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Proposed Rule: Importation, Interstate Movement, and Environmental Release of Certain Genetically Engineered Organisms (Docket No. APHIS–2015–0057)[1] ("Proposed Rule")

RIN 0579-AE15

Submitted electronically via Federal eRulemaking Portal (http://www.regulations.gov)

The Institute for Agriculture and Trade Policy (IATP)[2] appreciates this opportunity to comment on the Proposed Rule. IATP last wrote to the Animal and Plant Health Inspection Service (APHIS) on April 21, 2016 on the agency's Notice of Intent to Prepare a Draft Environmental Impact Statement on the Introduction of Products of Biotechnology. The following comment occasionally references that earlier comment as well as our comment on the revision to the "Coordinated Framework for the Regulation of Biotechnology" (Coordinated Framework).[3]

IATP is aware that APHIS, like all federal agencies, is under intense industry, legislative and executive branch pressure to preclude or reduce the number of regulations and enforcement actions and their costs to regulated entities.[4] However, since that legislation is far from enacted and since an Executive Order to cut two regulations for every one promulgated is being challenged in court[5], IATP strongly urges APHIS to deliberate on the Proposed Rule under current authorities, without anticipating the enactment of future changes to these statutes or to the rulemaking process.

General comment: APHIS's approach to non-target effects of GE modifications

IATP, like the public in general, is impressed by the rapidity of the evolution of the new Genetic Engineering (GE) techniques over the past 30 years. One overview exults, "life-science research has transformed from a manual and often tedious task to a high-tech, largely automated process of unprecedented efficiency."[6] However, GE efficiency, i.e. the speed, number and purported accuracy of genetic modifications to express desired traits, has resulted nevertheless in many non-target effects in the engineered organism.

Medical researchers have called for a detailed understanding of the non-target effects of CRISPR techniques employed to develop human therapies. For example, "Understanding

the scope of RGEN [CRISPR RNA-guided endonucleases]-mediated off-target effects in human and other eukaryotic cells will be critically essential if these nucleases are to be used widely for research and therapeutic applications."[7] IATP urges APHIS to emulate the medical researchers insistence on understanding non-target effects before the Agency applies its proposed "up front" risk assessment to determine not to regulate organisms edited by CRISPR and other genetic engineering techniques. IATP is alarmed that APHIS proposes to "generally not require data from outdoor plantings" (Federal Register / Vol. 82, No. 12 / Thursday, January 19, 2017, (FR) 7012) to verify its "up front" risk assessment of GE plants, even for plants engineered to produce industrial chemicals and pharmaceuticals.

Both agricultural regulators and the regulated entities have judged non-target effects to be below regulatory concern because they deem the non-target effects of transgenic manipulation to be no greater than the non-target effects of traditional plant breeding.[8] APHIS uses syllogistic reasoning in the Proposed Rule for organisms engineered by CRISPR and other new GE techniques:

> The second reason for the exclusions [from the definition of "genetically engineered organism"] is that GE plants as a class, which constitute the vast preponderance of GE organisms to date, pose no greater plant pest or noxious weed risk than their counterparts developed through traditional breeding techniques or chemical or radiation-based mutagenesis. Moreover, it is both impracticable and unnecessary to regulate plants created through traditional breeding techniques or chemical or radiation-based mutagenesis for plant pest or noxious weed risk. (FR 7015-7016)

The structure of the syllogism is a) GE plants and plants developed from traditional breeding techniques and mutagenesis pose the same quantity of risks; b) It is "impracticable and unnecessary to regulate plants created through traditional breeding techniques or chemical or radiation-based mutagenesis for plant pest or noxious weed risk;" c) therefore it is "impracticable and unnecessary" to regulate GE plants derived from the new engineering techniques. There is an exception to c) that would require regulation "in the event that a Federal noxious weed is genetically engineered (something that has not occurred to date)" (FR, 7010). As noted below, APHIS's interpretation of the Plant Protection Act's definition of "noxious weed" further reduces the likelihood that APHIS, under the Proposed Rule, will regulate GE organisms in plants grown for food, feed, industrial chemical or pharmaceutical purposes.

Most of the Proposed Rule consists of legal and policy reasons about why APHIS will not regulate GE organisms developed by techniques of advanced genetic engineering. The guiding principle for evaluating risks are not specific to the technique used, to the organism that is engineered or to the environment in which the organism lives. Rather the guiding principle comes from the Coordinated Framework.

