Position Paper:
Regulation of Plant Biotechnology-Derived Breeding Stacks
January 2015

Introduction

Since the previous CropLife International (CLI) position papers on plant biotechnology-derived breeding stacks, also known as combined event products or stacked trait products, were published in 2005 (CLI, 2005) and 2011 (CLI, 2011) an increasing number of new biotechnology-derived traits have been commercialized, and the number of stacked trait products continues to increase to meet customer needs and preferences for different trait combinations. Additionally, the increasing number of safety risk assessments continues to confirm that stacked trait products developed through conventional breeding are as safe as non-biotechnology products developed by conventional breeding practices.

Position

It is the position of CLI, based on scientific rationale, that the safety of breeding stacks of biotechnology derived traits (stacked trait products) is not different from the safety of breeding stacks of conventional (non-biotechnology derived) traits and therefore safety risk assessment of these products is, in most cases, unnecessary. Where crops containing individual single events have been determined to be as safe as their conventional counterparts, it can generally be concluded, based on the knowledge and experience of conventional breeding, that the breeding stack of the single events is also as safe as the stacked product of non-biotechnology-derived traits in conventional varieties (Steiner *et al*., 2013; Pilacinski, *et al*., 2011, Kok *et al*., 2014).

Rationale for the Position

Conventional plant breeding has a long, established history of safe use (HOSU), predictably providing safe food and feed products throughout history (Pilacinski *et al*., 2011; FAO/WHO, 2001). The World Health Organization issued food safety evaluation guidelines in 1995, and recognized then that, when two plants which are substantially equivalent to conventional varieties are crossed by conventional breeding techniques, the stacked event product is expected to be substantially equivalent to the individual events (WHO, 1995). Other international organizations involved in developing guidance on the safety evaluation of biotechnology derived plants do not consider the stacked trait products as new biotechnology-derived plant varieties or organisms. The Codex principles and guidelines have been broadly applied to the evaluation of single events and consider that, once these events have been proven safe, conventional breeding can be utilized to incorporate these events into the commercial cultivars, without the need for additional safety assessment (Codex, 2009).

In more than a century of plant breeding, hundreds of thousands of new varieties have been bred without the emergence of any novel allergens or toxins (Steiner *et al*., 2013). The safe use of conventional breeding has been shown to extend to discrete biotechnology-derived single events. Numerous publications support the conclusion that stacking traits (events) through conventional breeding poses no greater risk to food or feed safety than stacking non-biotechnology-derived traits (Pilacinski *et al*., 2011; Weber *et al*., 2012; Raybould *et al*., 2010; WHO, 1995; CLI, 2005; CLI, 2007). Given the history of safe use of plant breeding, including its

application to traits developed by biotechnology, further evaluation of stacked trait products that are produced through conventional breeding techniques is unnecessary.

The safety of stacked trait products has now been further demonstrated by more than a decade of safe use, with adoption of breeding stack products increasing year after year globally. In 2014, stacked trait products with two or more events were planted in 13 countries on 51 million hectares, equivalent to 28% of the 181 million biotech hectares planted. The harvests from these crops were used as food and feed in many countries around the world (ISAAA, 2014).

The widespread adoption of stacked trait products also illustrates the regulatory capacity required to regulate stacked trait products globally. In the past decade the European Food Safety Authority (EFSA) has extensively reviewed more than 20 stacked trait products without finding any safety concerns (Kok *et al*., 2014 and EU register of genetically modified food and feed). Recently, the Ministry of Health, Labor and Welfare (MHLW) in Japan has deregulated foods and feed from stacked trait products combining previously approved agronomic traits (MHLW Gazette, 2014). It did so after considering its historical (around 20 years) evaluation of more than 200 stacked trait products which showed no indication of safety concerns. Stacked trait products currently in commercial cultivation and consumed around the world have been reviewed by numerous regulatory authorities, consistently confirming that these stacked trait products are as safe as commodity products derived from conventional sources.

Despite the absence of indications of risk in regulatory evaluations, confirmed by their history of safe use in the broader context of the long history of the safety of conventional breeding, some country's regulations continue to evolve requiring even more extensive evaluation of the safety of breeding stack products. Regulatory assessment of stacked trait products is not justified where the likelihood of trait interactions can be excluded (Steiner *et al*., 2013). Maintaining or increasing the regulatory burden based on the assumption of harm from stacked trait products bears the risk of stalling innovative agricultural solutions and disrupting commodities trade without enhancing overall food and feed safety.

Countries Requiring Specific Assessments for Stacks

Regulatory policies and data requirements for the safety assessment and approval of stacked trait products for food and feed uses differ globally. This inconsistent approach to the regulation of stacked products is an important contributor to asynchronous approvals impacting global commodities trade.

If national authorities choose to regulate stacked trait products, despite the lack of valid scientific rationale and the absence of indications of risk, any data requirements should consider a bridging approach to confirm the presence or heritability of the individual traits (events) in the stacked trait product (e.g., detection of inserted DNA, expression of the transgene products, etc.). One of the main concerns cited for regulating stacked trait products is the possibility of interactions among the genes/proteins in the product. The need for additional data requirements should be predicated on the potential for gene or gene product interactions specific to the modes of action of the associated single trait (event), the outcome of an individual event risk assessments, and development of testable hypotheses for plausible risks. The potential for such interaction is rare, but predictable, and can be evaluated within the context of the single event. In the case where the potential for interactions cannot be excluded, additional equivalence data, such as composition or agronomic/phenotypic data, should be considered on a case by case basis where a testable hypothesis for interaction can be formulated (Steiner *et al*., 2013). These assessments should be conducted with a focus on confirming substantial equivalence between the stacked trait product and conventional crop, while acknowledging natural variation is inherent in plant populations.

