



## WG Guidance on Residue Definition for Dietary Risk

### The toxicological burden

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## Toxicological burden

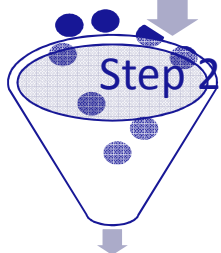
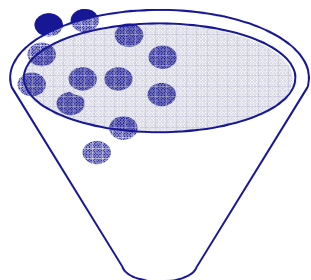
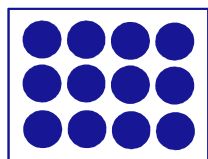
Basis for decision making

**Identified residue compounds  
without non-relevant metabolites**

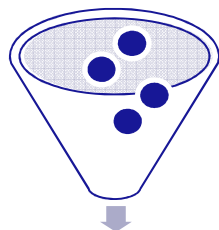
**$\geq 75\%$**



## Toxicological burden



Step 11



Step 13/Step 16

**Filter out non-relevant metabolites after toxicological and residue assessment**



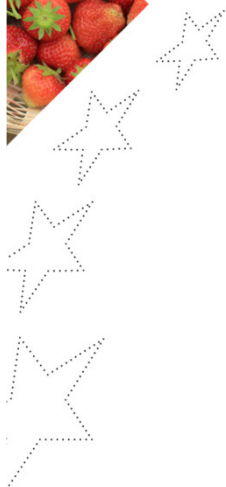
Metabolites of no toxicological concern  
(natural products)



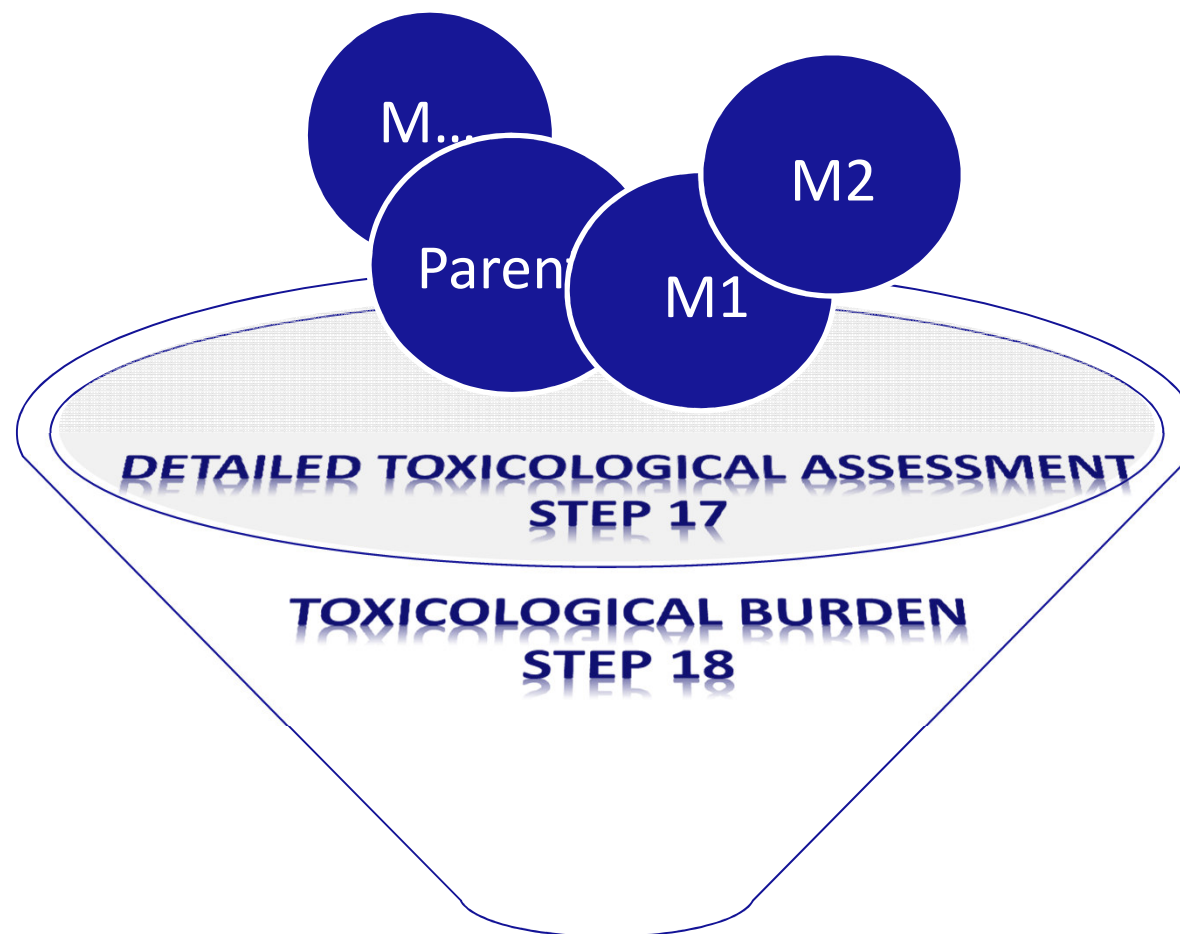
Metabolites with no exposure  
concern by TTC assessment (optional)



