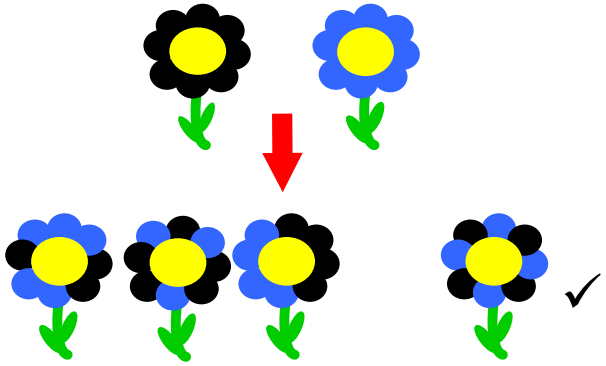
Risk assessment of GM breeding stacked product

1. Rationale for risk assessment
2. Subcombinations for segregating crops
3. Ways forward
    A. Decision tree
    B. Procedural efficiencies during risk assessment
    C. Parallel assessment

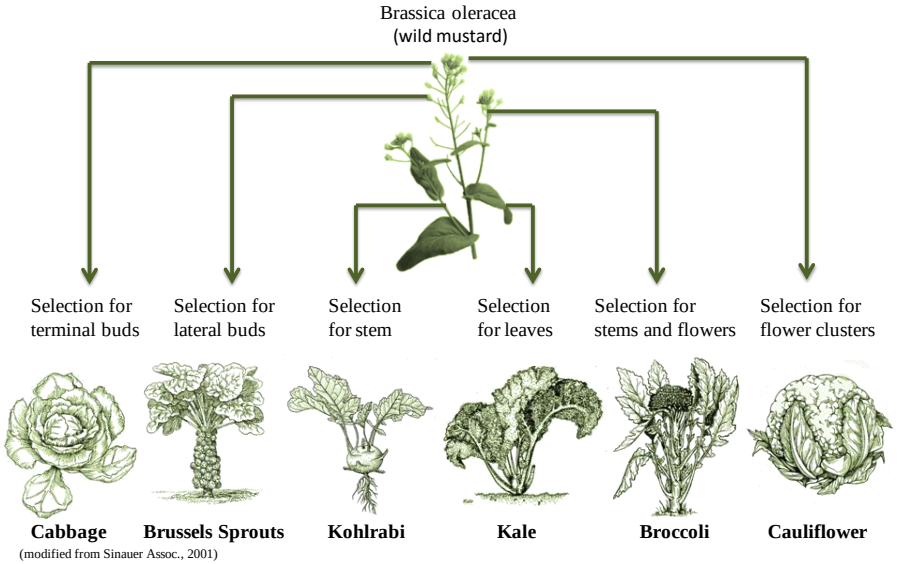
Simple crosses do not pose a new pathway to harm

Plant breeding is based on:

- Selecting parents to cross
- Generating progeny (where thousands of parental genes are recombined)
- Selecting the progeny



In traditional breeding thousands of genes can safely be combined



Simple crosses between commercial varieties do not pose a new pathway to harm*

* Acknowledged by WHO (1995)

1. Rationale for risk assessment

Implementing Regulation (EC) 503/2013 focusing on 3 aspects:

(a) stability of the transformation events;

(b) expression of the transformation events

(c) potential synergistic or antagonistic effects resulting from the combination of the transformation events shall be subject to an assessment in accordance with Sections 1.4 (Toxicology), 1.5 (Allergenicity) and 1.6 (Nutritional assessment).

Conduct **fit-for-purpose** and **case-by-case** risk assessment, considering the trait(s) and outcome of the above data

Stacking does not alter the trait's Mode of Action (MOA)

Enzymes are Specific

Glyphosate Tolerant
X
Glufosinate Tolerant

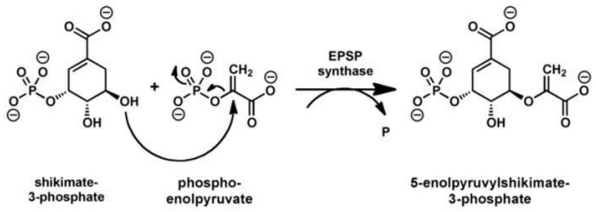
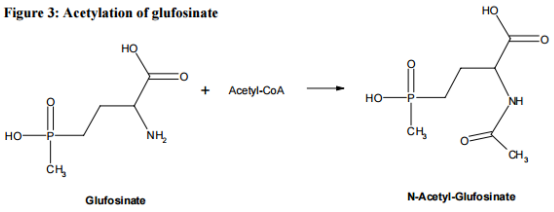


