Position Paper

Regulation of Plant Biotechnology Products Containing Two or More Traits Combined By Conventional Plant Breeding

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We support the following policy regarding plant biotechnology products containing two or more traits combined by conventional plant breeding:

Scope of position paper

Combined trait plant biotechnology products are those containing more than one biotechnology-derived trait, such as one for insect control and another for herbicide tolerance, or two different insect control traits. Combined trait products can be produced in different ways, but this position paper addresses only combined trait products produced through conventional breeding (crossing of plants carrying individual traits). More background information for this position paper can be found at Attachment A.

Regulatory oversight requirements

- Combined trait plant biotechnology products produced by conventional plant breeding practices should be subject to the same regulatory oversight that is applied to conventional crops produced using the same techniques. Additional safety assessments should be conducted only when the traits are related, or where they affect the same metabolic pathway[1].

- For unrelated combined traits, the safety assessments previously undertaken for the individual single trait products should be applicable for the combined trait product. Redundant regulatory reviews of multiple dossiers for such combined trait products will not contribute to enhanced safety for human or animal health or for the environment, and such products should therefore not be subject to specific regulatory oversight.

- When the traits have the potential to interact, further analysis may be required on a case-by-case basis to determine the impact of any additive, synergistic or antagonistic effects. Regulatory authorities are therefore urged to adopt science-based safety assessment and regulatory processes to appropriately address these products.

[1] Such a determination would be made on a case-by-case basis in consultation between the applicant and the regulatory authority.

- In addition, there is a critical need for international harmonization of the food, feed and environmental safety assessment processes for biotechnology-derived products with combined traits, to enable the global trade of these products. Recent publications by James (ISAAA 2003)[2] and USDA[3] clearly demonstrate the rapid adoption of plant biotechnology products overall and especially products with combined traits.

Necessary data set requirements

- There are no scientific reasons for undertaking additional safety assessments when combining unrelated traits; therefore no additional safety data should be required by regulatory authorities. However, in order to confirm the presence of the individual traits in the combined trait product, regulatory authorities might be supplied on request with characterization data such as:
    - Greenhouse bioefficacy **OR**
    - Field bioefficacy data **OR**
    - Expression levels (gene **OR** gene product).

  Data from any ONE of these sources is appropriate to demonstrate that the individual traits/phenotypes of interest are present and functioning as desired in the combined trait product.

- Additional safety data are scientifically justified only when the traits affect the same metabolic pathway or are otherwise expected to interact. Sometimes the combined trait product has a more favourable safety assessment such as the combination of two or more insecticidal traits that have different modes-of-action thus leading to a more robust insect resistance management strategy[4]. On a case-by-case basis, studies may be required to determine whether there are any interactions (i.e., synergistic or antagonistic effects) between the traits or to assess the products of the metabolic pathway.

- Where OECD unique identifiers are required, these should be implemented in accordance with the policy in Attachment B.

[2] James, C., "PREVIEW: Global Status of Commercialized Transgenic Crops: 2003", ISAAA, No. 30, 2003.

[3] http://www.aphis.usda.gov/brs/brs_charts.html

[4] Roush, R.T., 1994, Managing pests and their resistance to Bacillus thuringiensis: Can transgenic crops be better than sprays? Biocontrol Sci. Tech. 4: 501-516.

Attachment A – Position Paper on Regulation of Plant Biotechnology Products Containing Two or More Traits Combined By Conventional Plant Breeding

BACKGROUND

- The focus of this position paper is on combined trait products produced through conventional plant breeding. Combined trait products can also be produced using transformation techniques, either by introducing two or more traits at the same time in a single transformation event or by re-transforming a plant that contains an existing biotechnology-derived trait. These types of combined trait products would be subject to the same regulatory data requirements as other transformation events.

- Plant biotechnology products containing single traits such as insect protection and herbicide tolerance have created benefits such as more targeted pesticide use, increased conservation tillage, improved food quality from reduced consumer exposure to specific mycotoxins, increased agricultural productivity and lower production costs for growers, the environment and society.[5]

- The second generation of products, including nutritionally enhanced foods and feeds, will provide additional benefits. Maximum value for both growers and consumers will come from combining two or more traits into a single crop. An example of a future combined trait crop could be a corn plant that is protected against plant pests and produces oil that provides important nutritional and health benefits.

