



December 8, 2020

OPP Docket
Environmental Protection Agency Docket Center (EPA/DC) (28221T)
1200 Pennsylvania Avenue NW
Washington, DC 20460-0001

Submitted Electronically via Federal eRulemaking Portal (<http://www.regulations.gov>)

Re: Docket ID No. EPA-HQ-OPP-2019-0508, FRL-10014-10. Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived from New Technologies

Dear Sir or Madam:

The Biotechnology Innovation Organization (BIO) submits these comments in response to the U.S. Environmental Protection Agency's (EPA) request for public input on proposed revisions to regulations related to the oversight of certain plant-incorporated protectants (PIPs).¹ In particular, EPA's proposed revisions would create an exemption from certain requirements of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) for PIPs based upon sexually compatible plants developed using biotechnology.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members operate at the intersection of biology and technology to cure patients, protect our climate, and nourish humanity. As BIO looks to the future, we seek to advance disruptive innovation by 1) being a voice of science and for science; 2) uniting and empowering biotech innovators and their ecosystem to improve lives; 3) removing barriers to innovation; 4) championing broad access to biotech breakthroughs and scientific equality; and 5) catalyzing resilient and sustainable biobased economies.

EPA's proposed revisions come at a unique and critical time for technology developers and society. Scientific breakthroughs in biology and genetics will be responsible for pulling society out of the COVID pandemic crisis and will build much needed resilience in food and manufacturing supply chains.

BIO has stated that innovation flourishes when science and consumer values are aligned and complement one another. The U.S. government's regulatory approach toward innovative products cannot exist in isolation. It should be supported by credible transparency measures. A proactive approach to transparency stands to build trust and foster an inclusive environment to address our most pressing societal, nutritional, and environmental concerns. BIO encourages the U.S. government to ensure its regulatory policies are durable and legally defensible, based on science and risk, and to

¹ 85 FR 64308-64344 (October 9, 2020).



articulate to the public its rationale for regulatory approaches. BIO and its members will prioritize an inclusive and impactful approach to transparency, as outlined on BIO's *Growing Trust in Innovation* website.²

BIO also notes that this year marks the 50th anniversary of the EPA. The Agency can take pride in its reliance on the best available science to meet its goal of protecting human health and the environment, and FIFRA is no exception. Beginning in 1995, EPA has registered a succession of innovative PIP products that have been widely adopted in the United States and around the world. Today is no exception. As we are about to enter the 35th anniversary year of the Coordinated Framework for Regulation of Biotechnology, EPA is once again poised to assume a leadership role in clearing the path for adoption of a new wave of sustainable biotechnology products. Crops developed with these PIPs will be of inestimable value in tackling the challenges presented by climate change, while safely increasing productivity and conserving biodiversity.

EPA's role in the oversight of products of agricultural biotechnology is to regulate pesticidal substances produced in living plants. These substances, referred to as plant-incorporated protectants or PIPs, are typically substances that target a narrow range of crop pests. Historically, most PIP-containing plants produced using biotechnology have been the so-called "Bt" crops, which produce a protein derived from a common soil bacterium, *Bacillus thuringiensis*, to control certain insect pests that feed on the plant. As with conventional chemical pesticides, EPA regulates PIPs under FIFRA.³ Additionally, as with conventional pesticide residues, EPA also regulates PIP residues in food or feed crops under Section 408 of the FFDCA.⁴ EPA regulations defining regulatory requirements, criteria, and procedures for PIPs under FIFRA and FFDCA are codified in 40 CFR Part 174.

Plants naturally produce a wide range of substances that help fend off pests and diseases. While many of these substances are also "plant incorporated protectants," EPA exempts these kinds of naturally occurring PIPs from most requirements of its PIP regulations, allowing plant breeders to utilize these natural mechanisms to develop plant varieties more resistant to pests and diseases without the need for EPA registration. New gene editing tools now enable developers to create precise genetic alterations similar or identical to the kinds of changes that could be created via conventional breeding or found in nature. Acknowledging this, EPA is proposing to extend the PIP exemptions to also exempt from registration requirements certain alterations developed through the use of biotechnology, so long as the original substance is not altered, and its expression levels do not exceed what could be achieved via conventional plant breeding or found in nature.