> APHIS considers such additions, deletions, or substitutions [of genetic engineering] to present an acceptable plant pest and/or noxious weed risk when they are used to create an organism that could otherwise have been created through traditional breeding techniques and/or chemical or radiation-based mutagenesis; in other words, it is the product, rather than the techniques used to derive the product, that APHIS considers to present an acceptable level of risk. The Agency considers this to be consistent with the principles set forth in the Coordinated Framework. (FR 7017)

In contrast to this syllogistic policy prohibiting evaluation of risk of the steps by which a GE product is produced, APHIS should employ the following science-based approach to assessing risks of genetically engineered organisms:

> To assess the actual risks it is necessary to know which techniques were applied for which purposes. The relevant data have to be collected systematically and assessed independently. If these techniques are exempted from regulation, the relevant data will be kept as confidential business information. In this case, neither independent scientists nor authorities will be able to access the data in a way that will enable them to obtain a sufficient overview of the specific techniques, the relevant traits and the associated risks.[9]

IATP does not anticipate that APHIS will adopt this approach to risk assessment, which draws on a small but growing body of literature on possible risks associated with non-target effects of several new techniques of genetic engineering.[10] The announcement by the U.S. Trade Representative that the United States will launch World Trade Organization disputes to access new markets for U.S. biotechnology products[11] indicates to us that the United States will continue to claim that "science-based" regulation requires assessing risk without evaluating the process in which the GE techniques are employed.

APHIS' proposed options for oversight of plants engineered to produce pharmaceuticals and industrial chemicals

To APHIS' credit, the Proposed Rule requests comment on four options to remedy gaps in the oversight of Plant Made Pharmaceutical and Industrials (PMPIs). (FR 7012-7013) IATP's preferred option is informed by some assumptions about recent science that seeks to bio-contain planat GE organisms. Since PMPIs are designed to grow in open fields, bio-containing PMPI crops to prevent horizontal gene transfer to food and feed crops is paramount. A Preliminary Opinion of three scientific committee advised the European Commission that as of 2015, there were no reliable bio-containment techniques to prevent horizontal gene transfer.[12] The Preliminary Opinion, as well as the Presidential Commission for the Study of Bioethical Issues in synthetic biology, assume multiple genetic safeguards will be required to solve biosafety risks of horizontal gene transfer from organisms modified by the new GE techniques.[13]

However, as one biosafety research team noted, "the higher the complexity of a biosafety device, the more prone it may be to disturbance and failure" because of multiple physiological burdens placed on the microbial host by the multi-device safeguard.[14] The same researchers state that building a genetic firewall against HGT from combinations of DNA or RNA not found anywhere in nature "could lead to an effective semantic containment within decades; however, this would not stop a refactored microbe from competing at the physiological level with natural flora and fauna during environmental release."[15]

In view of the lack of reliable biocontainment mechanisms in general, the biosafety risks posed by PMPIs grown in outdoor plantings, and APHIS' proposal to "generally not require data from outdoor plantings" (FR 7012) from PMPI product developers, IATP support's APHIS's option one: "a statute would be enacted, or existing statutory authority amended, to grant one or more Federal agencies explicit authority to provide oversight of outdoor plantings of all GE PMPI-producing plants and to evaluate GE PMPI-producing plants for all possible risks, beyond plant pest and noxious weed risks." (FR, 7012-7013)

The disadvantages of this option are nearly self-evident. In the current political environment, the likelihood of enacting even an amendment to a statute to authorize a comprehensive interagency risk analysis approach for PMPIs is not great. However, the Coordinated Framework does not provide for a comprehensive means to evaluate GE PMPI producing plants, and the option of an interagency memo of cooperation or transferring oversight responsibility to a besieged Environmental Protection Agency will not ensure the resources necessary to provide oversight. The hearings, including field hearings, entailed in the proposed option one, will both inform members of Congress and perhaps even give them political impetus to cooperate to pass an amendment.

APHIS' interpretation of the definition of "noxious weeds" in the Plant Protection Act of 2000

To judge by the regulatory history summarized in the Proposed Rule, it appears that APHIS will regulate few, if any, genetically engineered organisms derived from new GE techniques. The Proposed Rule portrays risk to environmental health as a function of "weediness."

