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December 8, 2020

Deputy Director Anne Overstreet
Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
Environmental Protection Agency

Re: Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived From Newer Technologies
Docket Number: EPA-HQ-OPP-2019-0508
Federal Register Publication Date: 10/09/2020

Dear Deputy Director Overstreet,

The American Society of Agronomy (ASA), Crop Science Society of America (CSSA), and Soil Science Society of America (SSSA) represent more than 8,000 scientists in academia, industry, and government, 12,500 Certified Crop Advisers (CCA), and 781 Certified Professional Soil Scientists (CPSS). We are the largest coalition of professionals dedicated to the agronomic, crop and soil science disciplines in the United States, and we thank you for the opportunity to comment on this proposed rule.

Our members and certified professionals are committed to meeting the demands of a growing world population through the pursuit of agronomic, crop, and soil science and are supportive of judicious, risk-based regulations for genetically engineered crops based on science. We congratulate EPA on this proposed rule, which aims to democratize the application of gene-editing technologies by lowering the regulatory burden for low-risk applications. We are excited by the opportunities gene editing will provide in crops for pest and pathogen resistance, among other ways to mitigate the devastating effects of climate change.

EPA regulations that target gene-edited crops, irrespective of risk, have been a significant deterrent for their use, especially in the academic sector. This has led to fewer genetic advancements in specialty crops, fewer opportunities to improve the technology, and fewer occasions for teaching the next generation of scientists how to use it. We are pleased that EPA has proposed including certain plant-incorporated protectants created through gene-editing technologies in the exempted category of conventionally bred crops. This move will contribute to the goals outlined in the 2019 Executive Order on Modernizing the Regulatory Framework for Agricultural Biotechnology Products, such as reducing the burdens on smaller developers (including universities) and the developers of specialty crops. However, significant concerns remain regarding the many caveats EPA has connected to its exemption. These caveats will make it exceedingly difficult for the developers of specialty crops to qualify for exemptions, and, even if they do, EPA places regulatory burdens associated with the use of gene editing technology that do not apply to conventional breeding techniques.

Definition of conventional breeding

The Societies are delighted that EPA amended its definition of "sexually compatible" to be biologically sound and inclusive of vegetatively propagated crops like bananas and potatoes. Crop scientists consider this kind of propagation "conventional," a term that encompasses techniques that have been used by plant breeders for decades to produce safe food and feed varieties. We are concerned, however, about whether this proposed rule's definition of conventional breeding includes techniques like protoplast fusion, bridge crosses, and embryo rescue. These techniques were specifically included in EPA's definition of "conventional breeding" in its 1994 policy, as published in the Federal Register, but they were absent in this proposed rule.

Also concerning was the mention that EPA and USDA each define the term "conventional breeding" in "the context of its own regulations," implying a different definition. We hope the final rule specifies that these techniques listed above are, indeed, "conventional," and, in the spirit of the Coordinated Framework, we strongly suggest EPA simply use USDA's definition of conventional breeding. To avoid the need for future rule-making as breeding science continues to improve and develop, we also recommend that EPA include a method for adding techniques to be included in its exemption, as USDA has done.

Record-keeping and reporting requirements

All crops, including those conventionally bred, are subject to adverse effects reporting. Considering EPA acknowledges that the possibility of adverse effects from the PIPs proposed for exemption is highly unlikely, the normal process of reporting any adverse effects from gene-edited crops should be sufficient. It is inconsistent with the proposed intent of this rule, and with the Executive Order, for EPA to subject gene-edited crops to record-keeping and reporting requirements that are not asked of conventionally bred crops.

Breeding Technique	**Developers need to measure toxin levels in all tissues and developmental stages**	**Developers need to keep records for five years**
Conventional	No	No
Gene edited in a single variety, self-determined to be exempt	Yes	Yes
Gene edited in a single variety, requested confirmation of exemption	Yes	Yes
Gene edited in a variety of a crop that has already gone through a confirmation of exemption process	No	No

Table 1. Proposed record-keeping and reporting requirements. This table shows the scientific inconsistencies in EPA's proposed rule and demonstrates how specialty crops and smaller developers are disadvantaged.