BIO is broadly supportive of the objectives of the proposed revisions to EPA regulations and the intent to expand the existing exemptions to include similar products developed using newer more precise methods to introduce genetic variation in plants. We believe that the rationale behind the proposal is well-justified scientifically, will not result in any novel risks to the environment or to human health, and has the potential to facilitate the development of innovative applications of cutting-edge genetic tools in a wide variety of crops and economically important plant species.

² <https://www.bio.org/growing-trust-innovation>

³ 7 U.S.C. 136 *et seq.*

⁴ 21 U.S.C. 321 *et seq.*



We are concerned, however, that requirements of the proposed rule are needlessly prescriptive and may make it exceedingly difficult to demonstrate eligibility for the proposed exemptions, which will significantly limit their utility. In particular, the stipulation that exempt substances be *identical* to natural substances, in combination with the high hurdle to demonstrate expression levels across a panoply of tissues, developmental stages, and genotypes, will make it very challenging to meet the proposed exemption, effectively narrowing the exemption significantly. Despite EPA's acknowledgement that these naturally occurring substances have a long history of safety and that breeding is unlikely to lead to novel hazards or exposures, we believe that EPA's proposal still holds PIPs produced via biotechnology to a much different standard than the same substances produced via plant breeding. This approach of holding the same or similar products to two significantly different standards merely due to the method by which they were produced is scientifically unjustified and inconsistent with principles of effective regulation laid out in the Coordinated Framework.⁵ We would also encourage EPA to ensure that its proposed exemptions are, to the greatest extent possible, consistent with similar exemptions recently adopted by USDA.⁶

BIO provides below detailed analysis and commentary on EPA's proposed revisions, organized into five sections: 1) EPA's authority to regulate PIPs; 2) the proposed exemptions; 3) exemption eligibility determination procedures; 4) cost-benefit analysis; and 5) BIO responses to the five specific questions posed by EPA.

I. EPA AUTHORITY TO REGULATE PIPs

EPA regulations in 40 CFR Part 174 define a *plant incorporated protectant* (PIP) to be:

"a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance. It also includes any inert ingredient contained in the plant or the produce thereof" (40 CFR 174.3).

A *pesticidal substance* is further defined as:

"a substance that is intended to be produced and used in a living plant, or in the produce thereof, for a pesticidal purpose, during any part of a plant's life cycle (e.g., in the embryo, seed, seedling, mature plant)" (40 CFR 174.3).

In short, a PIP must be 1) a substance produced in a living plant, and 2) the substance must be produced for a pesticidal purpose. The regulations in 40 CFR Part 174 do not define the term *pesticidal purpose*, but the concept is presumed to derive from the FIFRA definition of a *pesticide*:

"(1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and (3) any nitrogen stabilizer" (7 USC §136(u)).

⁵ 51 FR 23302-23351 (June 26, 1986).

⁶ 85 FR 29790-29838 (May 18, 2020).



A significant shortcoming of the current regulations in 40 CFR Part 174 is that they are ambiguous about the kinds of substances resulting from genetic modification in plants that would be considered by the agency to be PIPs subject to 40 CFR Part 174; the proposed revisions do little to address this issue. The ability to create genetic variations in plants is becoming increasingly sophisticated and may result in traits which are unclear whether they would be considered PIPs under the current regulations. Example traits which could have direct or indirect effects on plant pests or susceptibility to pests include: altered cuticle thickness or composition; altered timing of growth or flowering; modified leaf shape or plant architecture; resistance to a disease or avoidance of pest conferred by *absence* of a substance produced; etc. While these kinds of genetic modifications and resulting traits bear some connection to “preventing, destroying, repelling, or mitigating” pests, it is less clear what “substance” would be considered a pesticide. Examples like these seem to fall well beyond the statutory definition of “pesticide” and would represent an implausible stretch of FIFRA authority beyond its original intent to regulate the safety of toxic chemical substances in the environment.

