Dr. Bernadette Juarez
Deputy Administrator
United States Department of Agriculture
Animal and Plant Health Inspection Service
Biotechnology Regulatory Services
4700 River Road Unit 147
Riverdale, MD 20737–1236

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July 27, 2023

Heather Anderson, M.Sc.
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Re: Request for a Regulatory Status Review for Protoporphyrinogen Oxidase Herbicide-Tolerant Maize MON 80616

Dear Ms. Juarez,

Bayer CropScience LP is submitting this request to USDA-APHIS for an initial Regulatory Status Review (RSR) of the enclosed information in regard to a determination of nonregulated status for the new genetically engineered (GE) corn product, MON 80616, and any progeny derived from crosses between MON 80616 and conventional maize or other GE maize not subject to 7 CFR Part 340 regulations.

Bayer has developed herbicide-tolerant maize MON 80616, which is tolerant to protoporphyrinogen IX oxidase (PPO) inhibiting herbicides and will offer growers an additional option for effective weed management. MON 80616 maize will be combined through traditional breeding methods, with other GE traits not subject to APHIS regulation that provide herbicide tolerance as well as protection against above-ground and below-ground maize insect pests. These next generation combined-trait maize products will offer broader grower choice, improved production efficiency, increased weed control and pest protection, the potential for increased yield, and promote a more sustainable agriculture system.

The enclosed information is being submitted in accordance with the Guidance for Requesting a Regulatory Status Review under 7 CFR part 340 (USDA-APHIS Document ID BRS-GD-2020-003).

We would be pleased to meet with you and other USDA officials and scientists to respond to any questions you may have, or to provide you with additional information that you may request. Should you have any questions on this letter, the enclosed information or wish to set up a meeting to further discuss MON 80616 please contact James Nyangulu, Federal Engagement Lead, at (202) 304-6594, or Heather Anderson at (636) 236-4499.

Yours sincerely,

DocuSigned by:
Heather Anderson
Signer Name: Heather Anderson
Signing Reason: I am the author of this document
Signing Time: 27-Jul-2023 | 4:16:06 PM CEST
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He ther Anderson, M.Sc
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Bayer U.S. – Crop Science

cc: Bayer Regulatory File
James Nyangulu, Federal Engagement Lead (202) 383-2866
Daniel L. Kendrick, Head of Regulatory Affairs Corn Traits (314) 922-4125

Enclosure: Request for a Regulatory Status Review for Protoporphyrinogen Oxidase Herbicide-Tolerant Maize MON 80616

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By llightle at 1:24 pm, Jul 27, 2023

Request for a Regulatory Status Review for Protoporphyrinogen Oxidase Herbicide-Tolerant Maize

MON 80616

OECD Unique Identifier: MON-80616-9

The undersigned submits this Regulatory Status Review (RSR) request under 7 CFR § 340.4 to request that the Administrator make a determination that the article should not be regulated under 7 CFR Part 340

July 27, 2023

DocuSigned by:
Heather Anderson
Signer Name: Heather Anderson
Signing Reason: I am the author of this document
Signing Time: 27-Jul-2023 | 4:16:47 PM CEST
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Heather Anderson, M.Sc.
Senior Global Regulatory Manager

Bayer RSR Number: CR293-23U1

Submitted by:

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Bayer CropScience LP
700 Chesterfield Parkway W.
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RELEASE OF INFORMATION

Bayer CropScience LP (hereafter Bayer) is submitting this request for a Regulatory Status Review (RSR) by the USDA. Bayer understands that the USDA complies with the provisions of the Freedom of Information Act (FOIA). In the event the USDA receives a FOIA request, pursuant to 5 U.S.C., § 552, and 7 CFR Part 1, covering all or some of the information in this request, Bayer expects that, in advance of the release of the document(s), USDA will provide Bayer with a copy of the material proposed to be released and the opportunity to object to the release of any information based on appropriate legal grounds, e.g., responsiveness, confidentiality, and/or competitive concerns. Bayer understands that a CBI-deleted copy of this information may be made available to the public in a reading room and made available via the internet as part of a public comment period. Bayer also understands that if the review proceeds to the plant pest risk assessment (PPRA) step and the RSR request has been deemed complete, a copy of the RSR request may be posted to the USDA-APHIS BRS website or other U.S. government websites (e.g., www.regulations.gov). Except in accordance with the foregoing and required under applicable law, Bayer does not authorize the release, publication or other distribution of this information without Bayer's prior notice and consent.