Metabolites with negligible risk  
potential (minor quantitative AND  
**non-potent** metabolites)



## Toxicological burden



**RESIDUE DEFINITION  
STEP 19**



## Potency considerations

Trigger of **0.01 mg/kg** – conclusive for exclusion?

TTC [µg/kg bw/d]	Chronic TTC exceeded at residue levels in ...			
	Apples [mg/kg]	Fruits [mg/kg]	Roots/tubers [mg/kg]	Plant food [mg/kg]
0.0025 (genotox)	<b>0.00021</b>	<b>0.00010</b>	<b>0.00009</b>	<b>0.00006</b>
0.3 (neurotox)	0.025	0.013	0.011	<b>0.007</b>
1.5 (other effects)	0.125	0.065	0.055	0.034

Trigger inconclusive for genotoxic/potent compounds



## Potency considerations

### Trigger of 10% TRR – conclusive for exclusion?

Active substance	10% TRR in mg/kg	10% TRR in µg/kg bw/d	% of TTC for genotoxicity	% of TTC for neurotoxicity
Sp...	0.7 (fruiting veg.) 0.1 (grapes)	4.2	168,000	1,400
Sp...	0.045 (cereal grain) 0.34 (grapes) 0.031 (banana)	1.6	6,400	530
SY...	0.006 (cereal grain) 0.015 (grapes) 0.16 (lettuce)	0.16	6,400	53
Si...	0.004 (cereal grain)	0.048	1,900	16
Su...	0.001 (cereal grain)	0.012	500	4

Trigger inconclusive for genotoxic/potent compounds

## Crop group specific or global residue definition?

Potential relevance	Fruit (% TRR)	Leafy (% TRR)	R & T (% TRR)	Cereals (% TRR)	P&O (% TRR)
Parent	40	40	40	no data	no data
Metabolite 1	40	5	9		
Metabolite 2	5	10	10		
Metabolite 3	5	5	20		
<b>% TRR</b>	90	60	79	-	-
<b>% TRR (relevant)</b>	80	50	60	-	-
<b>% tox burden*</b>	89	83	76	-	-

\* assumption RPF 1: toxicity profile is identical to parent; RPF  $\neq$  1 weights metabolite % TRR



## Crop group specific or global residue definition?

Potential relevance	Fruit (% TRR)	Leafy (% TRR)	R & T (% TRR)	Cereals (% TRR)	P&O (% TRR)
Parent	40	40	40	no data	no data
Metabolite 1	40	5	9		
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Metabolite 3	5	5	20		
Proposal 1* (% tox burden)	P + M1 89	P+M2 83	P+M3 76	P+M1+M2+M3	
Proposal 2* (% tox burden)	P + M1 + M2 +M3 100				

\* assumption: RPF 1



## Intra-crop group variabilities – Example fruit crops

Potential relevance	Fruit crops				
	Tomato (% tox burden)	Tomato (% tox burden)	Apple (% tox burden)	Apple (% tox burden)	Grape (% tox burden)
Parent	40	40	20	40	20
Metabolite 1	20	10	40	15	40
Metabolite 2	20	30	20	15	0
Metabolite 3	15	15	20	10	30
Metabolite 4	5	5	0	20	10