The FIFRA definition of a pesticide also includes *plant regulators*. The term “plant regulator” means “any substance or mixture of substances intended, through physiological action, for accelerating or retarding the rate of growth or rate of maturation, or for otherwise altering the behavior of plants or the product thereof” (40 CFR 174.3). Despite EPA’s authority to oversee the safety of substances applied to plants intended to regulate their growth through physiological action, stretching the concept of “plant regulators” into the context of genetic alterations in plants would create an incredibly broad scope of regulation disproportionate to actual risk. Genetic modification is often aimed at changes to a plant’s characteristics that may in some way relate to its altering growth, development, or behavior, despite the absence of any of the kinds of toxic chemical substances originally intended to be overseen by FIFRA. BIO strongly opposes the extension of FIFRA to oversight of *genetic* changes that alter the plant’s growth, development, or other physiological characteristics.⁷

BIO requests that EPA provide clarification consistent with the foregoing, via rulemaking or guidance, on the kinds of substances produced by genetic modification that would *not* result in a PIP, and therefore *not* subject to 40 CFR Part 174. We recommend that EPA clarify in the rule that the scope of regulation of PIPs under 40 CFR Part 174 is limited to *pesticidal substances intended to prevent, destroy, repel, or mitigate a pest through a specific toxic mode of action that acts directly on a pest*. We believe that such a clarification is particularly important in the context of the present rulemaking because it will help to draw a distinction between 1) substances which are considered PIPs but are exempt from certain FIFRA requirements in 40 CFR Part 174, versus 2) substances which are not considered PIPs in the first place, and therefore not subject to 40 CFR Part 174 or FIFRA more generally.

Inert Ingredients

EPA regulations in 40 CFR 174.3 define an *inert ingredient* to be:

“any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the

⁷ We also note that the term “plant-incorporated protectant” includes the word “protectant,” which suggests that the scope of 40 CFR Part 174 is limited to substances *protecting the plant (i.e. against a pest)*, and not “plant-incorporated plant regulators.”



genetic material necessary for the production of the substance, provided that genetic material is intentionally introduced into a living plant in addition to the active ingredient" (40 CFR 174.3).

We agree with EPA that many, if not most, uses of newer genome editing tools would not result in the insertion of coding sequences that lead to the production of any substance unrelated to the production of the "active ingredient." We can envision some scenarios, however, where this may not be the case. For example, the insertion of a cisgene that is identical to a native gene and presumed to meet the criteria for exemption, might be accompanied by a selectable marker gene to confirm the presence of the cisgene. We request that EPA clarify how it would handle such a case, and suggest that EPA consider revising the regulations to allow the exemption of native active ingredients when accompanied by inert ingredients such as selectable markers *if the inert ingredients have already been granted a tolerance exemption*. In such a scenario, there is no plausible justification why the inert ingredient would pose any incremental risk above that posed by the native active ingredient which would have otherwise been exempted.

Under the current regulations, "noncoding, nonexpressed nucleotide sequences" are not considered to be part of the genetic material necessary for the production of the active or inert ingredients. Such sequences include:

"noncoding, nonexpressed nucleotide sequences include, but are not limited to, linkers, adapters, homopolymers, and sequences of restriction enzyme recognition sites" (40 CFR 174.3).

Because it is possible that in some circumstances the use of gene editing tools may result in the insertion of noncoding, nonexpressed nucleotide sequences (e.g. border sequences), we ask that EPA confirm our understanding that such sequences do not affect the exemption status of a particular PIP, even if those noncoding, nonexpressed sequences are not found in a plant that is sexually compatible with the recipient plant.

EPA states in the notice it intended to "expand the scope of the existing inert ingredient exemption at 40 CFR 174.705 to include inert ingredients that are intermediary substances initiated through biotechnology so long as they still meet the existing criteria." We note, however, that no specific regulatory revisions were proposed to this part.

(See also BIO response to **EPA Question A**, below).

Loss of Function

EPA proposes that the new exemption would be extended to cases in which a genetic modification leads to the *elimination* of a substance produced by the gene. The example referenced by EPA is the removal of a receptor protein in the plant which confers resistance to a disease. As cited above, a plant incorporated protectant is defined as "a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for the production of such a pesticidal substance" (40 CFR 172). To justify oversight of genetic modifications that result in the *absence* of a substance, EPA proposes to interpret such a genetic modification to be simultaneously both the 1) *substance* and 2) *the genetic material necessary for the production of the substance*.



We strongly disagree with this interpretation and do not believe it is consistent with FIFRA or the regulatory definition of a PIP. FIFRA grants EPA no authority to regulate the *absence of a substance* as a pesticide, even if the absence of the substance is intended to prevent, destroy, repel, or mitigate a pest. In the case of loss of function resulting in elimination of a substance, no substance is “produced and used.” The same logic should apply to loss-of-function resulting from alteration of the substance (e.g. truncated proteins) such that it no longer has pesticidal properties. Once a substance has been altered in such a way as to no longer function, it is no longer a pesticidal substance. Moreover, regulating the genetic material alone as the “substance” likewise is not supported by FIFRA as the genetic material alone is not “necessary for the production of the [pesticidal] substance”, as there is no pesticidal substance being produced. Therefore, we request that EPA clarify, either in regulation or guidance, that genetic changes resulting in the absence or loss-of-function of a substance are not merely exempt from certain registration requirements; rather, they are not PIPs in the first place.

