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RE: Proposed Exemptions: Movement of Organisms Modified or Produced through Genetic Engineering (APHIS-2023-0022-0001)

The American Seed Trade Association (ASTA) and the Biotechnology Innovation Organization (BIO) together represent the majority of the plant breeding industry operating in the United States. ASTA and BIO members support farmers of conventional, biotech, and organic food products and farm commodities in the United States and around the world.

Established in 1883, ASTA has more than 130 years of history representing a range of entities involved in seed production and distribution, plant breeding, and related industries in North America. ASTA membership consists of nearly 700 members, many of which research, develop, produce, and distribute all varieties of seeds – including grasses, forage, flowers, vegetables, row crops, and cereals.

BIO is the world’s largest biotechnology trade association representing roughly 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 nations. BIO members are involved in the research and development of innovative agricultural, industrial, healthcare and environmental biotechnology products.

ASTA and BIO welcome the USDA APHIS proposal of additional genetic modifications a plant can contain to qualify for regulatory exemption under 7 C.F.R. §340. In order for the broad range of plant breeders to leverage plant breeding innovation, such as genome editing, to develop improved varieties, USDA APHIS must follow through on the May 2020 final rule¹. Specifically, in the preamble of the final rule, USDA APHIS acknowledged the limitations of the final scope of exemptions and the necessity for future improvements. The final rule noted that -

“APHIS realizes that in some species, a single targeted modification is often less than what could otherwise be developed through conventional breeding”, and

¹ <https://www.govinfo.gov/content/pkg/FR-2020-05-18/html/2020-10638.htm>

“APHIS anticipates scientific information and/or experience may, over time, allow APHIS to list additional modifications that plants can contain and still be exempted from the regulations so that the regulatory system stays up to date and keeps pace with advances in scientific knowledge, evidence, and experience.”

The proposal to add five additional types of genetic modifications proposed by USDA APHIS represent a positive step in acknowledging the extent of genetic variation occurring in nature and through conventional breeding and have the potential to provide regulatory consistency for limited multiplexing of modifications and certain modifications in polyploid plants. Prompt finalization of the proposal could both have some immediate positive impact on the development pipeline of improved plant varieties, and help alleviate, without impacting plant pest risk, the resource constraints limiting APHIS’ ability to meet its current regulatory timelines as defined in 7 C.F.R. §340.

ASTA and BIO believe that clear and unambiguous exemptions will support the development of innovative plant products and facilitate compliance by the regulated community and more predictable implementation of the part 340 regulations by APHIS regulators. Contrary to USDA APHIS’ stated expectation for the additionally proposed exemptions to decrease Regulatory Status Review (RSR) requests by 10-15%², we are concerned that the increased complexity in the currently proposed exemptions may push developers to continue to rely on the RSR process for regulatory certainty. This would defeat two of the key goals of the revised §340 regulation: 1) to exempt from premarket review modifications that could otherwise be achieved through conventional breeding methods; and 2) to provide regulatory relief. A lack of clarity in the exemptions will not alleviate resource demands on developers or regulators.

In general, we find the differentiation between exemptions allowed for autopolyploids and allopolyploids to be unnecessary, especially considering the distinction between auto- and allopolyploids is not always straightforward³, and creates undue complexity without added regulatory benefits. There is not a science-based justification for treating modifications in these plant types differently from a plant pest risk perspective. APHIS regulatory exemptions must be grounded in science, and when possible, APHIS’ regulatory exemptions should be consistent with global regulatory approaches to harmonize U.S. policy with other expert regulatory agencies around the world. The currently proposed differentiation between autopolyploids and allopolyploids makes APHIS policy an outlier. Regulatory agencies around the world do not consider ploidy as a criterion to determine whether a modified plant is exempted from biotech regulations. At minimum, APHIS’ approach to ploidy should be consistent with other regulatory agencies under the Coordinated Framework (CF).

