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Ms Sandra Gallina
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European Commission
Rue de la Loi 200
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CC: Ms Irene Sacristán Sánchez, Head of Unit Biotechnology, DG SANTE

CropLife Europe's reply to DG SANTE - Use of antibiotic resistance marker genes in GM crops

Dear Ms Gallina,

With the present letter, we are replying to your request for updates on the development of alternative technologies to antibiotic resistance marker genes (ARMG) and other steps from CropLife Europe member companies for the phasing out of ARMG in GM plants.[1]

CropLife Europe fully supports the European Commission's efforts to combat antibiotic resistance as one of the global public health threats.

ARMG were an efficient and reliable tool for the selection of GM events during the development process. In a 2004 EFSA scientific opinion, the GMO panel concluded that with regards to the safety of genes conferring resistance to kanamycin and hygromycin, including the *nptII* gene, "*there is no rationale for inhibiting or restricting the use of genes in this category, either for field experimentation or for the purpose of placing on the market.*" [2] The joint EFSA opinion of the GMO and Biohaz Panels from 2009 further complemented that "*There is no experimental evidence linking antibiotic resistance marker genes of GM plants to the environmental abundance of antibiotic resistances or their genes.*" [3]

Industry commitment to phase out ARMG in single events since 2010
CropLife Europe member companies committed to the phase out of ARMG in new GM single events not yet in development as of 2010. We would like to underline that CropLife Europe members have upheld their commitment and, as of 2010, stopped designing single GM events with ARMG in the final product. Post-2010, any submissions for products containing ARMG were either for products already in development pre-2010, or related to stacked products or renewals.

[1] Ref. Ares (2024)5250706 – 19/07/2024
[2] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2004.48
[3] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.1108

Progressive phasing out of events already present before 2010

Commercial products and those in development before 2010 are being progressively phased out in line with their product life cycles.[4] Factors developers consider in the product life cycle include: development and regulatory approval phase, trait combination (stack products) to meet grower needs and elements for effective resistance management, and finally considerations for discontinuance of products (*e.g.*, Low-Level Presence (LLP) in commodity markets).

The time required to develop and launch a new GM event is, on average, 16.5 years[5], with the regulatory phase accounting for slightly over half of the development time. These long timelines are driven by increasing regulatory requirements in a small number of markets such as the EU. As a result, the only new single event containing ARMG submitted to EFSA after 2010 was already advanced in development stages at the signature date of the 2010 commitment. Given the extensive development time for new events and importance of combinations of traits for resistance management, the product life cycle of approved events containing ARMG includes the use of stacked products. There are several factors that go into discontinuance of GM products[6], which include considerations for LLP and in countries that have time-limited authorisations facilitating renewals of authorisations as appropriate.

So far, the following phase out has been achieved: one single event (MON 863) and five stacked products (MON 863 x MON 810, MON 863 x NK603, MON 863 x MON 810 x NK603, MON 15985 x MON 1445, MON 88913 x MON 15985) containing ARMG have been withdrawn since 2010.

The Commission's letter from July 2024 references four specific events which contain ARMGs (MON 531, MON 15985, MON 1445, MON 87460) which are currently in the process of renewal for import in the EU. All these events were in development before 2010, as evidenced by the fact that the cotton products (MON 531, MON 15985, MON 1445) were renewed in 2015, and MON 87460 maize was approved in 2015 in the EU.

Impact of current EU policies on GM submissions

Older GM events continue to be used in a small number of markets, and companies need to maintain EU approvals to comply with the current interpretation of EU regulations given the implementation of a zero-tolerance policy on non-authorised GM material in the EU. All of these products have been assessed and considered safe by EFSA and other regulatory agencies around the world. The EU's policy on breeding stacks[7] and renewals[8] are an additional reason for the submission of applications including older events with ARMG, as such events were approved or in development before 2010.

We are open to discuss with the Commission alternative approaches to managing GM events containing ARMG, such as scope adaptations which better reflect the importance and use of such products and refinement of LLP definition.[9]

Investing in finding alternatives

Following the 2010 commitment, CropLife Europe member companies have invested in the development of alternative technologies for the selection of GM events during their

[4] Letter from CropLife International to Commissioner Dalli from 23 April 2010

[5] AgBioInvestor, 2022. Cost and Time Required for the Discovery, Development and Authorisation of a New Plant Biotechnology-Derived Genetic Trait. CropLife International.

[6] Excellence Through Stewardship: Guide for Product Discontinuation of Biotechnology-Derived Plant Products. Revised August 2021

[7] The requirement to risk assess and authorise stacked events obtained by conventional breeding of positively assessed GM single events (Part 2.2. of Annex II, Implementing Regulation 503/2013).

[8] The requirement to renew GM authorisation every 10 years (Art.11 of Regulation 1829/2003).

[9] Commission Regulation (EU) No 619/2011 of 24 June 2011 laying down the methods of sampling and analysis for the official control of feed as regards presence of genetically modified material for which an authorisation procedure is pending or the authorisation of which has expired Text with EEA relevance

development and remain committed to such a path. Examples of alternatives, which are used in new products and which have been thoroughly investigated for efficiency and adequacy, include the use of non-antibiotic resistance selectable markers such as phosphomannose-isomerase (PMI)[10], herbicide resistance genes, as well as the removal of ARMG from the final product via site-specific recombination (*e.g.* Cre-mediated auto-excision[11]). To demonstrate the advancement in this regard, since 2010, out of 48 submissions of new single events, only 1 single event contained an ARMG. Overall, since 2010, 93% of all GM applications for the authorisation of both new single and new stacked events submitted by CropLife Europe member companies in the EU have not featured any ARMG.

To conclude, CropLife Europe members remain committed to developing new events without ARMG and to phasing out commercialised GM events or those in development before 2010 in line with their life cycle. With this letter, we re-iterate our 2010 commitment and can confirm that CropLife Europe company members do not plan the submission of any applications for the authorisation of new single events containing ARMG in the EU. We hope the information and data provided satisfy your request for progress update in this regard.

Yours sincerely,

Olivier de Matos
Director General of CropLife Europe

[10] https://link.springer.com/article/10.1007/s002999900187
[11] https://link.springer.com/article/10.1007/s00299-022-02935-1