Combined trait products: addressing the market needs

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Agenda

- The market situation and the need for combined trait products („stacks“)
- The challenges for notifiers and regulators
- A proposed way forward

The market situation

The market is moving to GM-crops with multiple traits:

- Stack of GM-crops with individual traits, through breeding (=breeding stacks)

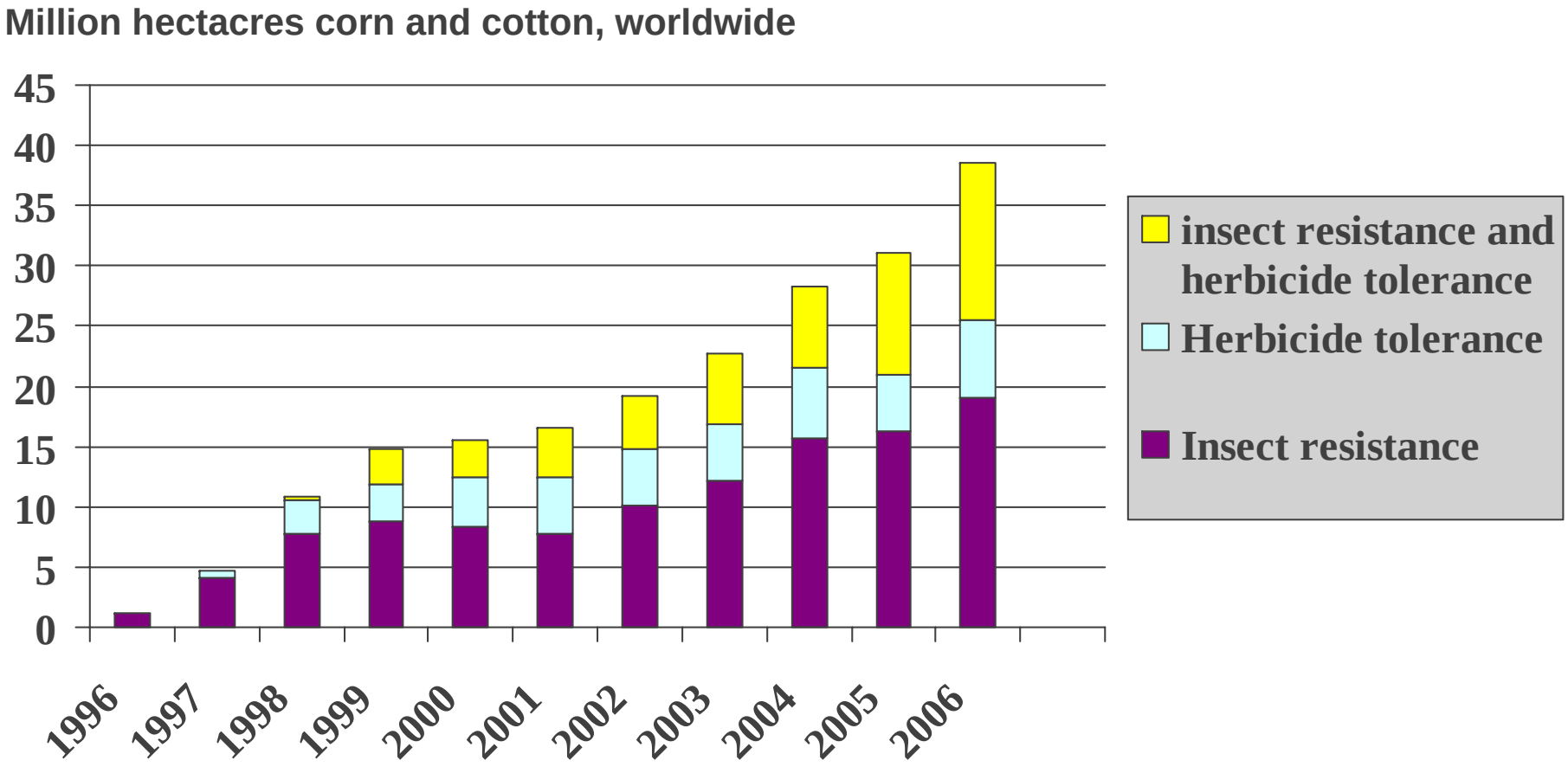
  short to middle term

- Transformation with multiple genes

  middle to long term

  will no replace completely breeding stacks

Combined trait products are becoming a major portion of worldwide crop acreage



Source: ISAAA

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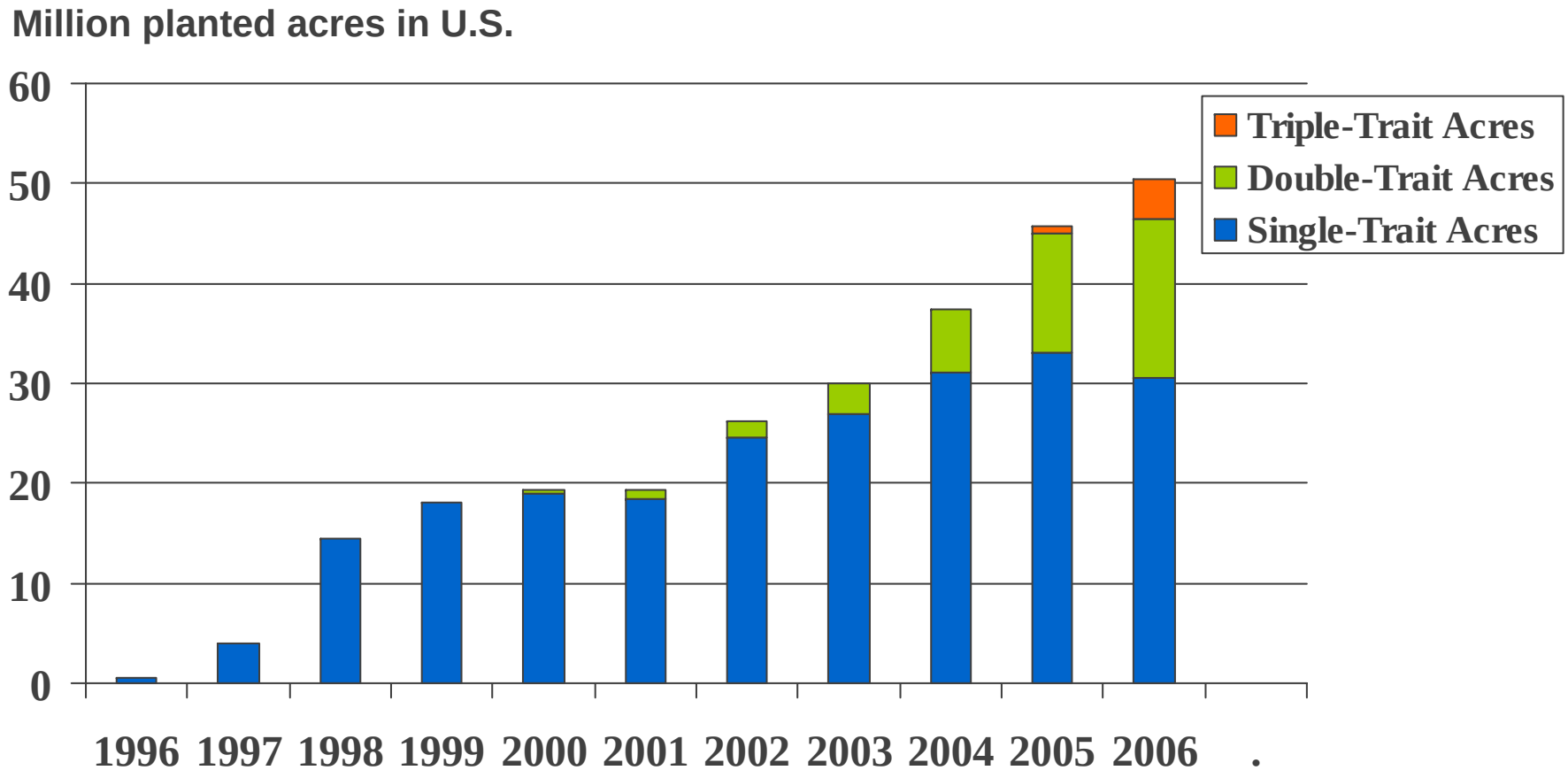
GM-maize in the US



