



WG Guidance on Residue Definition for Dietary Risk

The toxicological burden

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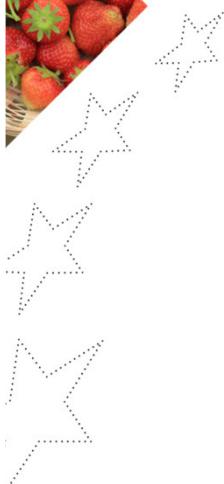


Toxicological burden

Basis for decision making

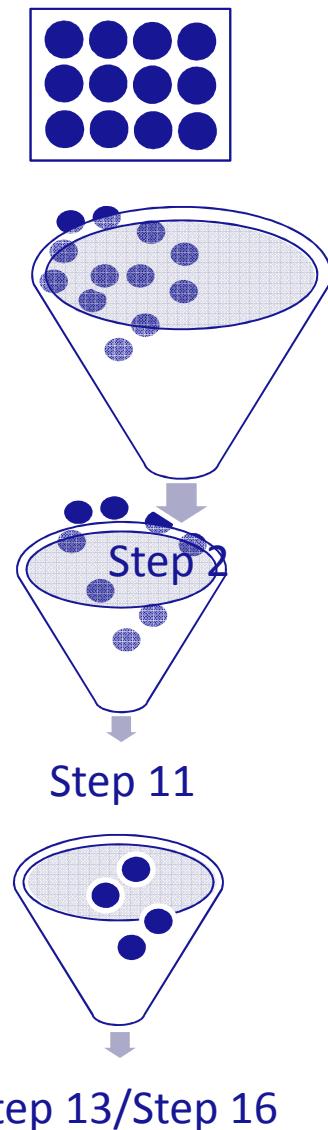
**Identified residue compounds
without non-relevant metabolites**

$\geq 75\%$





Toxicological burden



Filter out non-relevant metabolites after toxicological and residue assessment

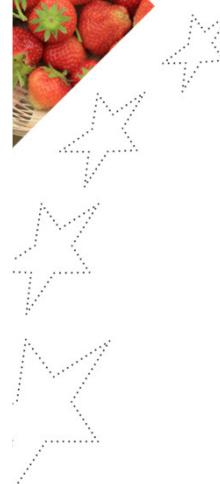
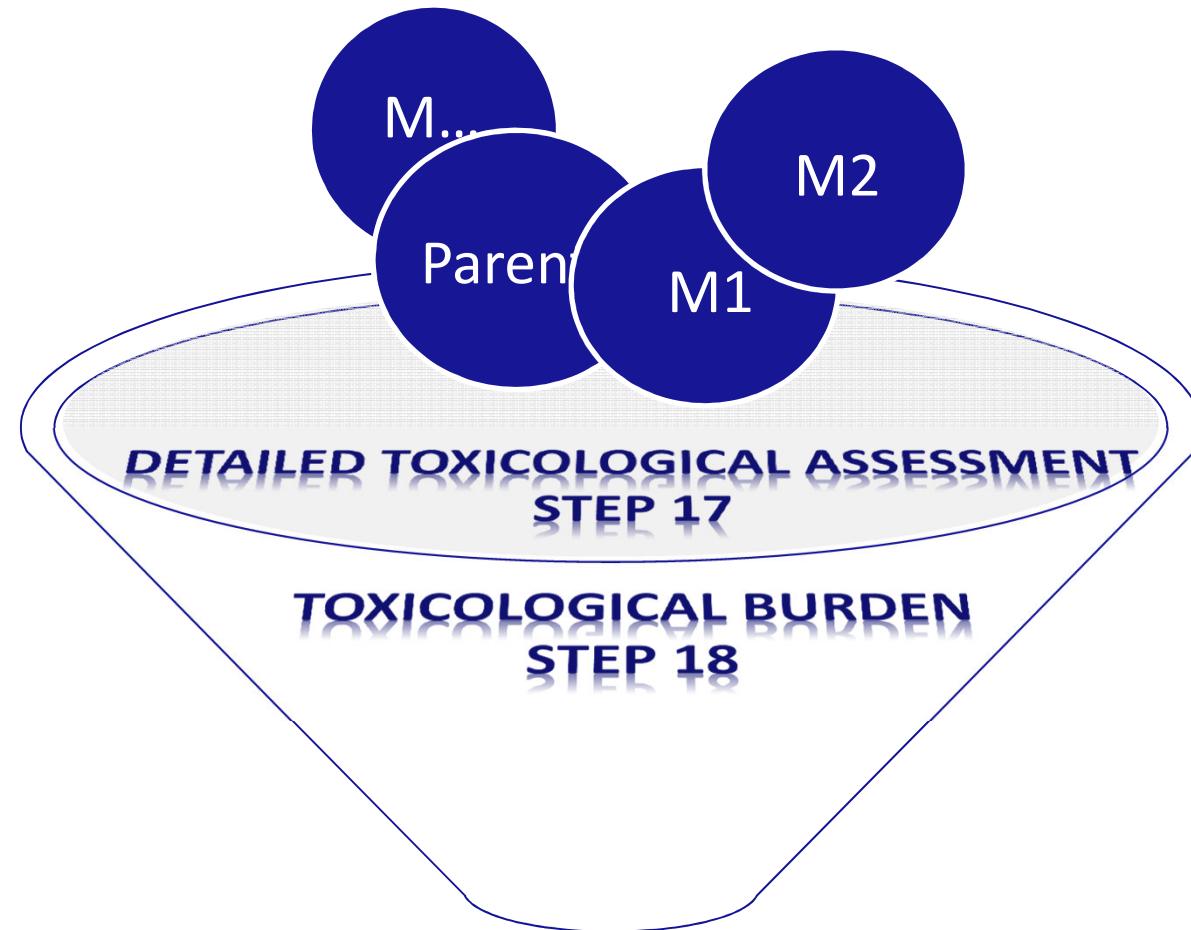
Metabolites of no toxicological concern (natural products)

Metabolites with no exposure concern by TTC assessment (optional)

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



Toxicological burden





Potency considerations

Trigger of 0.01 mg/kg – conclusive for exclusion?

TTC [$\mu\text{g}/\text{kg bw/d}$]	Chronic TTC exceeded at residue levels in ...			
	Apples [mg/kg]	Fruits [mg/kg]	Roots/tubers [mg/kg]	Plant food [mg/kg]
0.0025 (genotox)	0.00021	0.00010	0.00009	0.00006
0.3 (neurotox)	0.025	0.013	0.011	0.007
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	400
Sp...	0.045 (cereal grain) 0.34 (grapes) 0.031 (banana)	1.6	Trigger inconclusive for genotoxic/potent compounds	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



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		
% TRR	90	60	79	-	-
% TRR (relevant)	80	50	60	-	-
% tox burden*	89	83	76	-	-

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



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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%

≥75%

Completeness of information on GAPs and metabolism

Low risk profile

Conclusions build on experimental proof

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

$<75\%$

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$\geq75\%$

Global residue definition

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Acceptable toxicological burden



Conclusions on concept of toxicological burden

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