² [USDA APHIS | 2023 BRS Stakeholder Meeting](#)

³ Amadeu et al., 2020 - [Estimation of Molecular Pairwise Relatedness in Autopolyploid Crops - PubMed \(nih.gov\)](#)

Documentation of genetic modifications underlying observable phenotypes are inherently limited. Plant breeding utilizes potential genetic variability that is not limited to specific static changes and includes the process of deliberate combination of desirable characteristics. For any plant variety, the plant breeding process has been applied for hundreds of years, before the tools were developed to decipher the genetic modification(s) conferring the characteristics under selection. In many cases, because these selected characteristics are now standard for elite commercial varieties, there is no incentive or resources to characterize the genetic basis of standard characteristics. Therefore, while we understand APHIS' stringent alignment to formulate the proposed exemptions on what *has been* achieved in plant breeding through published scientific literature, such an approach is not in line with the revised part 340's stated objective that USDA APHIS exempt modifications that *could* otherwise be achieved through conventional breeding methods.

Instead of basing decisions for additional exemptions strictly on what has been published in scientific literature, we suggest APHIS take a more pragmatic approach to exemptions by basing them on scientific knowledge and experience to provide a more streamlined, plain language set of exemption criteria, consistent with the approach taken in several other global jurisdictions. This is also consistent with 7 C.F.R. §340.1(b)(4) which states "*The Administrator may propose to exempt plants with additional modifications, based on what could be achieved through conventional plant breeding.*"

For example, APHIS does not take into consideration the true nature of genetic recombination. Recombination is not based on autopolyploidy or allopolyploidy but based on homology. Homologous sequences, whether on homologous, heterologous, or homoeologous chromosomes can result in genetic recombination involving edits, deletions, and inversions. By basing exemptions only on examples of existing modifications in specific scientific literature, APHIS disregards the history of plant genetics and conventional breeding methods that have resulted in the diversity of crops we grow today. This diversity provides value to growers and consumers alike. It is in the spirit of plain-language policy that we provide the following comments.

- AM1: We support an exemption category based on functional outcome, loss of function, rather than specifying each and every genetic modification that can lead to loss of function. We suggest the exemption language to clarify that loss-of-function and gain-of-function mutations refer to a loss or change in the gene function and not to reduced or increased expression, respectively. We further suggest the exemption language be simplified to read, "any plant that contains any combination of loss-of-function modification(s) in one or all alleles of a single genetic locus, on one or more chromosomes, without the insertion of foreign DNA in the final plant." We recommend APHIS clarify the use of "exogenous DNA" in this section of the

proposal to mean foreign DNA (sequence outside of a plant’s gene pool) that is retained in the final plant. Loss of function modifications can be caused by indels (small insertions or deletions) or even larger insertions and deletions of genomic (i.e., endogenous) DNA at the repair site. We believe USDA did not intend that genomic DNA sequences that may be inserted during the DNA repair process should be considered “exogenous DNA.”

In the proposal, APHIS recognizes that newer techniques may be developed that can introduce loss of function mutations, noting that “Both base-editing and prime-editing can be used to make modifications that conform to the spirit of the modifications codified in §340.1(b)(1) that are exempt from regulation...” We ask APHIS to reaffirm that the focus of the exemption is on the outcome, loss-of-function, rather than any specific techniques used; and that the use of the terms “base-editing” and “prime-editing” does not exclude other targeted mutagenesis techniques, including those that employ templated repair, that can also be used to make modifications that “conform to the spirit of the modifications codified in 7 C.F.R. §340.1(b)(1) that are exempt from regulation.”