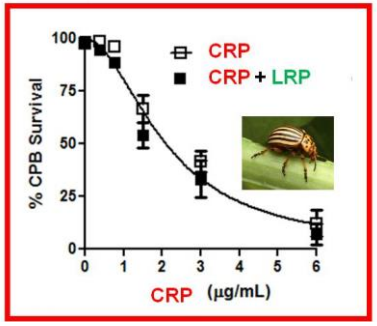
Figure 3: Acetylation of glufosinate

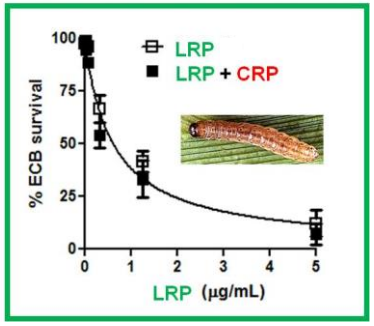


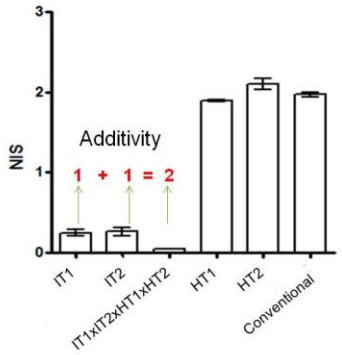
The inherent specificity of enzymes does not change when stacked

Insect Tolerance is Additive or Independent

Coleop Resistant Protein x Lep Resistant Protein







- Overlapping curves demonstrates Independent MOA
- Additivity demonstrates lack of interaction

Knowledge of MOA would predict no interaction (additivity)

Predictable assessment of synergistic or antagonistic effects

Based on **Characteristics and MOA** of the gene products of the single events, is there a **potential for interaction** between these products when combined in a stack that has **not been considered** in the risk assessments on the single events

A **Possible** mechanism of **interaction** or combined activity can be **identified** and a **hypothesis** on the **effect** of the interaction can be **formulated**

No potential interaction can be identified

Potential adverse effect is identified

No potential adverse effect is identified

A **targeted food/feed safety assessment** should be performed on the stack to characterize the potential interaction effect

No targeted food/feed assessment for the stack is warranted

If there is **no plausible hypothesis** for interaction then no further data should be required

Decision tree

Stability of stack
Expression comparison

Potential synergistic or antagonistic effects :
Based on **Characteristics and MOA** of the gene products,

Indication for interaction or hazard?

No

The trait impacts on the **plant metabolic pathways**

No

No further targeted food/feed assessment for the stack is warranted

Yes

Targeted compositional and/or agro/pheno assessment

No potential adverse effect identified

Yes

A **Possible** mechanism of **interaction** or combined activity can be **identified** and a **hypothesis** can be **formulated**

Potential adverse effect identified

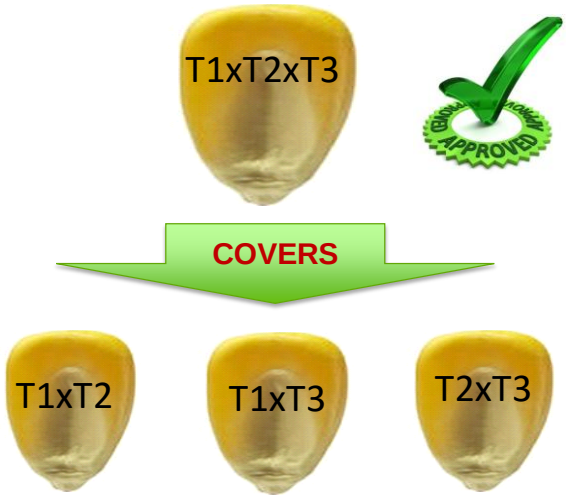
A **targeted food/feed safety assessment** should be performed

Risk assessment should be hypothesis driven

2. Subcombinations
for segregating crops

If **assessing** possible **interactions** the **higher order stack** evaluates this possibility with **all traits**

–The MOA of all the traits would inform on this possibility



Food/Feed safety

- All singles were determined to be as safe as their conventional counterparts – stacking does not change that
- If **no interaction** then **no** differential **impact** on the stack
- Combination of traits similar in comingled grain

Safety assessment on the **higher order stack is applicable to all subcombinations** regardless of commercial status or segregating nature of crops

2. Subcombinations

Risk assessment for a higher order stack also cover subcombinations independent of the origin

- Literature* and previously provided data show in case of GM stacks with agronomic traits that
  - Composition, agro/phenotypic traits and expression levels of newly expressed proteins are not impacted by stacking
- Analysis of the grain (F2) includes all subcombinations.
  - Protein expression of higher order stack can be used for exposure assessment of subcombinations as variation for subcombinations is similar as for other GM products which is taken into account in the margin of exposure
- If the stability and expression data show absence of interactions in the higher order stack, this is data showing absence of interaction also for subcombinations.

* Kramer et al. 2016 and reference therein

2. Expression & subcombinations

Influencing expression:

The natural and expected variability in protein expression should not have any adverse effect considering large **margin of exposures** and safety of newly expressed proteins has been assessed.

Substantial changes in protein expression values are expected if interactions at the DNA and RNA level occur (*e.g.* gene silencing).