We can envision some scenarios, however, in which the loss-of-function of one gene results in intentionally altered levels of pesticidal substances produced by other genes (e.g. deletion of a repressor protein could lead to intentional increases in secondary metabolites). Unlike “knockouts” where the absence of a substance directly results in a pesticidal effect, these more indirect scenarios may be consistent with EPA authority so long as the secondary substances whose levels are intentionally altered still meet the definition of a pesticidal substance.

The proposed loss-of-function exemption also includes “reduction” of the substance encoded by a gene. This exemption seems to be redundant, as it is adequately addressed by the proposed exemption for differential expression of native genes (proposed 40 CFR 174.26(a)(2)(i)).

(See also BIO response to **EPA Question E**, below).

II. PROPOSED EXEMPTIONS

EPA proposes to exempt from certain regulatory requirements a category of PIPs created using biotechnology that could have otherwise been created through conventional plant breeding, so long as: 1) the pesticidal substance is identical to a substance in a sexually compatible source plant; and 2) the pesticidal substance is not expressed at levels higher than those known to occur in sexually compatible relatives. This approach represents a logical extension of EPA’s longstanding exemption of naturally occurring PIPs in conventionally bred plants. New gene editing tools enable developers to create precise genetic alterations resulting in the production of substances that are the same or similar to the outcomes of conventional breeding or spontaneous mutations, and therefore are unlikely to create novel risks. We agree that it is reasonable to conclude that expanded exemptions for precise genetic alterations that are similar or identical to the kinds of changes that can be created via conventional breeding are unlikely to cause unreasonable adverse effects to the environment and provides a reasonable certainty of no harm in foods derived from crops containing the PIPs.

EPA introduces the terms “native allele” and “native gene” to identify the starting point for the basis of the new exemption. While we agree that the terminology is sufficiently clear to capture EPA’s intent, i.e. *genetic sequences known to exist* within a plant’s own gene pool (and not derived via transgenic means), we request two clarifications. First, it is our understanding that EPA intends “native” sequences to include genetic changes resulting from mutagenesis, both spontaneous and induced



(i.e. chemical or radiation). We request that make this clear in the definition of “native gene.” Secondly, as EPA acknowledges, plants are known to include many sequences derived from sources not sexually compatible with the plant via horizontal gene transfer over geological timeframes. We understand that EPA does not intend to exclude these types of genetic sequences from the definition of “native gene,” but a clearer confirmation may be helpful. (See also BIO response to **EPA Question D**, below).

We encourage EPA to adopt definitions of *conventional breeding*, *sexually compatible*, and related terms that are consistent with similar terminology adopted in USDA’s biotechnology regulations (7 CFR Part 340). For example, EPA proposes *sexually compatible* to mean that “a viable zygote can be formed only through the union of two gametes through conventional breeding” and that a *native allele* means “a variant of a native gene that is identified in the genetic diversity of plants sexually compatible with the recipient plant.” In comparison, USDA defines *gene pool* to be “germplasm within which sexual recombination is possible as a result of hybridization, including via methods such as embryo culture or bridging crosses.” It is unclear whether these definitions reflect the same scope and meaning of the concept of sexual compatibility. We would also encourage EPA to revise its definition of *conventional breeding* to clarify that it includes the use of spontaneous and induced mutagenesis, consistent with USDA’s position and with what we believe to be EPA’s intent.

EPA’s proposed exemption would apply to either 1) insertion of a native gene in a non-genic region, or 2) modification of an existing native gene. In both cases, the proposed rule states that the resulting pesticidal substance must be identical to that encoded by the native allele and may not be expressed at higher levels, in different tissues, or at different development stages than the native allele. Our reading of the proposed exemptions suggests that exemption eligibility would extend to *any* genetic modifications at the DNA level made to a native allele (including non-coding and coding sequence), so long as the modification meets the two criteria for substance identity and expression levels/patterns. In other words, there is no prerequisite that the genetic *modification* must exist in a known native allele in a sexually compatible relative. Rather, the native allele is the starting point on which modifications can be made, and the exemption is based upon whether the modification meets the two defined criteria. We ask that EPA confirm that our understanding of the proposed rule in this regard is correct. This is an important distinction because it allows developers much greater flexibility in designing genetic sequences to express the desired trait.