Source: CropLife / ISAAA

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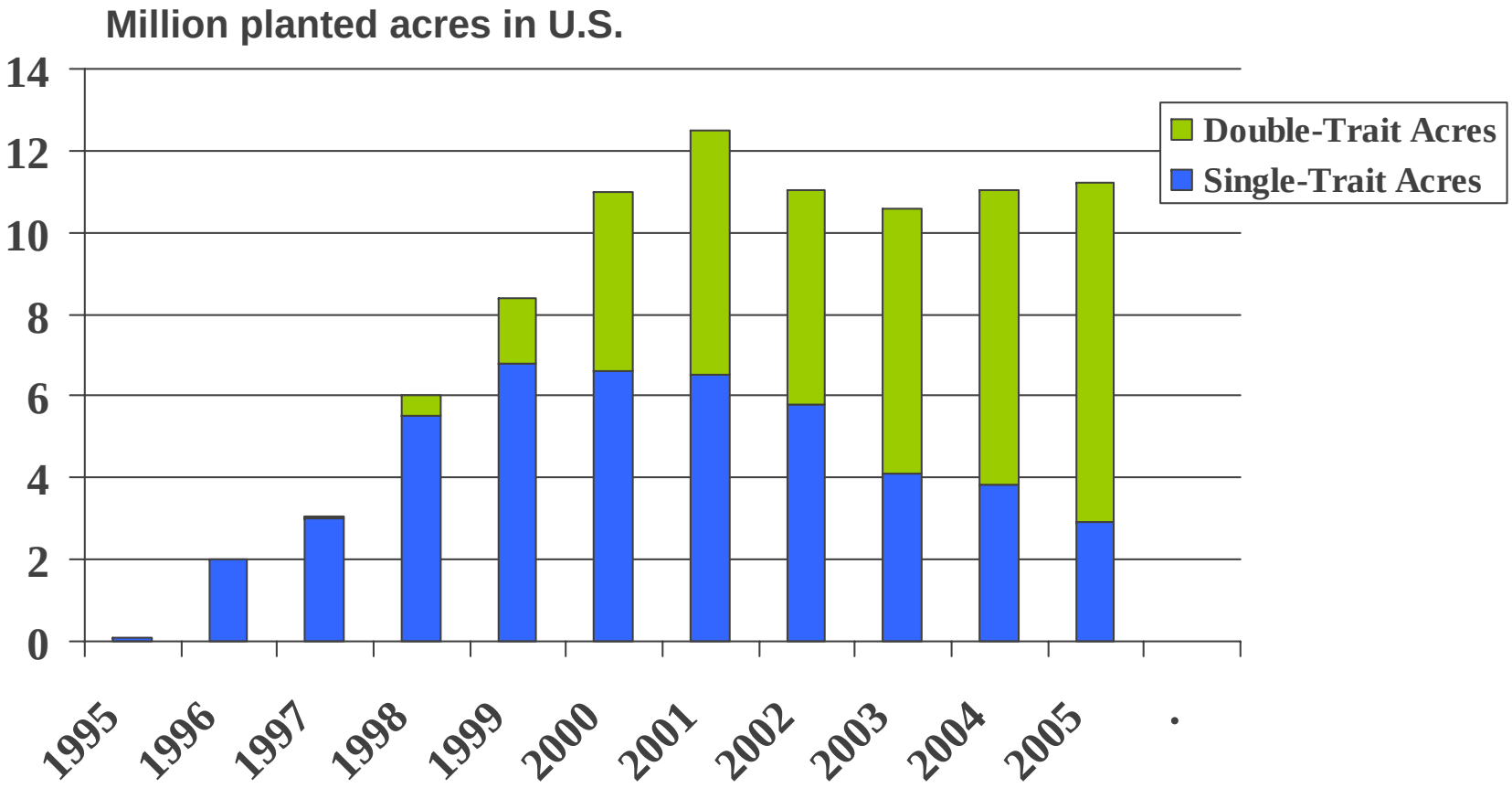
GM-cotton in the US



Source: CropLife

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Why is there a need for various combined trait products?

Agronomic reasons:

- To address different agronomic conditions (e.g. presence or absence of a given insect pest)
- To provide an additional tool for insect resistance management (e.g. stack of insecticidal proteins with different modes of action) and for weed resistance management
  - To provide for „refuges“, as part of IRM plan (e.g. plants with an output trait + herbicide tolerance used as refuges for fields with output trait + herbicide tolerance + insect resistance)
- To avoid „unnecessary traits“ where not needed

Why is there a need for various combined trait products?

