Final Registration Decision for the New Active Ingredient

1-Aminocyclopropanecarboxylic acid (1-ACC)

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1. Introduction

This document announces that the Environmental Protection Agency (EPA) has completed its initial evaluation of the new biochemical active ingredient, 1-Aminocyclopropanecarboxylic acid,herein referred to as 1-ACC, for use as 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). EPA sought public comments on its proposed decision during a 15-day public comment period. No comments were received.

1-ACC is a naturally occuring non-protein amino acid found in all plants. It acts as a PGR, precursing ethylene, a plant hormone that regulates a wide variety of vegetative and developmental processes. Indeed, 1-ACC residues degrade directly and exclusively into ethylene, which is a quickly dissipating gas of very low toxicity. Notably, ethylene is also a PGR that has been reviewed by EPA and is exempt from the requirement of a tolerance (40 CFR 180.1016). Humans have a long history of safe exposure to 1-ACC from the consumption of fruits and vegetables as part of the human diet. As a pesticide, the substance will be used to regulate fruit ripening, thinning on apples and stonefruit, and enhanced return bloom on apples.

After reviewing all submitted data, EPA has 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 granting the unconditional registration of the new active ingredient, 1-ACC manufacturing-use product (MP)/technical grade of the active ingredient (TGAI), ACC Technical Powder Plant Growth Regulator (EPA File Symbol 73049-LRA); and an end-use product (EP), Accede Plant Growth Regulator Liquid Concentrate (EPA File Symbol 73049- LRT), under FIFRA section 3(c)(5).

The EP is to be applied as a foliar spray in agricultural settings on apple and stone fruit. The at a maximum single application rate of 0.5 lbai/A requiring dilution and calibrated spray equipment (i.e. orchard air blast sprayer). Personal Protective Equipment (PPE) requirements include long-sleeved shirt and long pants, shoes and socks, and waterproof gloves.

2. Background

1-ACC was classified as a biochemical pesticide by the Biochemical Classification Committee (BCC) on October 22, 2015 due to its natural occurrence, history of exposure to humans and the environment and non-toxic mode of action to the target pest(s).

On July 19, 2019, EPA received applications from Valent Biosciences LLC, for the registration of two pesticide products (an MP and EP) containing the new biochemical active ingredient 1-ACC. Valent Biosciences LLC provided a battery of acute studies, a subchronic oral, prenatal developmental, and mutagenicity toxicity studies. Waivers were submitted for the 90-day dermal and 90-day inhalation data requirements. In the Federal Register of June 19, 2020 (85 FR 37096), EPA published a Notice of Receipt (NOR) that announced receipt of two new product applications containing the new active ingredient, 1-ACC. In the Federal Register of December

23, 2020 (85 FR 83889), EPA published a Notice of Filing (NOF) that announced a request to establish an exemption from the requirement of a tolerance in 40 CFR part 180 for residues of the plant regulator 1-Aminocyclopropanecarboxylic acid (1-ACC) in or on apple and stone fruit.

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 evaluates the potential toxicity of a product and the likelihood, amount, and types of exposure users and bystanders are likely to experience. In conducting a risk assessment, EPA must consider: (1) the hazards of a substance and (2) the exposure to that substance that a person will be exposed to as a consequence of use either directly or indirectly. EPA uses this combined information to assess and characterize the risk(s) and predict the probability, nature, and magnitude of the adverse health effects that may occur from use of the substance in the manner described.

On the toxicity side for biochemical pesticides, EPA typically requires a range of Tier I data: 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); 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 is suspected or known to be a carcinogen.

3.1.1 Toxicological Data/Information

The toxicology database is used for assessing the potential toxicity of 1-ACC. All acute toxicology data requirements for 1-ACC were satisfied by guideline studies using 1-ACC as the test substance. The chemical is classified as having low acute oral, dermal, and inhalation toxicity (Toxicity Category IV). It is considered mildly irritating to the eyes and slightly irritating to the skin (Toxicity Category IV) and is not a dermal sensitizer. Due to the low acute toxicity for all routes of exposure, no signal word is required. A signal word is required for all registered pesticide products unless the pesticide product is classified as Toxicity Category IV for all routes of exposure and is negative for dermal sensitization. If a signal word is used in this case, it must be "CAUTION." 40 CFR 156.64(a)(4).