A key criterion of the exemption is that the expressed pesticidal substance must be *identical* to the substance encoded by the native allele. We assume that this means that for proteins, the pesticidal substance must be identical at the amino acid level (i.e. not necessarily at the nucleotide level), and that the information needed to confirm identity for proteinaceous substances would be the amino acid sequence deduced from the nucleotide sequence. We would additionally request that EPA incorporate additional language to provide flexibility in how it interprets the “identical” criterion, allowing a developer to demonstrate “functional identity” or functional equivalence of a pesticidal substance compared to the native substance (for example, allowing minor changes in amino acid sequences in non-functional parts of a protein). This flexibility will also be important to consideration of non-proteinaceous pesticidal substances, like RNAi, where the ability to make minor changes to the native allele is important for their development. We appreciate, however, that in some instances this might require the developer to provide additional evidence or rationale to confirm functional equivalence or lack of incremental hazard.



The second major criterion for exemption eligibility is that the substance may not be expressed at higher levels, in different tissues, or at different development stages than at the level, in the tissue, or at the stage produced by the native allele. We are concerned that this particular aspect of the proposed rule will be central in determining the utility of the rule and how broad or narrow the exemptions will be in practice. For many, if not most, naturally occurring PIPs little is known about their specific expression patterns in various tissues and developmental phases, across the broad diversity of a plant's gene pool and the full range of environments a plant may reasonably be exposed to. This is particularly true for lesser-researched species (e.g. fruits and vegetables, trees, grasses), where there may be a greater dependence on genetic bases of pest resistance and simultaneously less availability of population-wide detailed genetic expression data.

We propose that EPA allow flexibility in how a developer may support a conclusion that expression levels are unlikely to lead to novel hazards. In conventional breeding contexts, often little is known about the expression levels of naturally occurring substances, and yet they are exempt from most FIFRA registration requirements and establishment of FFDCA tolerance levels in foods. Because these substances are not generally known to create safety hazards and are presumed not to be injurious to human health and the environment, considerable uncertainty about the natural range of the levels of such substances in plants and in foods derived from them is acceptable. Plant breeders have a long history of developing safe products and routinely screen for the presence of naturally occurring toxins.⁸ Confidence in the safety of potential exposure levels in conventional breeding is underscored by the fact that the agency only requires breeders to notify the agency when levels of these kinds of substances are found to be unsafe.

There is no scientific justification to suggest that genetic alterations replicating native alleles are any more likely to result in expression patterns significantly outside the range that could be attained by conventional breeding, such that these products should be held to two entirely different safety standards. Notification to EPA in the unlikely instance when exposure levels are found to be unsafe should be sufficient for both conventionally bred and biotechnology-derived plants. Accordingly, the proposed exemption should be revised to allow flexibility in expression patterns and levels of substances known to be safe and widely present in the environment and human diet. We suggest that the kind of population-wide, tissue- and developmental-stage analysis of expression levels proposed by EPA may only be justifiable in instances when a native allele has been altered with the specific purpose and intent of increasing expression levels significantly and there is a hypothesis-driven basis to conclude there may be an unreasonable adverse effect to humans or the environment.

We would also strongly encourage the agency to consider refining its exemptions to be more consistent with similar exemptions recently adopted by USDA.⁹ While we appreciate that USDA and EPA have distinct missions and authorities, both agencies have developed exemptions based upon a similar logic: there is a substantial scientific basis for exempting certain biotechnology-derived plants from certain regulatory requirements due to their similarity conventionally bred plants, which have a long history of safety. Yet USDA's new exemptions are built upon a more expansive view of the kinds of genetic variation that can exist in nature which EPA's proposed exemptions appear unable to accommodate for no particular safety-related reason. Some examples exempt under USDA's regulations but not EPA's proposal include: deletions of any size, protein truncations, alterations from

⁸ <https://www.sciencedirect.com/science/article/pii/S0924224419310817>

⁹ 85 FR 29790-29838 (May 18, 2020).



non-templated sequence insertions, minor templated changes to nucleotide sequence, etc. To the greatest extent possible, EPA should build exemptions broadly comparable to those adopted by USDA unless there is a clear safety-related justification unique to EPA's mission.