ABBREVIATIONS AND DEFINITIONS

APHIS	Animal and Plant Health Inspection Service
Cas12a	CRISPR Associated Protein 12a
DNA	Deoxyribonucleic Acid
FAD	Flavin Adenine Dinucleotide
GE	Genetically Engineered
gRNA	Guide Ribonucelic Acid
MOA	Mechanism of Action
mRNA	Messenger Ribonucleic Acid
OECD	Organization for Economic Co-operation and Development
PPO	Protoporphyrinogen IX oxidase
RSR	Regulatory Status Review
SDI	Site-directed Integration
T-DNA	Transfer Deoxyribonucleic Acid
USDA	United States Department of Agriculture

I REQUESTOR

The submitter of this initial Regulatory Status Review request for maize MON 80616 is:

Bayer CropScience LP

700 Chesterfield Parkway West

Chesterfield, MO 63017

Communications with regard to this submission should be directed to Heather Anderson, M.Sc., Senior Global Regulatory Manager, at the Bayer address listed above, or by email at heather.anderson@bayer.com.

II RATIONALE FOR THE DEVELOPMENT OF MON 80616

The Animal and Plant Health Inspection Service (APHIS) of the United States (U.S.) Department of Agriculture (USDA) has responsibility, under the Plant Protection Act (Title IV Pub. L. 106-224, 114 Stat. 438, 7 U.S.C. § 7701-7772) to prevent the introduction and dissemination of plant pests into the U.S. APHIS regulations at 7 CFR § 340.4, that are in effect on the date this Regulatory Status Review (RSR) request was filed, provide that an applicant may request a RSR of a plant developed using genetic engineering to evaluate whether the combination of the plant, introduced trait, and the trait's mechanism of action (MOA) pose an increased plant pest risk relative to the comparator plant.

II.A Basis for the Request

Bayer is submitting this request for an initial RSR to APHIS for the agency to evaluate whether the genetically engineered (GE) maize product MON 80616 and any progeny derived from crosses between MON 80616 and conventional maize or other GE maize not subject to 7 CFR Part 340 regulations should no longer be regulated by APHIS.

II.B Rationale for the Development of Herbicide-Tolerant Maize

Herbicide-tolerant maize MON 80616 is tolerant to protoporphyrinogen IX oxidase (PPO) inhibiting herbicides. MON 80616 contains a PPO gene (*H_N90 PPO*) from *Enterobacter cloacae* that expresses a PPO protein that is insensitive to PPO-inhibiting herbicides and thus confers tolerance to these herbicides.

MON 80616 maize will offer growers an additional option for effective weed management. The best management practices for minimizing the development of herbicide resistant weeds involve implementing diversified weed management programs, which include using multiple herbicides with different modes of action either in mixtures, in sequences or in rotation and other recommended integrated weed management principles. MON 80616 maize will be combined through traditional breeding methods, with other GE traits not subject to APHIS regulation that provide herbicide tolerance as well as protection against above-ground and below-ground maize insect pests.

III DESCRIPTION OF COMPARATOR PLANT

The MON 80616 transformation was conducted with maize (*Zea mays* L. subsp. *mays*) inbred line HCL301, which is a Bayer proprietary medium season yellow dent maize line of the Stiff Stalk background that is well adapted to the central regions of the U.S. corn belt. MON 80616 maize and its comparator plant, HCL301 as inbred or hybrid, share the same genetic background, with the exception of the presence of the biotechnology-derived trait.