To satisfy the human health assessment data requirements, guideline subchronic toxicity studies were performed using 1-ACC technical grade of the active ingredient (TGAI) as the test substance. The applicant submitted the following guideline subchronic toxicity studies: 90-day oral, 28-day dermal (in lieu of a 90-day dermal), prenatal developmental and genotoxicity data. The applicant submitted waiver rationales to satisfy the 90-day dermal and 90-day inhalation data requirements. Tier II and III studies have not been triggered at this time.

Findings from guideline studies for subchronic toxicity are as follows:

28-day oral toxicity
The no-observed-adverse-effect-level (NOAEL) was 11,600 ppm (target dose), equating to 1185 and 1245 mg/kg bw/day in male and female rats, respectively. A lowest-observed-adverse-effect-level (LOAEL) was not determined. (MRID 50826027)

90-day oral toxicity
Based on the results of this study, dietary administration of 1-ACC for 90 days was tolerated in rats at target doses of 750, 3000, and 12,000 ppm. The NOAEL is considered 794 and 963 mg/kg bw/day in males and females, respectively. A LOAEL was not determined. (MRID 50826028)

28-day dermal toxicity
The no-observed-adverse-effect-level (NOAEL) for the dermal application of 1-ACC was determined to be 1054 mg/kg/day (corresponding to 1000 mg/kg/day of the active ingredient) for both male and female Sprague Dawley rats. (MRID 50826032)

Developmental Toxicity
Based on the results from this study, an exposure level of 13,000 ppm (982 mg/kg/day), the highest exposure level tested, was considered to be the NOAEL for maternal toxicity. For developmental toxicity, the NOAEL is 8,000 ppm (618 mg/kg/day) and the LOAEL is 13,000 ppm (982 mg/kg/day) based on decreases in mean fetal body weights. (MRID 50826034)

One-generation reproductive toxicity
There was no evidence of reproductive toxicity at any exposure level based on evaluation of reproductive performance in the F0 generation and sperm measurements and estrous cyclicity in the F0 and F1 generations. Therefore, the NOAEL for reproductive toxicity, parental systemic toxicity, and offspring toxicity was considered to be 10,000 ppm (approximately 701 mg/kg/day for F1 males and 763 mg/kg/day for F1 females). LOAELs were not determined. (MRID 50826033)

Bacterial reverse mutation test and In vitro mammalian cell assay
The active ingredient 1-ACC is not considered to be genotoxic, based on the negative results in the available *in vitro* genotoxicity data. (MRID 50826036)

For the 90-day dermal, and 90-day inhalation toxicity, EPA accepted waiver rationales based on a weight-of-the-evidence (WOE) approach that considered all of the available hazard and exposure information, including the following considerations: (1) minimal toxicity, (2) natural occurrence and (3) a long history of human exposure without adverse effects. (MRIDs 50896106 and 50896107)

3.1.2 Dietary and Occupation exposure and risks

Dietary Exposure and Risk Characterization: A quantitative dietary exposure and risk assessment has not been conducted at this time because risk attributed to dietary exposure to residues of 1-ACC in food is expected to be negligible based on the following: (1) low toxicity profile; (2) 1-ACC is naturally occuring and has long been part of the normal human diet; and (3) 1-ACC is readily biodegradable (half-life of no more than 8.5 days), Therefore, significant residues are not anticipated.

Drinking Water Exposure and Risk Characterization: A quantitative drinking water exposure and risk assessment has not been conducted at this time because risk attributed to dietary exposure to residues of 1-ACC in drinking water is expected to be negligible based on the following: (1) low toxicity profile; (2) 1-ACC is naturally occuring and has long been part of the normal human diet; and (3) 1-ACC is readily biodegradable (half-life of no more than 8.5 days), therefore, significant residues are not anticipated.

Residential (Non-occupational) Exposure and Risk Characterization: As there are no residential uses for 1-ACC, there are no residential exposure contributions to aggregate exposure.

Occupational Exposure and Risk Characterization: Occupational handler exposure and post-application exposure to 1-ACC from the EP may occur, but there are no risks of concern based on low toxicity of the ai, infrequent application (only twice per season), 1-ACC is readily biodegradable and is a natural non-protein amino acid found in all plants to which humans have been exposed to through fruit and vegetable consumption, and PPE requirements (long-sleeved shirt and long pants, waterproof gloves, and shoes plus socks) that mitigate exposure. Dermal and inhalation mixer, loader and applicator exposure scenarios include broadcast application using airblast equipment. Based on a WOE approach, considering all the available 1-ACC hazard and exposure data , no occupational handler or post-application risks of concern have been identified.