If no biologically relevant changes in protein expression values are observed between the higher order stack and the singles, this would confirm absence of interaction at this level.

→ It can be reasonably assumed that no substantial changes on expression levels are expected for the subcombinations.

Subcombinations
Clarifications from EFSA

- Rationale for requiring expression data for subcombinations

- Ways forward

3. Ways forward

A. A decision tree approach that lays down the steps in risk assessment to be followed

B. Procedural efficiencies during risk assessment

C. Parallel assessment

A/B) Decision tree and procedure

Implementing Regulation is compatible with decision tree and is scientifically justifiable based on knowledge

- Other countries have adjusted procedures based on experience gained (HOSU)

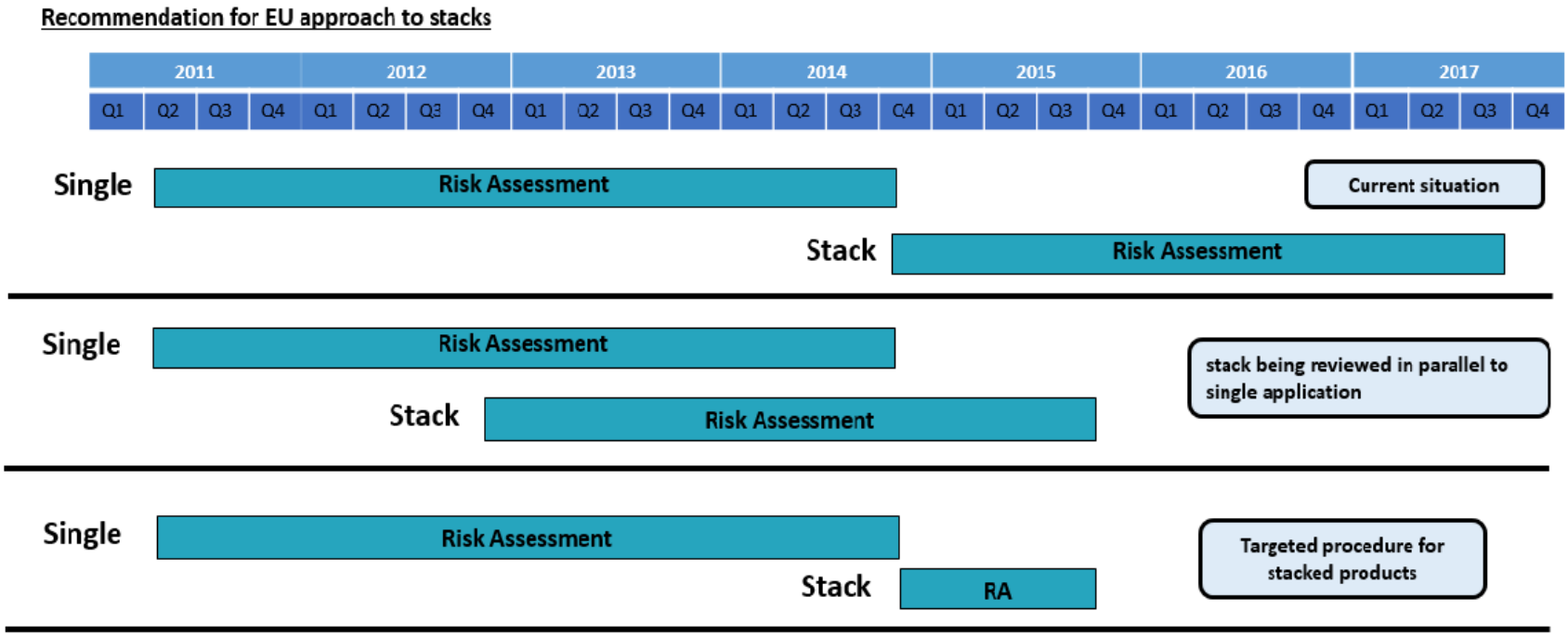
Good practices need to be employed both for stacks and singles

- The moment the application becomes valid, all contractors' work should start
- An application should be discussed in the WG within 3 months of the application becoming valid
- Stop-the-clock by EURL, or other WG(s) should not prevent discussion in other WGs
- Article 5 Implementing Regulation 503/2013

C) Parallel review

EFSA risk assessment of stacks specific data should be assessed even if single/s are under review

Specific requirements based on the outcome of the decision tree are dependent on the assessment of the singles



Conclusions

Globally, breeding stacks of current single products have been reviewed and approved establishing a **HOSU for breeding stacks of GM products**

In the absence of evidence of interactions that would result in adverse effects, breeding stacks should not require information above the 3 items indicated in the Implementing Regulation

- No re-assessment of singles
- Only assess the safety of stacks further when there is a plausible hypothesis for interaction that impacts safety
- Assessment of the **higher** order stack is applicable to all **subcombinations**

In addition, procedural suggestions will lead to improvements

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Thank You