IV GENOTYPE OF THE MODIFIED PLANT FOR MON 80616

This section contains information describing the genetic differences between the modified plant and the comparator plant, including nucleotide sequence and annotation of the genetic material that has been inserted into and remains in the genome of the modified plant, as described in the "Guidance for Requesting a Regulatory Status Review under 7 CFR part 340" (USDA-APHIS Document ID BRS-GD-2020-003).

IV.A Sequence, Identity and Sources of the Genetic Material Inserted into MON 80616

MON 80616 maize was produced by *Agrobacterium tumefaciens*-mediated transformation of maize tissue using the transfer DNA (T-DNA) transformation plasmid vector PV- ZMHT530724. This plasmid is approximately 17.4 kb and contains one T-DNA that is delineated by Right and Left Border regions. The T-DNA that was inserted initially contained *H_N90 PPO*, a *cp4 epsps* selectable marker, *Cpf1*(*Cas12a*), and gRNA cassettes. *Cpf1*(*Cas12a*) and gRNA cassettes were included in the T-DNA to enable site-directed integration (SDI) of the T-DNA into a specific location in the genome through non-homologous end joining (NHEJ) (Dong and Ronald, 2021). As shown in the Figure IV-1 below, the *cp4 epsps* selectable marker, *Cpf1*(*Cas12a*), and gRNA cassettes were flanked by two targeting sequences called *lox*P sites that allow for Cre recombinase-mediated excision. Transformed lines were screened to identify a line with an integrated T-DNA at the desired genome location. The *cp4 epsps* selectable marker, *Cpf1*(*Cas12a*), and gRNA cassettes were then excised by crossing the chosen line with a Cre recombinase-expressing maize line. Subsequently, segregation, selection, and screening were used to isolate plants that contained the *H_N90 PPO* expression cassette and lacked the *cp4 epsps* selectable marker cassette, *Cpf1*(*Cas12a*) cassette and gRNA cassette, and any sequences from the T-DNA of the Cre recombinase-expressing maize line. MON 80616 was selected as the lead event based on superior agronomic, phenotypic and molecular characteristics.

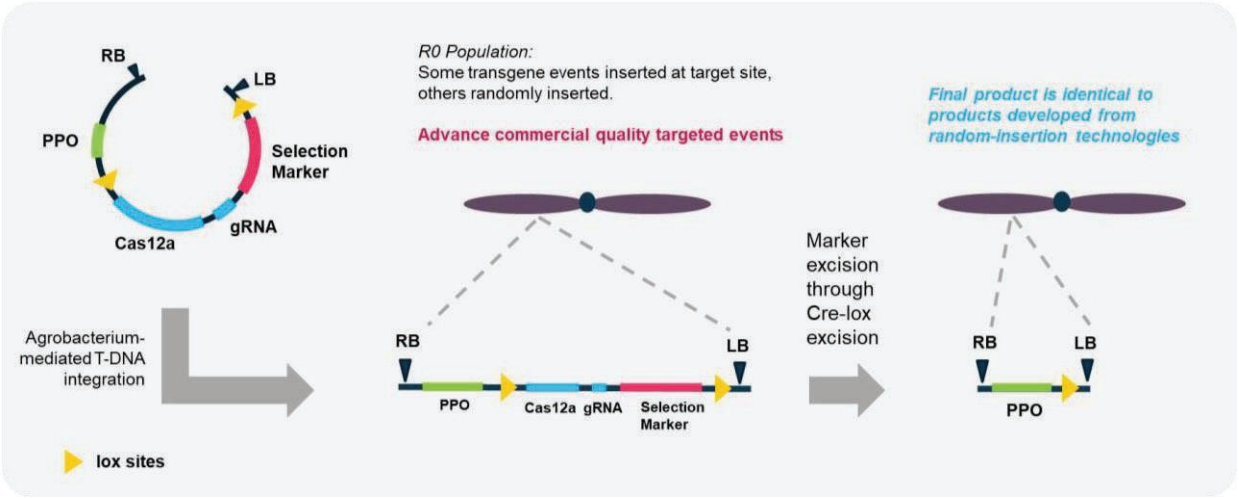

Figure IV-1. Overview of Site-Directed Insertion of PPO cassette to generate MON80616

The nucleotide sequence of the inserted genetic material in MON 80616 maize is provided in Appendix A, and an annotation of the different genetic elements is provided in Table IV-1.

