Registration Decision for the New Active Ingredient Methyl-alpha-D-mannopyranoside (Alpha Methyl Mannoside)

Approved by:

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1. Introduction

This document announces that the Environmental Protection Agency (EPA) has completed its evaluation of the new biochemical active ingredient methyl-alpha-D-mannopyranoside (alpha methyl mannoside), a plant growth regulator (PGR), and has concluded that it meets the regulatory and safety standards under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA).

Alpha methyl mannoside is a naturally occurring mannoside carbohydrate that can be metabolized into mannose sugars (monosaccharide). Humans have already been exposed to alpha methyl mannoside as it has long been part of the normal diet and is present in a variety of plant based foods in the form of mannose polymers. Exposure to alpha methyl mannoside occurs naturally via the breakdown of the mannose polymers. Examples of plant tissues containing substantial amounts of extractable alpha methyl mannoside include ivory nuts (palm trees of the genus Phytelephas), lotus beans, coffee beans and guar gum. The highest concentrations of alpha methyl mannoside are found in guar gum (~53%) and coffee (up to 21%). Guar gum is a commonly used food additive (21CFR184.1339). As a PGR, alpha methyl mannoside functions by unlocking the glucose bond from plant lectins (proteins). Once released, glucose is transported to growth points in the treated plant. The release of glucose in the plant results in increased plant growth including increased yields in fruit, flower growth and turgidity in turf.

As a biopesticide, alpha methyl mannoside is classified as a plant growth regulator. FIFRA Sec 2 (136) (v) establishes the definition of plant regulators and carves out terms of exclusion: "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 thereof, but shall not include substances to the extent that they are intended as plant nutrients, trace elements, nutritional chemicals, plant inoculants, and soil amendments." In making its determination that alpha methyl mannoside is a biopesticide, the Agency, based on data and open literature information reviewed, concluded that the use of alpha methyl mannoside does not meet the terms of exclusion and requires registration because its direct application to plants changes the behavior (physiology) of the plant and stimulates growth.

After reviewing the submitted and publicly available data and information, EPA concluded that there is reasonable certainty of no harm from residues of this new active ingredient and that its use will cause no unreasonable adverse effects to human health or the environment. Therefore, the Agency is registering a manufacturing-use product (MP), Technical α-Methyl Mannoside (EPA File Symbol 91428-R); and an end-use product (EP), iH026a, (EPA File Symbol 48813-G), containing the new active ingredient alpha methyl mannoside under FIFRA section 3(c)(5). The EP will be used as a PGR on a variety of crops such as vegetables, fruits, peanuts, bulb and root crops, as well as ornamentals, potted plants, bedding plants, cut flowers, in greenhouses and on turf grass to promote turgidity in turf. Application of the product is to be made directly to plants via foliar spray (ground or aerial) and chemigation at application rates ranging from 6 to 20 oz. active ingredient (a.i.) (0.046 – 0.152 lbs. a.i./A) for food crops at a minimum of two week intervals until the time of harvest and 0.1 to 0.13% (0.13% is equivalent to 1 quart of iH026a in 3,077 gallons of water) for nonfood crops (seedlings prior to transplanting; established plants and at 2-week interval when needed). Its application is intended to promote plant growth, and

increase yield and quality in the treated plants by modulating the availability of natural sugars within treated plants. As part of this decision, EPA is adding to 40 CFR 180 subpart D an exemption from the requirement of a tolerance for residues of alpha methyl mannoside in or on all food commodities.

2. Background

Alpha methyl mannoside was classified as a biochemical pesticide by the Biochemical Classification Committee (BCC) on October 9, 2014, due to its natural occurrence, history of safe exposure to humans and the environment and its nontoxic mode of action to the target pest.

On August 8, 2016, the U.S. Environmental Protection Agency ("EPA") received applications from J & T Associates on behalf of Brandt iHammer for the registration of two pesticide products (a MP and EP) containing the new biochemical active ingredient alpha methyl mannoside. J & T Associates, on behalf of Brandt iHammer, provided a combination of data, waiver rationales, and a request for the bridging of information from a substance that naturally contains high concentrations of the active ingredient. In addition, J & T Associates, on behalf of Brandt iHammer, submitted a petition proposing to establish an exemption from the requirement of a tolerance for residues of alpha methyl mannoside in or on all food commodities. In the Federal Register of October 12, 2017 (82 FR 47509), EPA published a Notice of Receipt (NOR) that announced receipt of two new products containing the new active ingredient, alpha methyl mannoside. In the Federal Register of December 4, 2017 (82 FR 57193), EPA published a Notice of Filing (NOF) proposing to establish an exemption from the requirement of a tolerance for residues of alpha methyl mannoside in or on all food commodities.

