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Open Letter to Commission President Juncker, Commissioner for Health Andriukaitis, Commissioner for Agriculture Hogan, Commissioner for Research, Science and Innovation Moedas, and Commissioner for Jobs, Growth, Investment and Competitiveness Katainen

Follow-up request to Open Letter dated 18 July 2018

Dear President Juncker, Dear Commissioners,

This is a follow-up to our letter dated 18 July 2018 concerning proposals for:

(1) a coherent interpretation of the GMO definition of EU Directive 2001/18/EC, including a proposal for exemption or inclusion for products coming from the use of certain new technologies;
(2) the designation of an EU authority for GMO status determination; and,
(3) the Commission's engagement in discussions with agricultural exporters and importers to harmonize the regulatory status of plants derived from genome-editing technologies.

Indeed, as we feared and as we had already pointed out in this letter, the judgment of the Court of Justice of the European Union (CJEU) of 25 July 2018 concerning the regulatory status of plants derived from mutagenesis techniques has not satisfactorily solved the status of certain plants obtained by genome editing technologies. Indeed, if these plants are subject to all the regulations in force in Europe for GMOs, such plants cannot be developed in Europe, which will be highly detrimental for the development of research and seed companies in Europe and will strongly penalize European agriculture. Moreover, it does not provide answers to other questions, which were not addressed in the request of the Conseil d'Etat, which had long been communicated by the European research and development community engaged in plant breeding.

Given this situation, it seems urgent to decide on the regulatory status of plants derived from these technologies, in the interest of research, of all European seed companies, the competitiveness of European agriculture at the global level, and European consumers. We believe that it is up to the Commission to clarify the current situation in order to allow the reasoned use of these technologies as quickly as possible. A rapid decision, which we think is necessary, should not preclude a more complete revision of Directive 2001/18/EC, but this revision seems only feasible in the longer term, a timeline that is incompatible with an urgent treatment of the regulatory status of the technologies in question.

Complementary information is presented below and in the attached annexes:

1. **Very short-term actions**: we believe that the Commission could take the following quick decisions, based on the items of our letter dated 18 July:

   a. Set up a validation process for plants obtained from the following technologies:

   - Null segregants – these are progeny of genetically engineered plants from which the GMO feature has been eliminated by sexual crossing;
   - Plants derived from the use of a genome editing technology and, in particular (i) those that have undergone deletions regardless of size, often referred to as plants derived from the so-called SDN1 technology and (ii) those which have undergone a substitution of a single nucleotide pair or an insertion of less than 20 base pairs, often referred to as plants derived from the so-called SDN2 technology (see further descriptions of SDN1 and SDN2 in Annex 1);
   - Cisgenic organisms which correspond to plants in which a native gene or a gene originating from a sexually compatible species has been inserted.

   In summary, this validation process could consist of a request for validation to be addressed to a European authority to be designated (see below), such request to be made at an early stage of the research or development of these plants and consisting of information on the proposed modification, the introduced trait and the technology utilized. Data requirements for regulatory status determinations should be proportionate and reasonable, consistent with those requested by other countries, so as not to inhibit public sector and small private companies from engaging in this field.

   Some countries such as, for example, the United States, Brazil, Argentina, Chile and Japan (ongoing) have taken a position on these technologies and put in place the corresponding procedures. To facilitate global trade, regulatory harmonization is essential. It is therefore recommended that the procedure that will be put in place in Europe is compatible with what has been put in place in other countries.

   In Annex 1 you will find additional information justifying our request for a validation process and in Annex 2 some elements on what this validation process might look like.

   b. Designation of an EU authority for the validation of the regulatory status of these plants (exclusion, exemption or inclusion) in relation to the regulations in force and in particular in relation to Directive 2001/18/EC and Regulation 1829/2003/EC. This authority should have the necessary resources and decision-making power to be able to confirm the regulatory status of the plant within a reasonable timeframe (e.g., 90 days). It can be the European Commission or another body from it having the capacity to handle such validation.

      Additional information is given in Annex 2.

   It is up to the Commission to decide the most appropriate decisional process to allow rapid implementation of what is presented above.