Table IV-1. Annotation of the Inserted Genetic Material in MON 80616

Genetic Element	Location in Sequence	Function (Reference)
T-DNA		
Co-insert	1-3	3 base pairs of co-inserted "synthetic" [2] DNA at the 5′ junction upon T-DNA integration
B[1]-Left Border Region[r1]	4-192	DNA region from *Agrobacterium tumefaciens* containing the left border sequence used for transfer of the T–DNA (Barker et al., 1983) **(GenBank accession: OK586894 positions 1 through 189)**
Intervening sequence	193-198	"Synthetic" sequence used in DNA cloning
***lox*P**	199-232	Sequence from Bacteriophage P1 for the *lox*P recombination site recognized by the Cre recombinase (Russell et al., 1992) **(GenBank accession: M10145) positions 24 through 57**
Intervening sequence	233-238	"Synthetic" sequence used in DNA cloning
P[3]-*ubq-Ag1*	239-2244	Promoter, 5′ UTR and intron from *Andropogon gerardii* (big bluestem grass) of a putative ubiquitin gene that directs transcription in plant cells (Joung and Kamo, 2006) **(GenBank accession: OQ383363)**
Intervening sequence	2245-2250	"Synthetic" sequence used in DNA cloning
TS[4]-*agp6-At1*	2251-2454	Targeting sequence of the *apg6* (albino and pale green) gene from *Arabidopsis thaliana* encoding an HSP101 (heat shock protein) homologue and acts as a transit peptide that directs transport of the protein to the chloroplast (Myouga et al., 2006) **(GenBank accession: ON111454)**
CS[5]-*H_N90 PPO*	2455-2991	Codon optimized coding sequence for the protoporphyrinogen oxidase protein containing amino oxidase, DAO (D amino acid oxidase) and NAD binding domains from *Enterobacter cloacae* that confers tolerance to PPO-inhibiting herbicides (Larue et al., 2019) **(GenBank accession: MN102108 positions 4 through 540)**
Intervening sequence	2992-3005	"Synthetic" sequence used in DNA cloning

Table IV-1. Annotation of the Inserted Genetic Material in MON 80616 (Continued)

T[6]-*TubA-Ad1*	3006-3503	3' UTR sequence of a putative alpha tubulin gene from *Arundo donax* (giant cane) that directs polyadenylation of mRNA. (Hunt, 1994) **(GenBank accession: OQ383365)**
Intervening sequence	3504-3509	"Synthetic" sequence used in DNA cloning
B-Right Border Region [r1]	3510-3552	DNA region from *Agrobacterium tumefaciens* containing the right border sequence used for transfer of the T-DNA (Depicker et al., 1982, Zambryski et al., 1982) **(GenBank accession: OQ383364 positions 315 through 357)**

[1] B, Border

[r1] Superscript in the Left and Right Border Regions indicates that the sequence in MON 80616 was truncated compared to the sequences in PV-ZMHT530724.

[2] The term "synthetic" used in this table is defined and described in the USDA/APHIS-BRS Guidance Document BRS-GD-2020-0003. In the context of this table, the word synthetic does not indicate that the sequence was manufactured but rather that the sequence is not purposefully obtained from a known source and does not have an assigned function, although some homology may exist to known DNA sequences.

[3] P, Promoter

[4] TS, Targeting sequence

[5] CS, Coding sequence

[6] T, Transcription termination sequence

V DESCRIPTION OF THE MON 80616 TRAIT

This section describes the intended MON 80616 trait, intended phenotype associated with the trait, and mechanism of action by which the intended phenotype will be conferred, as described in the Guidance for Requesting a Regulatory Status Review under 7 CFR part 340 (USDA-APHIS Document ID BRS-GD-2020-003).