Business reasons:

- To maintain the flexibility of the product offer
  - To continue offering relevant „previous traits“ with „new traits“ in the same product (e.g. to continue offering agronomic traits linked to output traits)

- To produce the commercial seeds with higher level stacks in production fields

Regulatory approaches (1)

2 potential approaches:

- GMO-A x GMO-B is a new GMO
  - Registration needed
  - Safety assessment needed

= the EU approach

- GMO-A x GMO-B is a product of traditional breeding
  - No registration needed
  - Presumption of safety
    - Unless a specific hazard is identified
      - Registration needed (e.g. EPA for stacks of insecticidal proteins)
      - Safety assessment needed, of this specific hazard

= the USA and Canadian approach

Regulatory approaches (2)

Intermediate approach:

- GMO-A x GMO-B is a new GMO
  - Registration needed
  - Presumption of safety, thus limited data requirement based on product behavior
    - If no change in bio-efficacy or protein expression, the safety data generated on the single events can be considered as the safety information for the combined trait product(s).

= the Japanese approach

Regulatory approaches (3)

What does the EU approach mean in practice for notifiers, risk assessors and authorities?

A multiplication of data generation and of dossiers!

# traits available	# possible stacks	# of dossiers (in addition to the dossier for the single events)
2	1 double	1
3	1 triple 3 double	4
4	1 quadruple 4 triple 6 double	11
5	1 quintuple 5 quadruple 10 triple 10 double	26

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A proposed way forward

Scenario 1:

The individual events have been independently assessed as safe:

- To develop a bridging data package, conducting the risk assessment on the combined trait product with the largest combination of events (e.g. on quadruple stack). This data package covers products combining a subset of the events (triple and double stacks).

Scenario 2:

The individual events have not been independently assessed:

- To develop a full data package on the combined trait product with the largest combination of events (e.g. on quadruple stack). This data package covers products combining a subset of the events (triple and double stacks), as well as the single events.
- This does not preclude that, on a case-by-case basis, some studies could be conducted on the individual events.

Rationale 1: use of test material

For import of maize grain:

- Assumption:
  - the hybrids are heterozygous for the traits
  - the traits segregate in an independent way
  - the gene conferring the trait is „dominant“

  -> The harvest will be a mixture of grain with different combinations of traits (=various stack levels)

  -> using segregating grain as test material de facto assess the various potential combinations of stacks

- If the plants are homozygous, there is no trait segregation

Segregation of trait in grain produced by hybrids

# trait	# of gametes	# of combinations	# of genotypes	# of phenotypes
n	2^n	4^n	3^n	2^n
1	2	4	3	2
2	4	16	9	4
3	8	64	27	8
4	16	256	81	16
5	32	1024	243	32
...				

Source: Strickberger, 1976

Rationale 2: testing the introduced proteins (human and environment safety)

Risk assessment on the introduced proteins (1):

- The safety of the proteins is assessed with purified proteins (-> applicable to the single events and to the combined trait products)

- If plant material is used, all introduced proteins are tested as all introduced proteins are present in the largest combination of events).
  - Data may be needed to confirm expression level and to calculate safety factors

Rationale 2: testing the introduced proteins (human and environment safety)

Risk assessment on the introduced proteins (2):

- An assessment of potential interactions between proteins will be done. If a potential interaction is identified, studies might be needed (e.g. 2 insecticidal proteins, case-by-case approach). There is no reason to believe that interactions, if any, will be different in different levels of stacks.

Event A with the insecticidal *protein α*

Event B with the insecticidal *protein β*

Potential interaction

Event C with the herbicide detoxyfying *protein γ*

No interaction predicted

➡ AxB = AxBxC regarding potential interaction

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Rationale 3: assessing potential unanticipated effects

- if an unanticipated effect is linked to a given event
  - it will be identified when assessing the single event
  - it will be identified when assessing the largest combination of events

- there is no reason to believe that „unanticipated effects“ would occur in lower combinations of traits, and no longer in larger combinations of traits.

- If the single events have been approved and are being grown, the history of the single events reinforces the non appearance of unanticipated effects

Rationale 4: stability in breeding

- if instability occured in a given event
  - it will be identified when assessing the single event
  - it will be identified when assessing the largest combination of events

  (such events would not reach market!)

- there is no reason to believe that „instability“ would occur in lower combinations of traits, and no longer in larger combinations of traits.

Conclusions (1)

- Products with combined traits are becoming the norm. The commercial life of single events is getting always shorter.

- The speed of breeding and the width of the product offer pose a challenge to the regulatory systems of some countries

Conclusions (2)

- The approach proposed allows to decrease the number of studies (and dossiers) without negatively impacting on the robustness of the safety assessment, applicable to the various combined trait products
  - Limit the overall number of animals used in toxicity or feeding studies, as decreased number of studies
  - Limit the number of reports to be generated and reviewed (this limiting the number of potential bottle necks in the approval system)

We strongly believe that the proposed approach is the way forward

Thank you