2. **Longer-term actions**

   The first European regulation on GMOs was put in place in 1990 with a revision that led to Directive 2001/18/EC adopted in March 2001 and still in force today. Since then the Cartagena Protocol has been ratified by the European Union on 27 August 2002, and transposed into European law by Regulation 1946/2003/EC dated 15 July 2003. In the wake of this transposition, the Commission adopted Regulation 1829/2003/EC dated 22 September 2003 on genetically modified food and feed, and on the same day, Regulation 1830/2003/EC concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC on these topics. In parallel, many countries have also put in place regulations for GMOs. Since 2001, much scientific data has

been published showing the safety of commercially produced GM seeds and derived products. In addition, the technologies utilized have also significantly evolved. Although European experience with cultivation of genetically modified plants has been mainly limited to the use of the MON810 event in Spain and Portugal, their global commercialization over the past 20 years has grown significantly, reaching a total surface area of 189.8 million hectares worldwide, planted by more than 17 million farmers in 24 countries, thus demonstrating the utility of these plants for the various actors engaged in the agricultural and food derived from them.

Taking all these elements into account, it seems to us essential to carry out a comprehensive evaluation of the regulations on genetically modified organisms in the light of accumulated scientific knowledge and practical experience with such organisms, and revise the legislation accordingly. This review should include, but not be limited to, the adjustments briefly presented below:

- Harmonization of the GMO Directives and related Regulations in force in Europe (see above), in particular with respect to the definition of a GMO, taking into account the definitions of the Cartagena Protocol. This harmonization should also aim at making European regulatory requirements compatible with the regulations of other countries in order to facilitate trade;
- Reduction and modification of current requirements taking into account accumulated knowledge over the last 20 years of commercialization of genetically modified plants worldwide;
- Return to the original intent of the regulatory regime and adjust requirements on a case-by-case basis, considering the nature of the product resulting from the use of these technologies, rather than imposing a set of studies that do not take into account the nature of the introduced trait. Ninety-day rodent feeding studies would be a good example.
- Ensure that the procedure implemented works and enables obtaining a final regulatory outcome in a timeframe compatible with the marketing or importation of these products.

Once our request for very short-term actions has been addressed, we would be happy to further discuss along with other stakeholders the content of these revisions.

We remain at your disposal to answer any questions you may have regarding the matters raised in this letter. We are ready to meet you and to participate in any working group you may designate to address the topics discussed in this letter.

Very Respectfully,

Prof. Dr. Klaus-Dieter Jany,

Wissenschaftlerkreis Grüne Gentechnik e.V (WGG)

Alain Deshayes

Association Française des Biotechnologies végétales (AFBV)

Annexes : 1 Explanatory note providing supporting documentation for short term actions
2 Designation of a specific competent authority

Annex 1: Additional information supporting our request for a validation process

A validation process *should be put in place quickly for the plants described below:*

1. **Null segregants**: they correspond to progeny of genetically modified plants whose GMO feature has been eliminated by sexual crossing. Two cases can be considered depending on the origin of the null segregant:

   - Null segregants derived from a genetically modified (GM) plant and marketed in a country on a worldwide scale. These null segregants should be allowed to be marketed freely;
   - Null segregants descending from a GM plant used as an intermediate in the process of creating the new plant. This is often the case when editing genomes where an intermediate plant is produced containing the editing mechanism, usually contained in a transgene, that is eliminated when the editing of the genome has been performed. A similar situation may exist for plants resulting from the use of certain technologies for hybrid production or DNA methylation. In these cases, the final plant could be subject to the validation process proposed here.

   It should be noted that a similar decision has been taken or is being considered by other countries such as the USA and Japan.

2. **Plants derived from genome editing technology:**

   These technologies are among the eight technologies grouped under the term “New Breeding Techniques” (NBT). In the judgment of the CJEU of 25 July 2018 they are referred to as "new techniques of site-directed mutagenesis". They have been analyzed at European level for more than ten years following several initiatives of the Commission and some Member States. In particular, we draw the Commission’s attention to Explanatory Note N° 2 dated 28 April 2017 from the Scientific Advice Mechanism (SAM), with which it is familiar as it was requested by the Commission. Below is a summary of the principal observations we feel are most relevant to the technologies considered in this Note.

