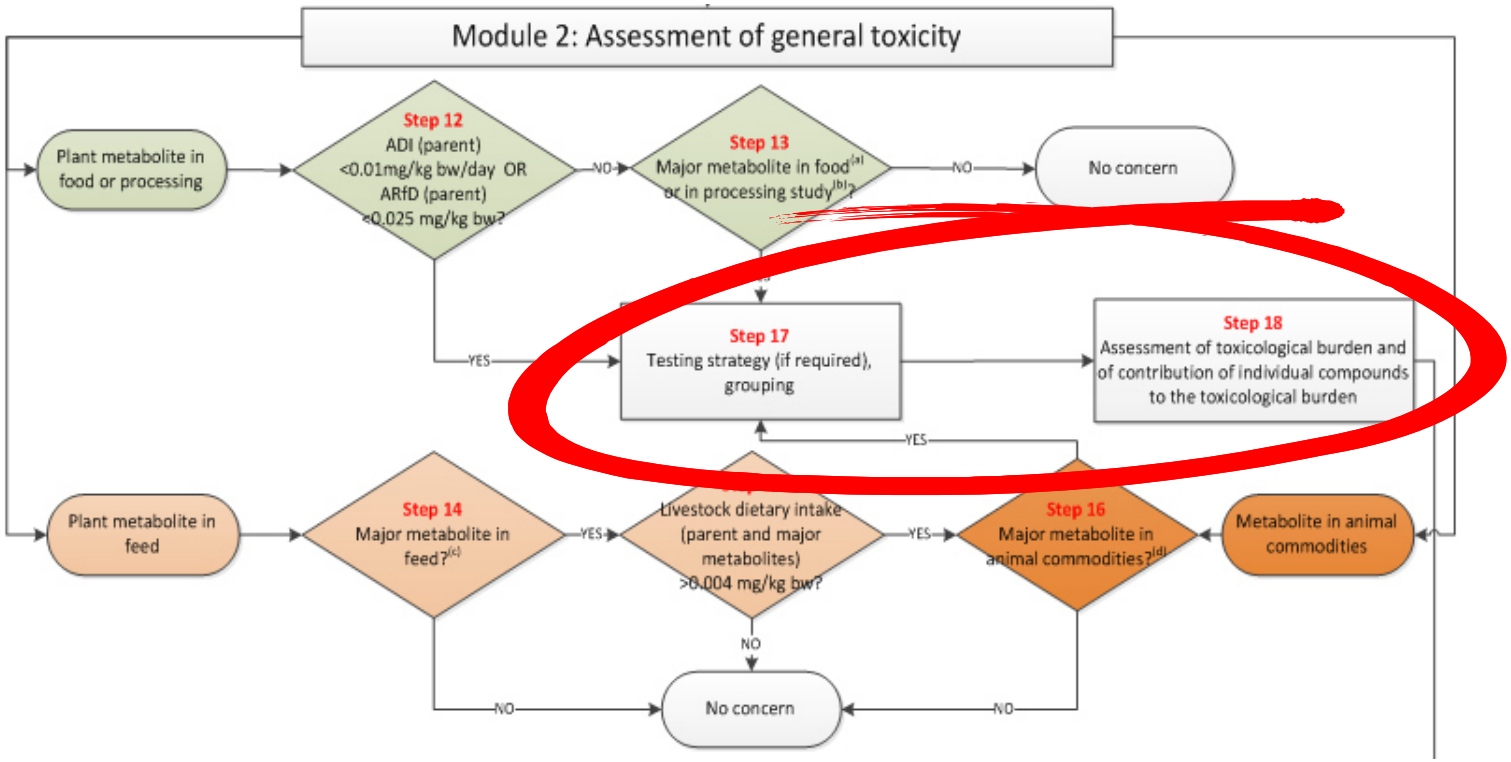


Additional evaluation of the similarity

Assessment of relevant groups:

- Threshold of Toxicological Concern (TTC)
- Selection and testing of lead chemical in the group

MODULE 2: GENERAL TOXICITY ASSESSMENT

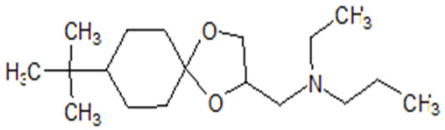


GENERAL TOXICOLOGY ENDPOINTS

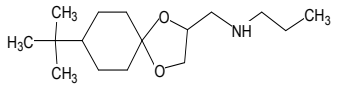
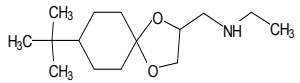
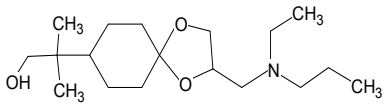
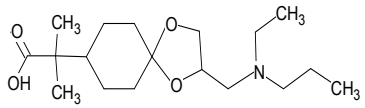
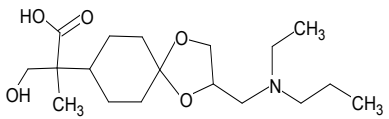
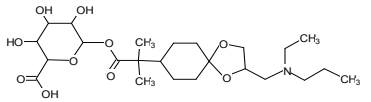
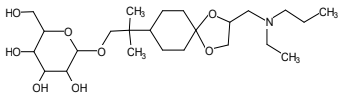
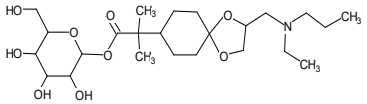
- Aim: *comparison (quantitative and qualitative)* of toxicity profile of metabolite(s) vs. parent
- Assessment scheme
  - Metabolites covered by the toxicological studies
  - Assessment of non-covered metabolites
    - Use of the TTC approach
    - **Grouping and read-across**
    - Testing
  - Quantification: Relative Potency Factors

CASE STUDY SPIROXAMINE; TOXICOLOGICAL ASSESSMENT

spiroxamine

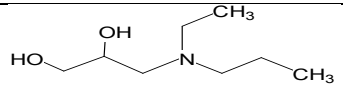
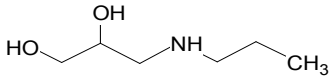
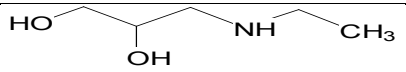


Group A (parent similar metabolites):M01, M02, M05, M06, M07, M19, M40, M44

 M1	 M2	 M5
 M6	 M7	 M19
 M40	 M44	

Group C - aminodiol

M28, M30, M31

 M28	 M30	 M31

CONCLUSIONS

- Pesticides are “data rich” chemicals, but grouping is very relevant for assessing metabolites
- The key process is setting the residue definition for risk assessment in food
  - General principles and tools are applicable, details are offered in EFSA guidance
- The assessment is triggered by “grouping” with the active substance
  - Covered by the test or by the assessment
  - Requiring additional testing and/or assessment
- Genotoxicity requires specific assessment

Thank you