3. Evaluation

In evaluating a pesticide registration application, EPA assesses a variety of studies to determine the likelihood of adverse effects (i.e., risk) from exposures associated with the use of the pesticide product. Risk assessments are developed to evaluate how the active ingredient might affect a range of nontarget organisms, including humans and terrestrial and aquatic wildlife (plants and animals). Based on these assessments, EPA evaluates and approves language for each pesticide label to ensure the directions for use and safety measures are appropriate to mitigate any potential risk. In this way, the pesticide's label helps to communicate essential limitations and mitigations that are necessary for public and environmental safety. In fact, the pesticide law has a provision that indicates it is a violation to use a pesticide in a way that conflicts with the label.

3.1 Assessment of Risk to Human Health

To assess risks to human health from use of biochemical pesticides, EPA typically requires a range of Tier I data requirements: acute toxicity data (acute oral toxicity, acute inhalation toxicity, acute dermal toxicity); irritation tests (primary eye irritation, primary dermal irritation and dermal sensitization); subchronic testing (90-day oral, dermal and inhalation tests); mutagenicity testing (bacterial reverse mutation test and *in vitro* mammalian cell assay) and developmental toxicity testing (prenatal development). Tier II and III testing is triggered only when there is indication, usually through lower tier testing, that a biochemical pesticide has

unusual characteristics such as subchronic toxicity, or being suspected or known to be a carcinogen.

In the case of the assessment for alpha methyl mannoside, all data requirements were satisfied by a combination of data, waiver rationales, and the bridging of information from guar gum where high concentrations of mannose polymers are present.

3.1.1 Toxicological Data/Information

All acute toxicology data requirements for alpha methyl mannoside were satisfied by guideline studies. All acute toxicity studies indicate that alpha methyl mannoside is of low toxicity for all routes of exposure: it is classified as Toxicity Category IV for all routes of exposure (oral exposure, inhalation exposure and primary eye irritation). No dermal irritation was noted; and the substance is not a dermal sensitizer. The Signal Word for both the MP and EP is "Caution."

All subchronic toxicity data requirements for alpha methyl mannoside were satisfied by a combination of data, waiver rationales and the bridging of information from guar gum, with the exception of a 90-day oral toxicity and mutagenicity guideline studies. Data from the 90-day oral toxicity study showed that alpha methyl mannoside was not subchronically toxic through the oral route of exposure at the limit dose. No toxicological end points through the oral route of exposure were identified. With regard to subchronic 90-day inhalation toxicity study, EPA accepted a waiver rationale, which demonstrated that its use as a PGR would not increase exposure above background levels. EPA accepted the rationale based on the following: alpha methyl mannoside is naturally occurring and has long been part of a normal diet; the acute inhalation toxicity study is classified as Toxicity Category IV; the calculated inhalation Margin of Exposure (MOE)s are >1000; low predicted vapor pressure of 1.42x10-8 mmHg limits inhalation exposure; and the NOAEL for the 90-day oral toxicity study was over the limit dose of 1000 mg/kg/day and alpha methyl mannoside is not expected to be metabolized differently through inhalation. With regard to the subchronic 90-day dermal toxicity study, EPA accepted a waiver rationale, which demonstrated that alpha methyl mannoside would not present effects of toxicological concern. EPA accepted the rationale based on the following: alpha methyl mannoside is a naturally occurring and long been part of the normal diet; has a low potential for absorption based on the predicted KOW; the acute dermal toxicity study is classified as Toxicity Category IV; (4) the subchronic oral study has a NOAEL greater than the limit dose and the active ingredient is not expected to be metabolized differently through the dermal route of exposure.

For the developmental toxicity study, EPA accepted a waiver rationale, which demonstrated that the use of alpha methyl mannoside as a plant growth regulator would not increase exposure to women of childbearing age above background levels. EPA accepted the rationale based on the following: alpha methyl mannoside is a naturally occurring and long been part of the normal diet of pregnant women without incident; bridging data from guar gum showed no adverse developmental effects in rats; the acute toxicity studies are classified as Toxicity Category IV, suggesting that the compound has low acute toxicity; and no adverse effects were observed in the available 90-day oral toxicity study.

Mutagenicity test data requirements were satisfied by mutagenicity data. Two genotoxicity studies performed on alpha methyl mannoside technical material were all negative for mutagenicity.

3.1.2 Aggregate and Occupational Exposure

No toxicological endpoints were identified from the available toxicity studies; therefore, a quantitative aggregate exposure assessment was not conducted. In consideration of the above information, the Agency has determined that there are no aggregate risks of concern.