   Indeed, this report covers all NBTs and we will only discuss here those relating to genome editing. As explained in the SAM Note these genome editing technologies aim to achieve a pre-defined modification in a cell or a random modification in a defined site of the genome. They use the properties of the natural DNA repair system and natural nucleases acting at defined sites (Site Directed Nuclease [“SDN”]) or oligonucleotides (Oligonucleotide Directed Mutagenesis [“ODM”]). Three types of modifications are obtained: either a modification, most often a deletion, randomly at a defined site of the genome (SDN1), or a pre-defined modification in a specific site of the genome (ODM and SDN2) or an insertion of one or more new allele (s) at a specific site in the genome (SDN3). It should be noted that SDN1 leads to a final result similar to that obtained for example during treatments with ionizing radiation and SDN2 leads to a final result similar to that obtained for example during treatments with mutagenic chemical agents.

   The SAM Note describes the characteristics of the different NBT products according to the modification performed in comparison with the so-called "conventional breeding technologies” (crossing) which include mutation breeding (mutagenesis), grouped under the heading of conventional breeding techniques (Conventional Breeding Techniques - CBT), see Tables 1A to 7A and the corresponding texts from the SAM Note. The analysis covers different domains. We summarize, below, the main conclusions with regard to SDN1, SDN2 and ODM technologies in comparison with CBT (crossing and mutagenesis):

- *Detectability and identification - Table 1A:* The change introduced is most often detectable and identifiable. If it is identical to a modification known in nature, its origin cannot be determined (natural or induced);

- *Unintended effects - Tables 2A:* These are mainly off-target changes due to ODM or SDN activity outside the targeted site. Depending on the experimental conditions, these effects may be limited or absent. In any case, they are less important than in the case of mutations induced by irradiation or chemical treatments. And, in all cases, they are eliminated during the breeding process through backcrossings done after the modification. Thus, on this subject, the conclusions of the SAM Note are very different from those mentioned by the Conseil d'Etat and therefore by the CJEU: see SAM Note at pages 17-19, 77 to 80, 87 to 89, and tables on pages 95 and 97.
- *Presence of exogenous DNA molecule - Table 3A:* There is no exogenous DNA in the final product. If, initially, an exogenous DNA has been introduced for the modification to occur, it is then removed by backcrossing after the modification has taken place;
- *End-products - Table 4A:* Modification occurs only on the targeted gene whereas in mutagenesis several genes are modified and in crosses multiple genes are mixed. The new plant characteristic will be directly related to this modification, e.g., resistance to a disease;
- *Ease of Use/Efficiency - Table 5A:* It depends on the technology used and on the plant species: low effectiveness with ODM, much greater efficiency with SDN, especially those known under the abbreviation CRISPR;
- *Speed/cost - Table 6A:* Faster and cheaper than techniques based on crosses and mutagenic treatments;
- *Maturity - Table 7A:* Proof of concept has been shown for many crop species and many traits, (disease resistance, quality of a product consumed directly or used by industry, agronomic behaviour). Waxy and drought tolerant corn field trials have been conducted in the USA. A corn trial has been launched in Belgium (yield improvement). Several plants have been declared as not regulated (not subject to GMO regulation) in the United States and Canada, for example: herbicide-tolerant rapeseed developed by the company CIBUS, high-oleic soybean developed by Calyxt, Inc.

In view of the conclusions presented in the referral decision of the Conseil d'Etat and in the judgment of the CJEU mentioned in our letter, we wish to point out that in the SAM report:

- In no instance is there any mention of significant risks or dangers justifying the invocation of the precautionary principle (which is never mentioned in the Note);
- Nowhere in the Note did the SAM mention the existence of risks associated with NBTs that are detrimental to humans or the environment in comparison with traditional breeding technologies, including induced mutagenesis;
- Regarding unintended effects, in general, according to SAM the use of genomic editing techniques leads to a much smaller number or a complete absence of unintentional mutations compared to organisms (plants, animals, microorganisms) obtained by CBT, particularly in relation to induced mutagenesis. As indicated by SAM, unintended effects, if any, are eliminated by subsequent crosses. Such crossings are indeed performed regardless of the technology used;
- On the positive side of genome editing technologies, the SAM highlights the absence of exogenous DNA, the precision of modifications made to a pre-existing gene, the ease of use, the efficiency, the saving of time and cost reduction compared to sorting and screening required by CBTs.