V.A Description of the Intended MON 80616 Trait

MON 80616 is intended to provide herbicide tolerance.

V.B Intended Phenotype of MON 80616

Herbicide-tolerant maize MON 80616 is intended to provide tolerance to PPO-inhibiting herbicides through expression of a bacterial sourced PPO which is insensitive to PPO-inhibiting herbicides.

V.C Description of the Mechanism of Action for MON 80616

PPO Protein

MON 80616 maize expresses protoporphyrinogen IX oxidase (PPO) protein encoded by the *H_N90 PPO* gene from *Enterobacter cloacae.* Protoporphyrinogen IX oxidase (PPO) catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by molecular oxygen. This enzymatic step is conserved across prokaryotic and eukaryotic organisms in the production of tetrapyrroles such as heme and chlorophyll. In plants, the PPO enzyme is the target of PPO-inhibiting herbicides which have been observed to bind in the active pocket of PPO enzymes when co-crystalized (Koch et al., 2004, Corradi et al., 2006). Application of PPO-inhibiting herbicides to sensitive plants results in a blockage of heme and chlorophyll biosynthetic pathways in the plastids, resulting in the accumulation of pathway intermediates which leak from the plastids and undergo non-specific oxidation to protoporphyrin IX in the cytosol. In the presence of oxygen and light, protoporphyrin IX rapidly generates singlet oxygen, resulting in uncontrolled membrane lipid peroxidation and plant death (Dayan and Duke, 2010), (Figure V-1).

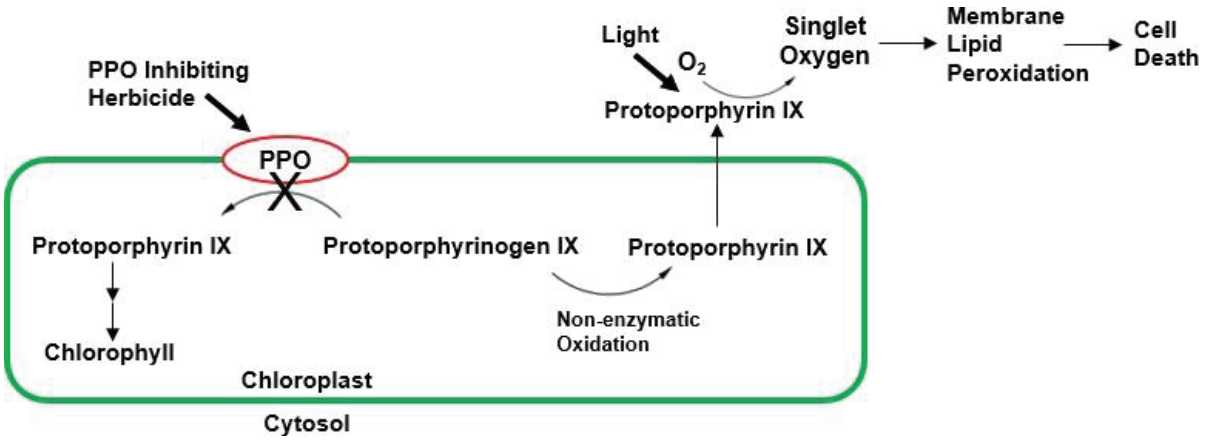

Figure V-1. PPO-Inhibiting Herbicide Mode of Action
Inhibition of PPO enzyme (localized in the outer membrane of chloroplasts) causes an unregulated accumulation of protoporphyrinogen IX, which is oxidized to protoporphyrin IX. Protoporphyrin IX is energized by light and causes formation of reactive singlet oxygen species that can lead to membrane lipid peroxidation and cell death.