> For GE plants that APHIS determines not to possess weedy traits prior to modification, APHIS would endeavor to determine whether weediness had been introduced into the organism through genetic engineering. Finally, in the event that a Federal noxious weed is genetically engineered (something that has not occurred to date), APHIS would endeavor to determine whether the GE plant is still a noxious weed and warrants continued regulation. (pFR, 7010-7011)

Based on APHIS' interpretation of the Plant Protection Act (PPA) of 2000, since 2011, the agency has determined that just 24 of the 1700 plants it has reviewed are "Federal noxious weeds" (FR, 7010 footnote 2). Given the broad definition of "noxious weed" in the PPA,

it is surprising that APHIS has found only 24 plant varieties that fit the statutory definition of "noxious weed" in the PPA: "''Any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment.'' (cited in FR, 7009) The International Survey of Herbicide Resistant Weeds identifies about 160 unique resistant weed cases in the United States as of 2016, compared to the APHIS identified 24 noxious weeds.[16]

Indirect injury from a noxious weed can result from the use of a biotechnology product per the product developer's written instructions, for example warning that a seed variety is engineered for use only with the developer's proprietary herbicide. Invited testimony to the National Research Council on how to improve biotechnology regulation, states

> . . . many of the greatest risks and harms are indirect, often several steps removed from the engineered organism itself. The development of pests resistant to controls is an obvious, and generally predictable, example. The engineered crop itself does not directly harm the environment, but rather the pest causes harm by developing resistance to the control. We have already seen this, with dire consequences, with weeds developing resistance to glyphosate, and several insect pests developing resistance to several Bt genes, resulting in increased herbicide use, and increasing tillage that contributes to soil erosion.[17]

It is likely that APHIS will ignore this and similar advice from National Research Council reports because of APHIS' circular reasoning about why it will not regulate noxious weeds, despite having the statutory authority to regulate according to full interpretation of the definition of "noxious weed". In APHIS' 2010 revision of its noxious weed rule,

> In general, APHIS lists a plant as a Federal noxious weed if APHIS determines the plant to be invasive and to have significant negative impacts, if introduced or disseminated within the United States, and if APHIS determines that Federal regulation could reduce the likelihood of such introduction or dissemination. If APHIS determines that Federal regulation of a GE plant— pursuant to the authorities granted in the PPA—is incapable of mitigating identified noxious weed risks, the plant would not be regulated. (FR 7009-7010)

The premise that Federal noxious weeds are invasive and have "significant negative impacts" in the United States, such as the negative impacts of millions of acres of glyphosate resistant weeds, leads APHIS to the false conclusion that Federal regulation is incapable of mitigating the risks and significant negative effectives and therefore the noxious weed would not be regulated. This decision not to regulate follows from APHIS' interpretation of the paragraph on Regulation in the PPA, which requires that noxious weeds and plant pests "be subject to remedial measures the Secretary determines to be necessary to prevent the spread of plant pests or noxious weeds."[18] If the Secretary makes no such determination, then APHIS takes no remedial measures.

APHIS' caveats to the organisms it proposes for exclusion from definition of "genetically modified organism"

IATP believes that APHIS is less than satisfied with its Proposed Rule because of the caveats offers to it.

> The second caveat is that the proposed exemptions are based on APHIS' statutory authority under the PPA. They should therefore be taken as a statement of one Agency's regulatory policy, rather than scientific findings regarding all possible risks posed by such organisms. Accordingly, for organisms that APHIS determines to present negligible plant pest or noxious weed risk, FDA and EPA may anticipate more substantial human or animal food adulterant or pesticide risks, and therefore not reduce their oversight of the same organisms. (FR, 7016-7017)

As indicated above, IATP believes that APHIS has chosen to interpret its statutory authority so narrowly and with such exemptions in the Proposed Rule that it can scarcely make scientific findings about any risks associated with organisms modified by the new GE techniques, much less "all possible risks." APHIS appears to claim that its regulatory policy does not enable it to make scientific findings regarding these possible risks and so warns EPA and FDA not to reduce their oversight of GE organisms in that way that APHIS's regulatory policy has restricted it from conducting science-based risk assessments of organisms modified by advanced genetic engineering.