As the Commission is well aware, EFSA and competent authorities of some Member States have issued opinions and recommendations on these plants. See in particular the reports below:

- United Kingdom - ACRE – Report dated June 2013
- Germany – BVL – Opinion dated 7 December 2015
- Europe – EFSA – letter to the Commission dated 15 October 2015, Scientific opinion on the Safety Assessment of Plants Using Zinc Finger Nuclease 3 and Other Site-Directed Nucleases with Similar Function, dated 18 October 2012, Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis, January 2012
- Swedish Board of Agriculture – November 2015
- France – Haut Conseil des Biotechnologies – January 2016

- Europe - EASAC – July 2015 and March 2017

As stated in our letter of 18 July we believe that the plants below should be subject to the specific procedure proposed here:

- Plants having undergone deletions of any size (such as obtained by SDN1);
- Plants that have undergone a single nucleotide pair substitution or an insertion of less than 20 base pairs (such as obtained by SDN2).

3. Cisgenic plants:
In these plants a native gene or a gene from a sexually compatible species has been inserted by a genetic engineering technique, for example transformation with Agrobacterium or by biolistics. The SAM has examined these types of plants and concluded, as did the EFSA Panel in January 2012, that these plants are similar to those obtained by conventional breeding techniques (page 78 of the Note).

Annex 2: Key aspects of what could be the validation process; designation of a competent authority

Described below are key aspects of a validation process for the plants described above, with the exception of null segregants descending from GM plants currently marketed in a country in the world. The Developer of a plant as described above would be required to file with an authority to be designated (see below) a request for determination of the regulatory status of this plant: i.e., whether excluded, exempted or included under EU GM regulations.

- *Content of the application*: The application file must contain information on what the developer plans to do, for example:
  - The name of the Developer and contact information. If the filing of the application is made by a country, the Developer will have to have a legal entity in the country of the application. If the application is made directly to the Commission, the Developer must have a legal entity in one of the EU countries;
  - The taxonomic description of the plant that will be altered;
  - The description of the genetic alteration envisaged in the final plant (insertion, deletion, substitution and the origin of this alteration);
  - In the case of genome editing, the technology used and the main steps envisaged, in particular production or not of an intermediate transgenic plant. In the case of negative segregants, the description of the GM plant and the modalities of elimination of the transgene. In the case of cisgenesis, the description of the gene that will be inserted;
  - The description of the expected phenotype;
  - The description of the analytical tests that will be carried out to characterize the final plant. For example: confirmation that the expected sequence has been produced, that there are no other modifications (off targets), that the effector, if inserted into the genome, has been eliminated;
  - The description of the activities that are intended to be carried out: confined activities only, deliberate release and/or commercialization
  - A proposal for the regulatory classification of the plant obtained.
- *Timing of request*: It can intervene at any period deemed appropriate by the Developer, probably early enough in the development of the plant and before any field testing.
- *Whom to apply*: In our opinion, this process requires the designation of an appropriate competent authority that can receive, process and decide on the response to the request. Since the status of the plant must be valid at the European level, it seems to us that this authority should be located at the European level. This authority could be the Commission or another dependent entity that has the capacity to manage such validation. For applications limited to research-only activities, the appropriate country-based competent authority should be able to process such applications, as is currently the case for field trial requests for GMOs.
- *Decision-making timeframe:* The authority should have the necessary resources to process such requests in a time period appropriate to the development of this type of product. A period of 90 days seems reasonable.
- *Expected response from the designated competent authority (or the Commission)*: confirmation or not of the developer's proposal for classification. In the event that an exclusion or exemption is confirmed, the plant can be developed according to the regulations in force for the development of a plant resulting from a conventional breeding technique. If the plant is subject to GMO regulations, its development and marketing must follow such regulations.