In the discussion related to meeting FFDCa tolerance exemption requirements, EPA appears to identify additional criteria above and beyond the criteria that expression levels do not exceed the naturally occurring range: "levels may not be injurious or deleterious to human health." It is unclear what additional information may be required to meet this criterion, and whether it would trigger a need to request a tolerance exemption, independent of meeting the other criteria articulated in the proposed rule. Moreover, EPA has not provided a reasoned basis to support why changes developed using biotechnology must meet a different standard than plants that could be accomplished via conventional breeding. We would argue that the criteria related to expression levels, properly defined in context of what could be obtained via conventional breeding, should be sufficient to ensure exposures are not injurious or deleterious to human health, without the need to independently demonstrate human health safety of those levels.¹⁰ EPA should clarify in the rule that there is no need to apply for a separate tolerance exemption.

Finally, we encourage EPA to consider adding to the regulations a mechanism by which EPA may add new categories of exemptions for low-risk PIPs, either of their own initiative or in response to public petition. This will help EPA to future-proof their regulations and increase the agency's ability to adapt and respond to changes in science and continued innovation. USDA adopted a similar mechanism in its recent revisions to 7 CFR Part 340, and we would encourage EPA to consider doing the same.

III. EXEMPTION ELIGIBILITY DETERMINATION PROCEDURES

EPA proposes two new mechanisms to determine whether a PIP is eligible for exemption. In one option, the developer may submit a short "self-determination" letter to EPA, and the exemption becomes effective when EPA confirms receipt of the letter. In the second option, the developer may submit more detailed information to EPA and request that the agency confirm that the PIP meets the exemption. Requests for confirmation would be submitted using the M009 PRIA category and associated fees, and the agency would provide a formal determination response within 120 days. Developers would be free to use one or both mechanisms.

In general, BIO supports in principle the two proposed procedures for determination of exemption eligibility (but see discussion above about information requirements). We appreciate the flexibility provided by being able to choose among two mechanisms. We believe that many developers may elect to use the self-determination process for PIPs early in development, and then later submit a more formal eligibility confirmation request as a PIP product moves closer to commercialization. BIO believes that, at a minimum, notifying EPA of exemption self-determinations will provide more confidence in EPA oversight of PIP products and give the agency visibility into the kinds of exempt PIPs in development. (See also BIO response to **EPA Question C**, below).

The proposed rule is ambiguous regarding the timing of when a developer would be required to follow the new exemption eligibility determination procedures. EPA states that a self-determination letter

¹⁰ We also note that in some instances the pesticidal substance may not be present in food.



must be submitted “prior to engaging in activities subject to FIFRA.” The large variety of different activities subject to FIFRA (e.g. experimental use in contained facilities, outdoor field tests, importation, distribution, sale) makes it unclear at what point in the development of a new PIP the procedural requirements would be triggered. We assume that the “10 acre rule” threshold for experimental use permits would also be the trigger to require developers follow the exemption eligibility procedures, but we request confirmation from the agency that this will be the case. We believe this threshold would be consistent with EPA’s interest in completion of the new processes “prior to a PIP being brought to the market.” This would also prevent developers from having to notify the agency of every potentially-exempt PIP in its earliest stages of research and development, and help focus EPA’s review on those PIPs more likely to be proceeding into commercial-scale activities subject to FIFRA.

The proposed rule does not address whether the results of EPA eligibility determinations would be made public (e.g. by posting on the Agency’s website). BIO supports publication of EPA’s exemption confirmations in response to confirmation requests from developers, subject to normal protections for confidential business information. We believe that this provides important transparency to stakeholders and the public about new PIP products potentially entering commerce. In contrast, we suggest that self-determination letters and EPA acknowledgement of receipt *not* be published, because they are likely to represent products much earlier in development, contain less information, are more likely to include sensitive business information, and thus shed less light on products likely to be entering commerce.

We would also encourage EPA to include language in self-determination response letters and exemption confirmations to help non-technical audiences understand what the exemption means and why it applies, and to promote confidence in the safety of products meeting the exemption. We believe this will be a critically important aid in communications with the public and stakeholders, markets, trading partners, and other governments. We encourage EPA to coordinate with USDA, so that EPA language related to exemptions is similar to and compatible with USDA language associated with their new analogous exemption process under 7 CFR Part 340.