Conclusion

In the Proposed Rule, APHIS would end its current practice of requiring GE product developers to petition to the Agency to deregulate its product following APHIS review of the product's field trial data. This deregulatory process has shortcomings, due to product developer Confidential Business Information claims about the data. Nevertheless, this deregulatory petition process is preferable to the Proposed Rule's non-regulation process, based on an "up front" review of product developer selected information about a GE product without any field trial data. APHIS' proposal to "generally not require data from outdoor plantings" (FR, 7012 et passim) is apparently based on the belief that field trial data collected and analyzed for products of transgenic modification provide assurance that no further field trial data need be collected and analyzed the for the more complex modifications of the new genetic techniques (FR 7018). Elimination of the petition process for deregulation is a reckless use of APHIS's statutory authority, particularly for experimental crops to produce industrial chemicals and pharmaceuticals. IATP strongly urges APHIS to redraft the Proposed Rule, making full use of its authority under the PPA.

Finally, IATP wishes to note that it is a signatory to a letter on the Proposed Rule from the Center for Food Safety.[19] We urge APHIS to redraft this Proposed Rule notwithstanding the enormous anti-regulatory pressures on the Agency.

[1] https://www.aphis.usda.gov/brs/fedregister/BRS_20170119.pdf

[2] The Institute for Agriculture and Trade Policy (IATP) is a nonprofit, 501(c)(3) nongovernmental organization, headquartered in Minneapolis, Minnesota, with offices in Washington, D.C. and Berlin, Germany.

[3] "Modernizing the Regulatory System for Biotechnology Products," Office of the President, July 2, 2015. https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf

[4] E.g Allison Cassidy and Myriam Alexander-Kerns, "The Powerful Corporations Pushing to Unravel Protections for Consumers, Public Health and the Environment," Center for American Progress, May 9, 2017. https://www.americanprogress.org/issues/green/news/2017/05/09/432053/powerful-corporations-pushing-unravel-protections-consumers-public-health-environment/

[5]Evan Weinberger, "Groups Sue to Block Trump's Regulatory 2 for 1 Order," *Law360*, February 8, 2017. https://www.law360.com/articles/889781/groups-sue-to-block-trump-s-2-for-1-regulatory-order

[6] E.g. "Third Years of Progress," *The Scientist*, October 2016. http://www.the-scientist.com/?articles.view/articleNo/47150/title/Thirty-Years-of-Progress/

[7] Yanfang Fu et al, "High-frequency off-target mutagenesis induced by CRISPR-nucleases in human cells," *Nature Biotechnology*, September 2013. Vol 31:9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3773023/

[8] Gregory Ladics et al, "Genetic basis and detection of unintended effects in genetically modified plants," *Transgenic Research*, February 26, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504983/

[9] Christoph Then, "Synthetic gene technologies used in plants and animals for food production," Test Biotech, 2016, p. 5. http://www.testbiotech.org/en/node/1597

[10] E.g. Michael Eckerstorfer, Marianne Miklau and Helmut Gautisch, "New plant breeding Techniques: Risks Associated with their Application," Environment Agency Austria, 2014. http://www.umweltbundesamt.at/fileadmin/site/publikationen/REP0477.pdf

[11] Isabelle Hoagland, "Lighthizer eyes cases at WTO to ensure trade barriers are science-based," *Inside U.S. Trade*, June 16, 2017.

[12] "Preliminary Opinion [on] Synthetic Biology Risk Assessment Methodologies and Safety Aspects," European Commission, January 2015, at 6. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_048.pdf.

[13] http://bioethics.gov/node/172

[14] Oliver Wright, Guy-Bart Stan and Tom Ellis, "Building-in biosafety for synthetic biology," *Microbiology* 159 (July 2013), 1223.

[15] Ibid., 1227.

[16] Ian Heap, "Increase in Unique Resistant Weeds for the USA", Slide 5, in International Survey of Herbicide Resistant Weeds. www.weedscience.org. Accessed June 15, 2017.

[17] Doug Gurian Sherman, Invited Comments to the National Research Council Committee on "Future Biotechnology Products and Opportunities to Enhance the Capabilities of the Biotechnology Regulatory System" Center for Food Safety, April 2, 2016, 6. http://www.centerforfoodsafety.org/files/cfscommentsnationalresearchcouncilcommittee_53582.pdf

[18] PL 106-224, Section 402, paragraph c3) https://www.aphis.usda.gov/plant_health/plant_pest_info/weeds/downloads/PPAText.pdf

[19]http://www.centerforfoodsafety.org/files/2017-6-16-part-340-rules-sign-on-letter--final-sen-chase_53068.pdf