Additionally, CLI's position on regulation of plant biotechnology-derived stacked trait products considers that:

- Any regulatory assessment of the largest stack of events is applicable to and covers all smaller stack combinations of those events. For example, safety data submitted in support of the stacked trait product A x B x C x D should be sufficient to inform on the safety of all possible sub-combinations of events (e.g., A x B x C, A x C x D, A x D, etc.). This practice has been adopted already by regulators in some countries that regulate stacked trait products (e.g., Argentina, European Union, Japan, Philippines) where specific safety assessments for commercial sub-stacks are not required.

- In countries where additional specific safety assessments are required for stacked trait products, these assessments should be targeted to the scope of the approval being sought. For example, environmental safety evaluations for countries assessing a product intended for import and food/feed uses are considered unjustified.

- Conducting additional in-country studies to support food and feed safety assessments of stacked trait products is not necessary, as confirmatory bridging studies conducted in any one geography are sufficient to demonstrate lack of interactions.

- Parallel review of applications for single event and corresponding stacked trait products should be allowed in countries requiring specific assessments for stacked products. Such parallel review systems maximize resource efficiency for both governments and industry by reducing the potential for delays related to limited regulatory capacity and the occurrence of asynchronous approvals.

- In the case of a country deciding to implement new requirements where previously there were none, CLI member companies strongly encourage the country to consider an appropriate transition period to accommodate products that are currently in commerce. For products where the safety of the single events has previously been assessed and the corresponding stacked products are offered commercially, countries should exempt the stacked products from the new requirements, as they will have an established history of safe use. Furthermore, depending on the nature of the new requirements, governments should allow adequate time to adjust existing regulatory programs. Special care should be taken in implementation of new regulations to ensure that global markets are not disrupted.

Conclusions

A long history of safe conventional breeding and a considerable history of safe breeding of plant biotechnology derived products has demonstrated that the use of conventional plant breeding to stack previously approved events poses no greater risk to food and feed safety than breeding of conventional varieties. Based on the existing safety assessment paradigm applied to single events which consists of robust, comprehensive analyses and data packages that also take into account potential unintended effects of the transgene(s) with endogenous plant genes and their products, the conclusions from the safety assessments of the single events serve as the foundation on which to conclude on the safety of stacked trait products.

While some countries have reduced the scope of stacked trait product regulation in recent years others countries continue to expand the regulation of these products. CLI encourages governments to review critically about the need to continue to routinely require additional specific data for such stacked trait products. Where countries decide to require additional data, the data should be limited to data required to bridge to the demonstrated safety of the parental events.

As the number and importance of stacked trait products increases in the global marketplace, it is vital that these products have a simplified path to regulatory approval in view of the safe history of conventional breeding. This will promote the availability of products that will enhance agronomic productivity to ensure that the food and feed necessities of the growing global population are met without compromising safety.

References

1. Codex Alimentarius Commission. (2009) Principles for the risk analysis of foods derived from modern biotechnology (CAC/GL 44-2003) and guideline for the conduct of food safety assessment of foods derived from recombinant-DNA plants (CAC/GL 45-2003). In Foods Derived from Modern Biotechnology, Ed 2. Food and Agriculture Organization/ World Health Organization, Rome, pp 1–5, 7–33
2. Crop Life International (CLI) position paper. (2005) Regulation of plant biotechnology products containing two or more traits combined by conventional plant breeding.
3. Crop Life International (CLI) position paper. (2007) Assessing and approving multiple combinations of biotechnology-derived events through conventional breeding.
4. FAO/WHO. (2001) Food and Agriculture Organization of the United Nations/World Health Organization. “Evaluation of allergenicity of genetically modified foods.” Report of a joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, January 22–25, Rome, Italy.
5. ISAAA. (2014) Global Status of Commercialized Biotech/GM Crops: 2014: Executive Summary. ISAAA Brief 49-2014. http://www.isaaa.org/resources/publications/briefs/46/executivesummary/ (Accessed January 14, 2015).
6. Kok, EJ, Pedersen, J, Onori, R, Sowa, S, Schauzu, M, De Schrjver, and Teeri, TH, (2014) Plants with stacked genetically modified events: to assess or not to assess? *Trends in Biotechnology*, 32 (2): 70-73.
7. MHLW Gazette No. 6320 (June 27, 2014)
8. Pilacinski, W, Crawford, A, Downey, R, Harvery, B, Huber, S, Hunst P, Lahman LK, Macintosh S, Pohl M, Rickard, C, Tagliani, L, Weber, N (2011) Plants with genetically modified events combined by conventional breeding: An assessment of the need for additional regulatory data. *Food and Chemical Toxicology*, 49 (1): 1-7.
9. Raybould, A, Grasser, G, Hill, K, and Ward, K. (2012) Ecological risk assessments for transgenic crops with combined insect-resistance traits: the example of Bt11 x MIR604 maize. *Journal of Applied Entomology*, 136:27-37.
10. Steiner, *H-Y,* Jez, JM, Kough, J, Parrott, W, Underhill, L, Weber, N, and L. Curtis, H (2013) Evaluating the Potential for Adverse Interactions within Genetically Engineered Breeding Stacks. *Plant Physiology*, 161 (4): 1587-1594
11. Weber, N, Halpin, C, L. Curtis, H, Jez, JM, Kough, J, and Parrott, W (2012) Crop genome plasticity and breeding stacks*. Plant Physiology,* DOI:10.1104/pp.112.204271
12. WHO Workshop. (1995) World Health Organization. “Application of the principles of substantial equivalence to the safety evaluation of foods or food components from plants derived from modern biotechnology.” WHO workshop, pp. 1-80.