Regarding the recordkeeping requirements in the proposed rule, we believe these requirements are unnecessary and provide little value, as they require developers to retain little more than the documentation already provided to the EPA as part of the exemption eligibility procedures. The adverse effects reporting requirements should be sufficient to ensure that EPA is notified of any relevant new information that may affect exemption eligibility.

IV. COST-BENEFIT ANALYSIS

EPA estimates that the differential cost of submitting a self-determination letter and a (non-exempt) full registration to be “about \$444,000 - \$459,000 per product.” Costs of data development and regulatory submission for full registration typically runs in the millions of US dollars for most developers. While we agree that the proposed exemption procedures may result in substantial cost savings, we are concerned that the extremely high bar set to meet the exemptions will still make commercialization of PIPs in minor or specialty crops, which are often more reliant on genetic resistance to pests, prohibitively expensive.



EPA estimates that the agency only expects one new PIP product annually to meet the new exemption. We believe this could be a significant underestimate, especially if EPA adopts revisions to the proposed rule that streamline information requirements and thereby facilitate innovation in a broader range of crops. Further, the clearer and broader the exemptions, the more likely developers will be to utilize the self-determination process (as opposed to agency confirmation), thereby additionally freeing up limited agency resources.

V. BIO RESPONSES TO EPA QUESTIONS

The section that follows includes BIO's responses to the five specific questions posed by EPA in the notice. As noted below, in several instances, more in-depth discussion related to these questions is included in earlier sections of BIO comments.

Question A: What inert ingredients could be present in PIPs based on sexually compatible plants created through biotechnology?

We agree with EPA that many, if not most, uses of newer genome editing tools would not result in the insertion of coding sequences that lead to the production of any substance other than the "active ingredient." In some instances, however, a developer may wish to insert a native PIP gene into the genome linked to a selectable marker. We request that EPA clarify how it would handle such a case, and suggest that EPA consider revising the regulations to allow the exemption of native sequences accompanied by inert ingredients such as selectable markers if the inert ingredients have already been granted a tolerance exemption. Further, we ask that EPA confirm our understanding that noncoding, non-expressed sequences do not affect exemption status, even if those sequences are not found in a plant that is sexually compatible with the recipient plant.

Question B: What process should EPA use to provide notice that a PIP no longer meets the criteria for exemption if new information is provided?

If EPA receives new information, either from the developer or other sources, to suggest that a PIP may no longer meet exemption criteria, EPA should notify the developer and provide the developer with due process, including but not limited to an opportunity to respond to the new information and/or challenge the potential loss of exemption. If, after consultation with the developer, EPA reaches a determination that a PIP is no longer exempt, EPA should work directly with the developer to determine appropriate actions.

Question C: Should EPA consider other approaches for its confirmation process?

In general, BIO supports in principle the two proposed procedures for determination of exemption eligibility (but see discussion above about information requirements). We appreciate the flexibility provided by being able to choose among two mechanisms. We believe that many developers may elect to use the self-determination process for PIPs early in development, and then later submit a more formal eligibility confirmation request as a PIP product moves closer to commercialization. BIO believes that, at a minimum, notifying EPA of exemption self-determinations will provide more confidence in EPA oversight of PIP products and give the agency visibility into the kinds of exempt PIPs in development.



Question D: Is EPA's intent behind the use of the terms "native" and "never derived" clear?

While these are not terms widely used in the field of genetics, we agree that the terminology is sufficiently clear to capture EPA's intent. We ask that EPA clarify that "native" sequences include sequences that have resulted from mutagenesis (both spontaneous and induced) and is not intended to exclude sequences originating via horizontal gene transfer.

Question E: Should EPA issue a clarifying exemption for loss-of-function traits that result in pesticidal effects?

EPA should clarify that it has no authority under FIFRA to regulate the *absence of a substance* as a pesticide, even if the absence of the substance is intended to prevent, destroy, repel, or mitigate a pest. Further, there is no need for an exemption for loss-of-function that results in *reduced* production of a substance, as this is adequately addressed by the proposed exemption for differential expression of native genes (proposed 40 CFR 174.26(a)(2)(i)).

Thank you for the opportunity to provide comments on this draft proposal. Please feel free to contact me directly if you have any questions about our comments.

Sincerely,

A handwritten signature in black ink, appearing to read "Clint Nesbitt".

Clint Nesbitt
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