Food Exposure and Risk Characterization: While there is a potential for dietary exposure from food as a result of the pesticidal use of alpha methyl mannoside, it will be negligible compared to background levels of alpha methyl mannoside that are naturally found in foods that are commonly consumed. Further, alpha methyl mannoside is readily biodegradable and will degrade rapidly in the environment. Nonetheless, exposure is not of concern for alpha methyl mannoside (when applied in accordance with label directions and good agricultural practices), as no toxicological endpoints were identified from the available toxicity studies, and data indicate that the compound is of low toxicity.

Drinking Water Exposure and Risk Characterization: Residues of alpha methyl mannoside in drinking water are unlikely and unexpected. Further, alpha methyl mannoside is applied at low concentrations, is soluble in water and will degrade rapidly in aqueous environments. Nonetheless, exposure is not of concern as alpha methyl mannoside and mannose are ubiquitous in the environment and pesticidal use of alpha methyl mannoside is unlikely to contribute significantly to overall human exposure including drinking water exposure. In addition, no toxicological endpoints were identified from the available database and the compound is of low toxicity

Non-occupational, Residential Risk Characterization: Alpha methyl mannoside is not currently registered for residential use. It is intended for agricultural and commercial application only. Accordingly, significant residential exposures are not expected. Even if non-occupational exposure should occur, exposure to alpha methyl mannoside would not pose a risk as the data indicate that the compound is of low toxicity; and no toxicological endpoints have been identified for this compound.

Occupational Exposure: Exposures to alpha methyl mannoside are expected to be low. Alpha methyl mannoside is biodegradable and degrades rapidly in the environment. Additionally, the labeling establishes protections to further prevent exposure: personal protective equipment (PPE) includes coveralls, waterproof gloves (made from any waterproof material) and shoes plus socks. A 4-hour re-entry interval (REI) for mixers, loaders, applicators and other handlers also make the likelihood of any potential exposure negligible. Even in the event of exposure, there are no risk concerns because no toxicological endpoints were identified for alpha methyl mannoside and the compound is of low toxicity.

3.1.3 Cumulative Risk

Data have not been identified to suggest that alpha methyl mannoside has a common mechanism of toxicity with other substances. Therefore, the EPA has not made a common mechanism of toxicity finding for alpha methyl mannoside and any other substances.

3.1.4 Human Health Conclusions

EPA concludes that use of alpha methyl mannoside will not result in unreasonable adverse effects to humans and that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of alpha methyl mannoside. EPA does not expect dietary (food and drinking water) or other non-occupational risks from use of alpha methyl mannoside as an active ingredient in the pesticide products. Data demonstrated that alpha methyl mannoside is of low toxicity through all routes of exposure. Any risks resulting from exposure to individuals handling alpha methyl mannoside such as sensitization resulting from repeated exposures are expected to be minimized by use of the required PPE.

The database of studies required to support the assessment of risk to human health is complete. For more information on the human health risk assessment of alpha methyl mannoside please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2017-0419" at http://www.regulations.gov).

3.2 Assessment of Ecological Exposure and Risk

To assess risks to the environment from the use of biochemical pesticides, EPA initially requires a wide range of studies, including Tier I testing done on the following nontarget organisms: birds (oral and dietary), freshwater fish and aquatic invertebrates, plants, and insects. Testing is organized in a tiered structure, where Tier I studies test worst-case exposure scenarios and higher tiers (Tiers II and III) generally encompasses definitive risk determinations and longer term greenhouse or field testing. Higher tier testing is implemented only when unacceptable effects are seen at the Tier I screening level. All data requirements may be addressed with guideline studies or scientific rationales.

For alpha methyl mannoside, all nontarget toxicology data requirements have been satisfied per 40 CFR 158.2060 through guideline studies.

3.2.1 Terrestrial Animals and Plants

Birds

An avian acute oral study and an avian dietary toxicity study conducted on the active ingredient indicate that alpha methyl mannoside will be practically nontoxic to birds. Additionally, the use of alpha methyl mannoside is not anticipated to result in significant exposures to birds. Due to low exposure and the low toxicity of alpha methyl mannoside, no adverse effects to birds are anticipated.

Nontarget Insects

Guideline nontarget insect testing conducted with honeybees indicate that alpha methyl mannoside will be practically nontoxic to honey bees and other nontarget insects. Additionally, the use of alpha methyl mannoside is not anticipated to result in significant exposures to nontarget insects. Due to low exposure and the low toxicity of alpha methyl mannoside, no adverse effects to nontarget insects are anticipated.

Nontarget Plants

Nontarget plant studies showed no effects on height, weight or plant condition from acute exposure to alpha methyl mannoside, thus demonstrating that alpha methyl mannoside is not phytotoxic. Additionally, the use of alpha methyl mannoside is not anticipated to result in significant exposures to nontarget plants. Due to low exposure and the low toxicity of alpha methyl mannoside, no adverse effects to nontarget plants are anticipated.