3.1.3 Cumulative Risk

Data have not been identified to suggest that 1-ACC has a common mechanism of toxicity with other substances. Therefore, the EPA has not made a common mechanism of toxicity finding for 1-ACC and any other substances.

3.1.4 Human Health Conclusions

EPA concludes that the use of 1-ACC 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 1-ACC. EPA does not expect dietary (food and drinking water) or other non-occupational risks of concern from use of

1-ACC as an active ingredient in these pesticide products. Data demonstrated that 1-ACC is of low toxicity through all routes of exposure and no toxicological end points have been identified.

Any potential occupational risks resulting from exposure to individuals handling 1-ACC are expected to be negligible and further reduced by use of the required PPE.

The database of studies required to support the hazard assessment to human health is complete. For more information on the human health hazard assessment of 1-ACC please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2019-0516" at http://www.regulations.gov).

3.2 Assessment of Ecological Exposure and Risk

To assess ecological risks from use of biochemical pesticides, EPA evaluates the likely environmental impacts as a result of exposure of the chemical to plants and animals in the environment and to whether that exposure will cause harm or ecological effects. EPA uses this combined information and considers the overall toxicity to characterize the risk(s) in order to identify what levels may cause harmful effects on the plants and animals of concern that may occur from use of the substance in the manner described.

On the toxicity side, EPA initially requires that a wide range of studies including Tier I testing be done on the following nontarget organisms: mammalian (acute, subchronic, prenatal developmental, and mutagenicity), birds (acute oral and dietary), fish (acute 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 encompass 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 1-ACC, all nontarget toxicology data requirements have been satisfied per 40 CFR 158.2060 through acceptable guideline studies.

Non-target organism and environmental fate information submitted in support of the MP/EP demonstrate that 1-ACC will have minimal toxicity on non-target organisms on an acute, dietary and/or chronic basis when it is used in accordance with the use directions for this EP. The active ingredient is applied at low rates (no more than 0.504 lbs. 1-ACC/A/application), dissipates rapidly in the environment (half-life 2.79 to 8.5 days), and is not bound tightly to the soil (Koc = 1; US EPA, 2012) following application. Based on these factors, including minimal toxicity, low application rates, and rapid dissipation from the environment, the Agency does not anticipate any adverse effects as a result of the labeled EP applications of 1-ACC.

3.2.1 Terrestrial Animals and Plants

Birds (850.2100 & 850.2200):
Avian acute oral toxicity and avian dietary toxicity data requirements were satisfied by acceptable guideline studies. 1-ACC is moderately toxic to birds when exposed to a single dose. The acute LD_{50} = 343 mg a.i./kg. The NOAEL was 91 mg a.i//kg-bw. In the avian dietary toxicity study, 1-ACC is identified as slightly toxic to birds. The acute dietary LC_{50} was determined to be 5106 ppm a.i. (1517 mg/kg-bw). The No Observed Effect Concentration

(NOEC) was 562 ppm a.i. (167 mg a.i./kg-bw/d) and the No Observed Effect Limit (NOEL) (body wgt/food consumption) = 56.2 ppm a.i. (MRIDs 50826012 & 13)

Nontarget Insects Testing (880.4350):

A guideline nontarget honeybee acute contact toxicity study indicates that 1-ACC is practically non-toxic to honeybees and other nontarget insects. The 48-hour LD_{50} was > 125 µg/bee via contact exposure and the LD_{50} was > 263.1 µg/bee via oral exposure. (MRID 50826017)

Nontarget Plants (850.4100 & 850.4150):

Ten species of terrestrial plants were tested. A NOEC) > 600 g a.i./ha was reported. For bean, the dry weight NOEC = 2.3 g a.i. and the chlorosis/necrosis NOEC = 37 g a.i./ha. For tomato, the shoot length NOEC = 37 g a.i./ha and Lowest Observed Effect Concentration (LOEC) = 37 g a.i./ha; and the dry weight NOEC = 0.6 g a.i./ha and LOEC = 2.3 g a.i./ha. (MRIDs 50826015 and 50826016)