- Conventional breeding of plants that contain single beneficial traits is often used to produce plants with combined traits. The individual traits used in the development of the combined trait products have previously been extensively assessed for safety. The conclusions of the safety assessments conducted for each of the individual traits apply to the combined trait products when the traits are unrelated and do not affect the same metabolic pathway. The World Health Organization[6] confirmed this approach in 1995, stating that when two plants that are substantially equivalent to conventional varieties are crossed by conventional breeding techniques, the combined trait product is expected to be substantially equivalent to the single event products.

- Combined trait products were first introduced in 1997 and were grown on 5.8 M ha globally in 2003 (ISAAA 2003). More than one third of the biotechnology-derived cotton planted globally in 2003 contained both insect-protection and herbicide tolerance traits.

- Countries such as the US, Australia and Canada do not require submission of additional safety data on combined trait products developed by conventional

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[5] Munkvold, GP, Hellmich, RL, and Showers, WB. 1997. Reduced *Fusarium* ear rot and symptomless infection in kernels of maize genetically engineered for European corn borer resistance. Phytopathology 87: 1071-1077.
Munkvold, GP, Hellmich, RL, and Rice, LG. 1999. Comparison of fumonisin concentrations in kernels of transgenic *Bt* maize hybrids and nontransgenic hybrids. Plant Dis. 83: 130-138.

[6] World Health Organization, "Application of the Principles of Substantial Equivalence to the Safety Evaluation of Foods or Food Components From Plants Derived by Modern Biotechnology". WHO Workshop, pp 1-80, 1995.

breeding if the single trait products have completed the regulatory process and the two traits are unrelated. The US EPA does regulate combined trait products that contain two insect control traits to ensure that there are no synergistic effects and that the insect resistance management (IRM) plan for the combined trait product is appropriate. Canada and Australia require that developers notify them of their intent to commercialize combined trait products. Canada also reserves the right to request data demonstrating that combined trait products are substantially equivalent to the single event products.

- The Japanese regulatory authorities recently issued guidelines for combined trait products, based on a classification system. Category 1 traits include those traits that do not alter the metabolic pathway of host plants and would include agronomic traits such as insect protection (or control) or herbicide resistance. Category 2 traits include traits that alter (promote or inhibit) the metabolic pathway of host plants and Category 3 traits include those that introduce new metabolites that have previously not been present in the host plant. Based on this classification scheme, there is no need for a separate review by the Food Safety Committee (FSC) for combined trait products developed by conventional breeding of Category 1 X Category 1 traits, as long as the individual traits have been previously reviewed. A separate food safety review is required for combined trait products comprised of Category 2 or Category 3 traits.

- In contrast, the EU and Argentina require new authorisations for all combined trait products. In such cases, extensive bridging regulatory data on the specific combined trait product needs to be generated resulting in a prolonged and costly regulatory procedure which is disproportionate to any potential safety concern arising from such products.

Attachment B – Position Paper on Regulation of Plant Biotechnology Products Containing Two or More Traits Combined By Conventional Plant Breeding

Application of the OECD unique identifier system to combined trait products

- The purpose of a unique identifier is for use as a "key" to access information on biotechnology-derived products that may have multiple designations (event numbers, brand names, etc.).

- The Organisation for Economic Co-operation and Development (OECD) has provided specific guidance regarding the format for identifying biotechnology-derived products (OECD, 2002)[7], which is based on unique identification of the transformation event.

- When two or more transformation events are combined using conventional breeding techniques, the appropriate unique identifier should be comprised of the unique identifiers for each of the single event products (e.g., unique identifier 1 X unique identifier 2, etc).

- This approach provides maximum transparency in that the format clearly shows that the product is the result of a conventional cross and gives direct access to the unique identifiers of the single trait products as well as a direct link to regulatory dossiers and associated clearances.

- Where, in the unlikely case that unanticipated adverse effects are linked to a particular event that warrant specific actions with products containing that event, such an identification system would also be a transparent link allowing other products containing the unique identifier of the event in question to be rapidly identified.

- Combined trait products that are developed by combining two or more genes in a single vector would be new transformation events and would therefore require a distinct unique identifier.

[7]OECD, 2002 , " OECD Guidance For The Designation Of A Unique Identifier For Transgenic Plants". Series on Harmonization of Regulatory Oversight in Biotechnology, No. 23, 2002.