As visualized in Table 1, above, there is no difference in the amount of data developers would need to compile whether they self-determine their exemption or if they request confirmation. This makes the self-determination option useless. Furthermore, a science and risk-based approach would include no difference in reporting or record-keeping requirements between conventional crops and those self-determined to be exempt. Lastly, exempting subsequent varieties of a crop from reporting and record-keeping requirements disadvantages small developers and the developers of specialty crops whose products are less likely to have already gone through the confirmatory process. This is at odds with

EPA's objective to democratize gene-editing technology by reducing the regulatory burdens on these developers.

Beyond advantaging commodity crop developers, the exemption for record-keeping and reporting of subsequent varieties makes no scientific sense. If the pesticidal substance itself were the only thing EPA is proposing to regulate, then, indeed, subsequent incorporations of this substance, once reviewed and approved the first time, would have no need for additional approvals. But this logic falls apart in the proposed rule, in which EPA supposes that the risk comes not only from the pesticidal substance but also how it is incorporated into the plant – the DNA modifications used. If EPA is concerned about a single DNA modification event, it makes sense to offer exemptions only to varieties derived through conventional breeding from previously approved, gene-edited varieties. And yet, EPA has acknowledged that there is little risk from crops with modifications that are virtually indistinguishable from ones that were conventionally bred. The logical conclusion would be to treat these crops the same, regardless of the method of their development.

Metabolite levels in tissues and developmental stages

Crop breeders routinely attempt to increase pest resistance through conventional practices, and it is known that levels of bioactive compounds, including those that increase pest and pathogen resistance, can vary widely based on environmental conditions.[1,2] However, breeders rarely monitor the expression levels of such compounds except in cases where it is known that such levels must be kept below a certain threshold. By requiring metabolite levels to be reported in every tissue and developmental stage of a gene-edited crop, EPA is wrongly focused on perceived ideas of theoretical natural boundaries, which are known to fluctuate, rather than on whether the metabolite accumulates to a level of toxicological concern. Metabolite level reporting and record-keeping should not be mandatory for gene-edited crops when the pesticidal substance is not regularly monitored for toxicity in conventionally bred varieties. This would be incredibly burdensome to small producers and not in the spirit of the 2019 Executive Order.

Another significant challenge with this requirement is that metabolite levels for all plants in all tissues and developmental stages are not known. There would need to be established, baseline metabolite levels for developers to use as comparisons, but such a metabolic database does not exist nor would be simple to create – environmental conditions can cause metabolite levels to vary widely, and there would need to be widespread agreement on how to define different plant tissues and developmental stages. Once again, implementation of this proposed rule would disproportionately burden the developers of specialty crops, who are less likely to have any kind of baseline metabolic information and for whom such information would likely be difficult to gather – imagine needing to test metabolite levels in all developmental stages of long-lived crops like fruit trees.

Inert ingredients

[1] Harrigan, G. G., Glenn, K. C., & Ridley, W. P. (2010). Assessing the natural variability in crop composition. Regulatory Toxicology and Pharmacology, 58(3), S13-S20.

[2] Davies, H. V., Shepherd, L. V., Stewart, D., Frank, T., Röhlig, R. M., & Engel, K. H. (2010). Metabolome variability in crop plant species–When, where, how much and so what?. Regulatory Toxicology and Pharmacology, 58(3), S54-S61.

Since the publication of its 1994 policy,[3] EPA has given exemptions from tolerance requirements to three categories of plant pesticides: plant pesticides commonly found in food, coat proteins from plant viruses, and nucleic acids. The nucleic acids, which is to say, the DNA used to create a pesticidal substance, were considered "inert ingredients." Since then, EPA has proposed to include certain nucleic acids as "active ingredients" and others "inert," but there is no regulation, historical precedent, or scientific basis to justify this distinction. The DNA itself is not a pesticidal substance.

Furthermore, there is no EPA regulation or precedent for limiting inert ingredients to only the most necessary to achieve a certain function. Crop breeders using gene-editing technology will still need to use marker genes, especially in the case of seedless varieties of specialty crops (e.g. bananas) or crops that do not breed true (e.g. apples), and there is no scientific reason to exclude marker genes from exemption.