PPO has several isoforms in prokaryotic and eukaryotic life forms including HemY and HemG (O'Brian, 2009). HemY is a PPO enzyme of roughly 50 kDa three-domain monomer that includes a flavin adenine dinucleotide (FAD)-binding, a substrate-binding, and a membrane-binding domain. The active site is located between the FAD- and the substrate-binding domain (Koch et al., 2004). HemG is a much smaller PPO enzyme of approximately 20kDa. The HemG PPO protein structure is a single-domain monomer which appears similar in structure to the FAD-binding domain in HemY (Boynton et al., 2009). In conventional plants containing a HemY-type PPO, PPO-inhibiting herbicides block the biosynthesis of heme and chlorophyll. In MON 80616 maize, which is tolerant to PPO-inhbiting herbicides, the oxidation of protoporphyrinogen IX to protoprophyrin IX is maintained by the continued action of the expression of a HemG-type PPO expressed by the bacterially-sourced *H_N90 PPO* gene in the presence of PPO-inhibiting herbicides (Figure V-2).

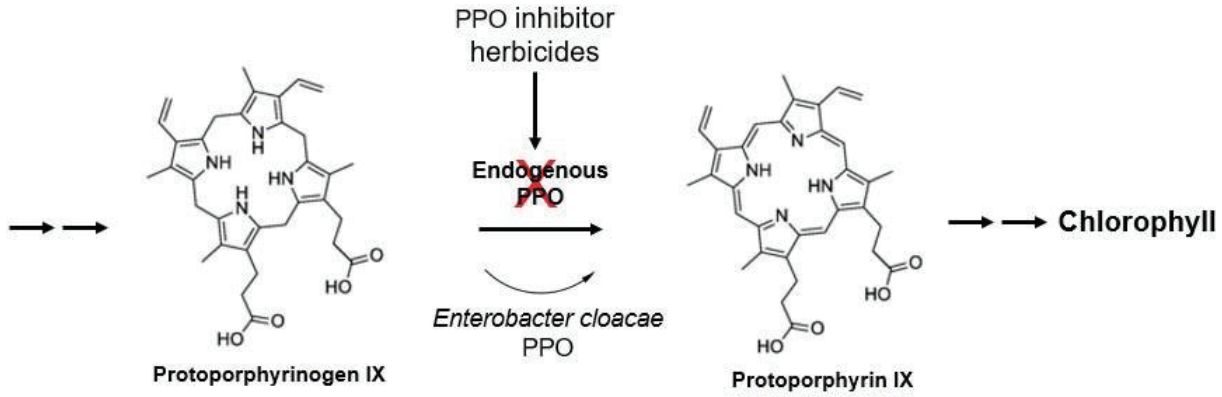

Figure V-2. PPO Mechanism of Action
PPO catalyzes the oxidation of protoporphyrinogen IX to protoprophyrin IX by molecular oxygen. In most plants, the endogenous PPO is inhibited by PPO-inhibiting herbicides, while the *Enterobacater cloacae* PPO protein is insensitive and thus renders the plant tolerant.

The data and information summarized in this section as well as data collected during the development of this product confirm that the molecular mechanism of the MON 80616 PPO protein that provides tolerance to PPO-inhibiting herbicides is well understood, and is not expected to have an impact on metabolism, physiology, and/or the development of the maize plant.

Conclusion

This request for Regulatory Status Review (RSR) of MON 80616 provides details on Bayer's next generation herbicide-tolerant genetically engineered maize product following the guidance outlined in the Agency's document titled "Guidance for Requesting a Regulatory Status Review (RSR) under 7 CFR part 340", Document ID BRS-GD-2020-003. Molecular characteristics as well as mechanism of action of the expressed protein are provided herein and support the conclusion that MON 80616 maize is not expected to have an impact on metabolism, physiology, and/or the development of the maize plant due to the trait/genetic modification.

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APPENDICES

Appendix A Sequence of the Insertion for MON 80616

cccTTACCAATTTTTTTTCAATTCAAAAATGTAGATGTCCGCAGCGTTATTATAAAATGA
AAGTACATTTTGATAAAACGACAAATTACGATCCGTCGTATTTATAGGCGAAAGCAATAA
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