- AM2: We suggest simplifying the language to read “a single contiguous deletion of any size resulting from cellular repair of targeted DNA break(s) at one genetic location on one or more chromosomes, without the insertion of foreign DNA, would qualify for exemption.” To minimize unnecessary complexity, we believe the exemption should apply regardless of the nature of ploidy.
- AM3: Consistent with our recommendations for AM1 and AM2, we suggest simplifying the language in AM3 to read “The modifications described in the exemptions found at §340.1(b)(2) and (3) are extended to all alleles of a genetic locus on one or more chromosomes.”
- AM4: While we find limiting the exemption to a maximum of four modifications to be unnecessarily conservative as compared to the number of modifications that a plant can accumulate through conventional breeding, we welcome an exemption category to allow for combining multiple modifications. Exempting plants produced using multiplexing is vital as accumulation of multiple desirable characteristics into elite commercial varieties is the essence of plant breeding. Growers need yield gains, pest resistance, and agronomic characteristics all in one plant.

We recall ASTA comments to the 2021 proposed notice of additional exemption.⁴ Specifically, the ASTA comments requested that USDA APHIS delete from the guidance for Preparing Proposals to Exempt Plants with Additional Modifications from

⁴ FRN 2021-15236 <https://www.regulations.gov/document/APHIS-2020-0072-0001>

Regulation Pursuant to 7 C.F.R.§340, footnote #1 that reads, “evidence that multiple desired traits or genetic modifications can be introduced in a plant in a single step on a practical basis is needed to meet this standard.” We emphasize that plant breeding is an iterative process, involving selectively and intentionally accumulating genetic changes through multiple generations to achieve desired phenotypic outcomes. This science-based process has successfully delivered safe and effective products that do not pose plant pest risks into the marketplace for decades. Multiplexing of genetic modifications may also be necessary to achieve one desired characteristic, for example with recessive traits; more often multiplexing is used to combine a number of valuable characteristics, of which some may be dominant traits, while others may be recessive traits. Setting the standard at “evidence of introduction in a single step” negates the impact of plant breeding innovation, such as genome editing, to streamline plant breeding processes. We therefore find the inclusion of multiplexing in this exemption consistent with what breeders have done for decades and is consistent with conventional breeding.

- AM5: This exemption reflects the basic practice of modern plant breeding as specified in the bullet above, iterative improvements by adding new desirable characteristics. We believe that this exemption category is intended to include all modified plants that are not subject to regulation under 7 C.F.R.§340, including those that have completed regulatory status review and found to be not regulated, as well as those exempted plants for which a developer chooses to not progress through the USDA’s voluntary confirmation process. As such, we suggest rewording so the exemption reads, “plants not subject to 7 C.F.R.§340 regulation could be further modified in accordance with the exemptions.” Further, we recognize that APHIS wishes to restrict hypothetical, successively modified plants from this exemption category, we think that APHIS can address this restriction in APHIS guidance regarding the confirmation process consistent with the language used in the current proposal, “Plants that are merely hypothetical in nature would not be eligible for subsequent hypothetical modifications because they have not yet been produced, grown, and observed consistent with conventional breeding methods for the appropriate plant species.”
- With regards to AM4 and AM5, we note that the exemptions are applicable to polyploid plants, and to multiple heterozygous modifications. We request confirmation that the heterozygosity refers to genomic rather than allelic heterozygosity.

In closing, we wish to recall the scientifically supported principles outlined in the May 2020 Final Rule on which the exemptions under §340.1(b) are promulgated:

1. Plants created through conventional breeding have a history of safe use related to plant pest risk;
2. The types of plants that qualify for these exemptions can also be created through conventional breeding; and
3. There is no evidence that use of recombinant deoxyribonucleic acid (DNA) or genome editing techniques necessarily and in and of itself introduces plant pest risk, irrespective of the technique employed.

It is important that APHIS gives serious consideration to future improvements to the exemption categories to avoid ever increasing complexity.

In the meantime, the viability of developers, especially startups, small and medium sized companies, and public entities working with polyploid plant species and in multiplexing, depends on immediate regulatory relief. Therefore, ASTA and BIO support and request the timely finalization of these new exemptions.

Sincerely,



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