Cases in which no pesticide is produced

EPA seems to assume that any genetic loss-of-function edit would create not only a pesticidal trait but a pesticidal substance. However, in a case in which a modification eliminates the protein a pathogen needs to access plant cells, there is no substance to regulate, only a change in DNA sequence. EPA has previously defined an "active ingredient" as "a pesticidal substance that is produced in a living plant and the genetic material necessary for the production of the substance, where the substance is intended for use in the living plant."[4] But if no "pesticidal substance" is produced, then the altered DNA should not be considered an "active ingredient." The proposed rule's requirements for reporting metabolite levels and five years of record-keeping are especially unreasonable in this case, where the genetic change in question is a deletion or loss of function.

Consistency with USDA's SECURE rule is another reason to exempt plants edited with a deletion, regardless of whether the DNA sequence matches a sequence found in a wild relative. The SECURE rule exempts deletions of any size, but a targeted deletion within a gene intended for loss-of-function, while acceptable for exemption under SECURE, would likely lead to a DNA sequence akin to a pseudogene. Plant genomes naturally contain hundreds of pseudogenes, many of which lead to the production of mRNA and then truncated or misfolded proteins that are promptly recycled, but this strategy for eliminating a functional protein would seemingly not qualify for EPA's exemption. Plants naturally contain hundreds or thousands of pseudogenes, and the creation of pseudogenes through mutagenesis, a conventional breeding practice, has never resulted in adverse effects.

In 1994, EPA determined that "genetic material that encodes for a pesticidal substance or leads to the production of a pesticidal substance" does not include regulatory regions or noncoding, nonexpressed nucleotide sequences, and this would certainly include DNA sequences created through CRISPR-mediated loss-of-function edits. The Societies would not encourage EPA to create a separate exemption category for loss-of-function edits, rather EPA should clarify that these products are already exempt under its prior policy.

EPA's 1994 policy also exempted from regulation plant-pesticides that "are not directly toxic to the target pest," which is to say, enhancements of plant defenses. Plants edited to have a thicker waxy cuticle or reduced stomata size, which may enable a plant to avoid pests, should not represent

[3] Environmental Protection Agency 40 CFR Part 2, et al. Public Information and Confidentiality Regulations; Proposed Rule, 59 Fed. Reg. 60,446-60,518 (November 23, 1994).
[4] Ibid

"pesticidal substances" and should also be exempt from record-keeping and reporting under this rule. This would be consistent with historic exemptions outlined in the 1994 policy, in which EPA exempted pesticidal substances that act "primarily by affecting the plant so that the target pest is inhibited from attaching to the plant, penetrating the plant, or invading the plant's tissue" as a "structural barrier," or that it "acts in the host plant to inactivate or resist toxins or other disease-causing substances produced by the target pest," or that it creates "a deficiency of a plant nutrient or chemical component essential for pest growth on/in the host plant."[5]

Native genes

EPA's proposed rule aims to define a group of genes that is acceptable for exemption based on what is already found in the plant's gene pool. This is consistent with the 1994 policy, which determined that EPA regulations were limited to pesticidal compounds "new" to the plant, such as Bt toxin, and it is a sound idea. But the definition EPA proposes for "native genes" in the proposed rule is not scientifically sound.

The proposed rule notes that "native genes" are those developed through the process of mutation, selection, and genetic exchange. But it should be noted that "genetic exchange" happens between many kinds of organisms and is not limited to those in a plant's gene pool. EPA's proposed definition of "native genes" is that they "have never been derived from a source that is not sexually compatible with the source plant." But this does not take into account the many genes that exist in all kinds of organisms that are derived through horizontal gene transfer from sources like bacteria, viruses, and fungi that are not sexually compatible with the plant.[6,7] We propose that instead of referring to "native genes" or "native alleles," EPA should specify that it will exempt genes or alleles that "were never introduced into a plant by recombinant DNA technology."

Thank you for the opportunity to provide comments on this proposed rule, which is important, necessary, and has the potential to democratize gene-editing technologies for the benefit of universities, small developers, and specialty crops. Please do not hesitate to contact the Societies' Science Policy Office with any further questions.

Sincerely,

Nick Goeser, CEO
American Society of Agronomy
Crop Science Society of America
Soil Science Society of America

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[5] Ibid

[6] Wang, Hongwei, et al. "Horizontal gene transfer of Fhb7 from fungus underlies Fusarium head blight resistance in wheat." Science 368.6493 (2020).

[7] Matveeva, T. V., & Otten, L. (2019). Widespread occurrence of natural genetic transformation of plants by Agrobacterium. *Plant Molecular Biology*, *101*(4-5), 415-437.