All species, except for tomato, the NOEC > 600 g a.i./ha in cabbage (*Brassica oleracea*), radish (*Raphanus sativus*), ryegrass (*Lolium perenne*), lettuce (*Lactuca sativa*), onion (*Allium cepa*), corn (*Zea mays*), soybean (*Glycine max*), wheat (*Triticum aestivum*). For tomato (*L. esculentum*), the shoot length NOEC = 37 g a.i./ha and LOEC = 37 g a.i./ha; and the dry weight NOEC = 0.6 g a.i./ha and the LOEC = 2.3 g a.i./ha. Survival of all plant species was unaffected at > 600 g a.i./ha (equivalent to 0.535 lbs a.i./A) in both studies. Tomato appeared to be the most sensitive plant in both studies, but survival was unaffected and it unknown if the observed effects would have been relieved if the plants had been grown to maturity. It is noted that the highest single application rate on the EP product label is 0.504 lbs a.i./A (on stone fruit), which is below the highest rate tested at which no effects on survival were observed.

3.2.2 Aquatic Organisms

Freshwater Fish and Aquatic Invertebrates (850.1075 & 850.1010):

1-ACC is practically non-toxic to invertebrate and freshwater fish. The 24 and 48-hr LC_{50} >105 mg a.i./L; NOEC = 105 mg a.i./L and 96-hr LC_{50} >117 mg a.i./L; NOEC = 117 mg a.i./L, respectively. (MRIDs 50826010 and 50960901)

3.2.3 Endangered Species Conclusion

1-ACC is minimally non-toxic to birds, mammals, and bees, is applied at low application rates, rapidly dissipates from the environment, and is not expected to pose a risk or cause any adverse effects to nontarget organisms as a result of its use. As a result of the overall low toxicity profile and limited exposure from the use, the EPA is able to the make a “no effect” determination for direct and indirect effects to federally listed threatened and endangeredand their designated critical habitats.

The database of studies required to support the hazard assessment to the environment is complete. For more information on the environmental hazard assessment of 1-ACC, please see

the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2019-0516" at http://www.regulations.gov).

4. 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. Beyond the benefits of using a plant growth regulator, there is a demand for a pesticide with a toxicity profile like 1-ACC that is able to regulate fruit thinning and enhanced bloom. To that end, the registration of 1-ACC would be a valuable addition to the pesticide tool kit as a "safer pesticide" to address these increasing demands and can be a viable alternative to conventional pesticides such as Carbaryl.

5. Public Comments

On June 19, 2020 , EPA announced receipt of two applications in the *Federal Register* to register an MP, ACC Technical Powder Plant Growth Regulator (EPA File Symbol 73049-LRA) and an EP, VBC-30445, Plant growth Regulator Liquid Concentrate (EPA File Symbol 73049-LRT, containing the new biochemical active ingredient 1-ACC (85 FR 37096). No substantive comments were received in response to this Notice of Receipt. On 3/17/21, the EP product name was changed to Accede Plant Growth Regulator Liquid Concentrate.

On December 23, 2020 (85 FR 83889), EPA published a Notice of Filing (NOF) that announced requests to establish an exemption from the requirement of a tolerance in 40 CFR part 180 for residues of the plant regulator 1-Aminocyclopropanecarboxylic acid (1-ACC) in or on apple and stone fruit. No comments were received in response to this Notice of Filing.

Because the pesticide products contain 1-ACC, which is a new active ingredient, EPA opened a 15-day public comment period on May 4, 2021. The comment period closed May 19, 2021. EPA took this action in accordance with a policy, first implemented in October 2009, designed to provide a more meaningful opportunity for the publicto participate in major registration actions. No comments were received as a part of that process.

6. Regulatory Decision

The 1-ACC database is considered to be complete with regard to the human health and environmental fate data requirements and supports a pesticidal food use. In considering the hazard assessment to human health and the environment, the Agency concludes that 1-ACC meets the regulatory standard under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Therefore, the EPA is proposing to grant the unconditional registration of 1-ACC as a new active ingredient with food uses (apples and stone fruit) under Section 3(c)(5) of FIFRA.

Two products are being registered: A Technical Grade Active Ingredient

(TGAI)/Manufacturing-use product (MP), ACC Technical Powder (EPA File Symbol 73049-LRA), and an End-Use Product (EP), Accede Plant Growth Regulator Liquid Concentrate (EPA File Symbol 73049-LRT) containing the new active ingredient 1-ACC.

The risk assessments and labels supporting this decision can be found in the associated regulatorydocket (search for "EPA-HQ-OPP-2019-0516" at www.regulations.gov).