Proposal

**P + M1 + M2 (+ M3)**

## Deviations from 75% - The role of uncertainties

<75%

Completeness of  
information on GAPs  
and metabolism

Low risk profile

Conclusions build on  
experimental proof

≥75%

Low ID rate

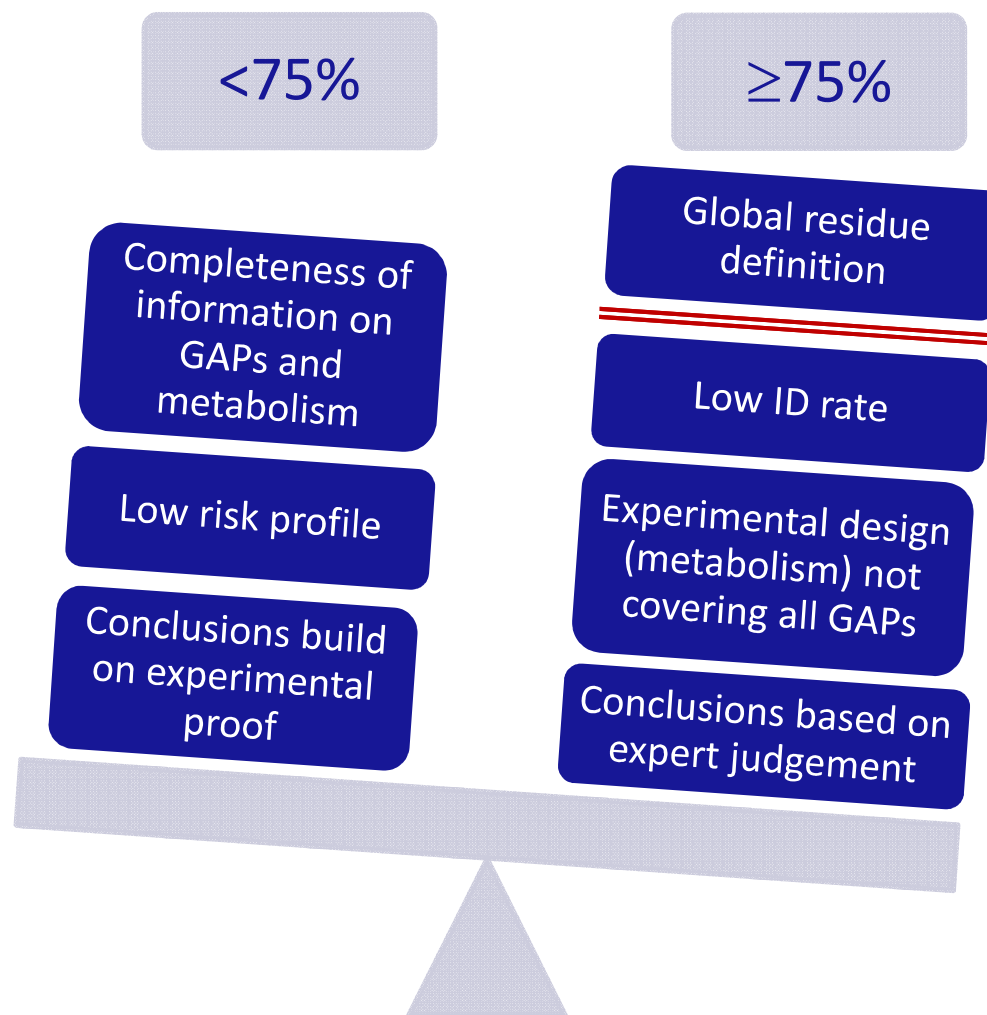
Conclusions based  
on expert  
judgement

Experimental design  
(metabolism) not  
covering all GAPs

Acceptable toxicological burden




## Deviations from 75% - The role of uncertainties



Acceptable toxicological burden

## Conclusions on concept of toxicological burden

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1. Qualitative (toxicity) and quantitative (exposure) criteria for metabolite relevance
  2. Filter functions reduce number of relevant metabolites
  3. Target: 75% of toxicological burden for each crop group
  4. 75% is case specific
  5. Acceptability of  $<75\%$  possible by reducing uncertainties