3.2.2 Aquatic Organisms

There are no labeled sites with direct applications to aquatic environments. Furthermore, alpha methyl mannoside is readily biodegradable, is applied at low concentrations, is soluble in water and will degrade rapidly in aqueous environments. Therefore, no significant exposure is anticipated for aquatic organisms relative to the use of alpha methyl mannoside.

Freshwater Fish and Aquatic Invertebrates

An acute freshwater fish study and an acute aquatic invertebrate study conducted on alpha methyl mannoside indicate that alpha methyl mannoside will be practically nontoxic to fish and aquatic invertebrates. Given the low toxicity of alpha methyl mannoside to aquatic organisms, the agency has no concerns for aquatic organisms when alpha methyl mannoside is used according to EPA-approved label use directions.

3.2.3 Endangered Species Conclusion

EPA has concluded that adverse effects are not anticipated to birds, mammals, freshwater fish and aquatic invertebrates, nontarget plants and nontarget insects (including honey bees) from the pesticidal use of alpha methyl mannoside as a PGR. The Agency also determined that effects to federally listed threatened and endangered species and their designated critical habitats are not expected from these uses. Therefore, a "No Effect" determination is made for direct and indirect effects to federally listed threatened and endangered species and their designated critical habitats for the uses of alpha methyl mannoside as labeled.

The database of studies required to support the assessment of risk to the environment is complete. For more information on the environmental risk assessment of alpha methyl mannoside, please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2017-0419" at http://www.regulations.gov).

4. Alternatives

While there are other PGRs, they are not all functionally equivalent, nor directly interchangeable with alpha methyl mannoside. However, as with most PGRs, alpha methyl mannoside is expected to generally reduce the amount of conventional fungicides and insecticides required for

commercial crop production. By producing stronger and healthier plants, this active ingredient will allow the target plant/crop to better resist insects and disease, thereby diminishing the need for conventional pesticide applications.

5. Benefits

By definition, biochemicals are favorable when compared to currently registered conventional alternatives because biochemicals are naturally-occurring substances (or substances structurally-similar and functionally identical to naturally-occurring substances) with a history of exposure to humans and the environment demonstrating minimal toxicity and a nontoxic mode of action to the target pest(s). Benefits of biochemical pesticides as compared to conventional pesticides typically include lower toxicity profiles for humans and nontarget organisms, and faster degradation in the environment. And as outlined above, when used as a PGR alpha methyl mannoside has the potential to reduce the amount of more toxic pesticide applications by producing more robust stress-resistant plants.

6. Public Comments

On October 12, 2017, EPA announced receipt of an application in the *Federal Register* to register a manufacturing-use product (Technical α-Methyl Mannoside) and an end-use product (iH026a Plant Growth Regulator) containing a new active ingredient, alpha methyl mannoside (82 FR 47509). No substantive comments were received in response to this Notice of Receipt.

On December 4, 2017, the EPA issued a notice pursuant to FFDCA section 408(d)(3), 21 U.S.C 346a(d)(3), announcing the filing of a pesticide tolerance petition (PP 6F8506) by Brandt iHammer (82 FR 57193). The petition requested the establishment of an exemption from the requirement of a tolerance for residues of alpha methyl mannoside in or on food commodities. That document referenced a summary of the petition prepared by the petitioner Brandt iHammer, which is available in Docket ID Number EPA-HQ-OPP-2017-0314 via *http://www.regulations.gov*. No substantive comments were received in response to this Notice of Filing.

Overall, the Agency has provided the public two opportunities to comment on this registration action.

Because the pesticide products contain alpha methyl mannoside, which is a new active ingredient, EPA opened a 15-day public comment period on February 23, 2018. This comment period closed March 10, 2018. EPA took this action in accordance with a policy, first implemented in October 2009, designed to provide a more meaningful opportunity for the public to participate in major registration actions. No substantive comments were received.

7. Regulatory Decision

The alpha methyl mannoside database is considered to be complete, and supports a pesticidal food use. In considering the assessed risk to human health and the environment, the Agency concludes that alpha methyl mannoside meets the regulatory standard under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Therefore, the EPA is granting the unconditional registration of alpha methyl mannoside as a new active ingredient with a food use under Section 3(c)(5) of FIFRA.

Two products are being registered: Technical α-Methyl Mannoside (EPA File Symbol No. 91428-R) is a manufacturing-use product (MP) and iH026a Plant Growth Regulator (EPA File Symbol No. 48813-G) is an end-use product (EP). The EP is intended for use as a PGR on a variety of agricultural crops such as vegetables, fruits, peanuts, bulb and root crops, as well as ornamentals, potted plants, bedding plants, cut flowers, in greenhouses and on turf grass to promote turgidity in turf.

The risk assessments and labels supporting this decision can be found in the associated regulatory docket (search for "EPA-HQ-OPP-2017-0419" at www.regulations.gov).