New Use Decision for the Active Ingredient

Thymol

A nematicide & fungicide for use on fruiting vegetables, cucurbits & grapevine

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Approved by:

Digitally signed by EDWARD MESSINA
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Ed Messina, Esq.,
Director, Office of Pesticide Programs
Office of Chemical Safety & Pollution Prevention
U.S. Environmental Protection Agency

1. Introduction

This document announces that the Environmental Protection Agency (EPA) has completed its initial evaluation of a new food use for (5-methyl-2-isopropyl-1-phenol), herein referred to as thymol, and has concluded that it meets the regulatory and safety standards under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) to prevent and control grey mold on grapevines and nematodes on agricultural use sites. EPA is seeking public comment on this new use decision.

Thymol is a federally registered pesticide active ingredient and was classified as a biochemical in 1997 by the Biochemical Classification Committee. Its current use patterns include: fungistat, medical disinfectant, tuberculocide, and virucide. It is a constituent of oil of thyme, a naturally occurring mixture of compounds in the plant, *Thymus vulgaris* (thyme). It is considerably volatile and dissipates rapidly in water and in soil under aerobic conditions. Thymol has a long history of safe use as a direct food additive (21 CFR 172.515) and is commonly consumed as it is used in ice cream, non-alcoholic beverages, candy, baked goods, chewing gum, lime blossom honey and pesto sauce. The source plant (thyme), from which thymol is extracted is acknowledged by FDA as generally recognized as safe (GRAS) (21 CFR 182.10 and 21 CFR 182.20). Uses for thymol are supported by 40 CR 180.1240, which currently provides for an exemption from the requirement of a tolerance for residues of thymol in or on food commodities when applied/used in/on public eating places, dairy processing equipment, and/or food processing equipment and utensils. The Agency conducted its most recent assessment of thymol through registration review and in March 2020, issued an Interim Registration Review Decision (ID).

After reviewing all submitted data, EPA concluded that there is reasonable certainty of no harm from residues of thymol, and that its use on all food commodities will cause no unreasonable adverse effects to human health or the environment. Therefore, the Agency is proposing to grant the registration of the manufacturing-use product (MP)/technical grade of the active ingredient (TGAI), Thymol Technical (EPA File Symbol 92331-E) under section 3(c)(5) of FIFRA to allow its use in the formulation of thymol end-use products (Eps) Cedroz (EPA File Symbol 92331-U) to control nematodes on fruiting vegetables and cucurbits and Mevalone (EPA File Symbol 92331-R) to control grey mold (*Botrytis cinerea*) on grapevine, respectively. In support of this action, the Agency is publishing a final rule to amend the regulation at 40 CFR 180.1240 paragraph (a) by adding a tolerance exemption for residues of thymol on all food commodities. This tolerance exemption will replace the time-limited tolerance exemption for residues of thymol on honey and honeycomb which expired on June 30th, 2007.

2. Background

On April 5, 2018, EPA received applications from Eden Research, PLC for the registration of three pesticide products (one manufacturing-use product (MP)/technical grade of the active ingredient (TGAI), Thymol Technical (EPA File Symbol 92331-E), and two end-use products

Cedroz (EPA File Symbol 92331-U) and Mevalone (EPA File Symbol 92331-R**)** containing the biochemical active ingredient thymol, and a petition to amend 40 CFR part 180.1240 to add an exemption from the requirement of a tolerance for residues of thymol in or on all raw agricultural commodities or processed foods. Eden Research, PLC provided data, waiver requests and information from the open scientific literature to address product chemistry and human health and ecological toxicity data requirements.

In the Federal Register of September 12, 2018, EPA published a Notice of Receipt (NOR) that announced receipt of three new product applications containing the active ingredient, thymol. No comments were received in response to the NOR. In the Federal Register of September 12, 2018, 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 thymol in or on all raw agricultural commodities or processed foods. No significant comments were received in response to the NOF.

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 ofuse 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 occurfrom 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

Adequate mammalian toxicology data/information are available to support the food-use registration of thymol on all food commodities. All toxicology data requirements for thymol have been satisfied and an updated dietary risk assessment is available at http://www.regulations.gov (search for "EPA-HQ- OPP-2018-0521"). In summary, based upon the results of the acute toxicity studies available, thymol is of low acute oral toxicity (Toxicity Category III), inhalation toxicity (Toxicity Category IV) and dermal toxicity (Toxicity Category III). It is corrosive to the skin and eye (Toxicity Category I) and may or may not be a dermal sensitizer (inconclusive). The signal word, "DANGER" will be used on the label.

In conducting its hazard assessment for thymol, EPA relied on data from the open scientific literature which includes a combined repeated dose oral toxicity study with the reproduction/developmental toxicity screening test, several genotoxicity studies, and a six-month inhalation study. Based on the data, no adverse effects were seen at the highest dose tested of 200 mg/kg/day. For guideline studies, EPA generally recommends testing at a limit dose of 1000 mg/kg/day. However, based on the data reviewed from the open literature along with a body of knowledge regarding thymol such as its low toxicity; rapid degradation into the environment; and natural occurrence and widespread use in foods that are commonly consumed and a part of the human diet, EPA would not expect to see adverse effects at higher doses.

In the case of subchronic oral, dermal, inhalation and prenatal developmental toxicity, data waivers were granted based on a weight of the evidence approach (WOE) due to the reasons listed below. Further, thymol is not genotoxic and there is no evidence of chromosome aberrations over background-or induced mutant colonies over background with and without S9 activation.

90-day inhalation toxicity

EPA granted a waiver of this data requirement due to: 1) a 6-month inhalation toxicity study from the literature that showed no adverse effects, 2) thymol's physical/chemical properties, 3) low acute inhalation toxicity, 4) natural occurrence and long history of thymol in human diet, 5) thymol is rapidly biodegradable, 6) it listed as food additive by FDA, 7) thyme and thyme oil are recognized as GRAS, and 8) it is currently used in human medicine for treatment of colds and upper respiratory tract infections (EPA, 2021).

90-day oral toxicity

EPA granted a waiver of this data requirement due to 1) there are no adverse effects applicable to humans, 2) thymol's overall low oral toxicity, 3) its natural occurrence and long history of thymol in human diet, 4) rapidly biodegradable, 5) thymol listed as food additive by FDA, and 6) thyme and thyme oil are recognized as GRAS (EPA, 2021).

90-day dermal toxicity

EPA granted a waiver of this data requirement due to 1) thymol is a severe dermal irritant which

would make it difficult to test for a subchronic study, 2) there are no adverse effects applicable to humans, 3) thymol has a long history of thymol in human diet, rapidly biodegradable, 4) thymol listed as food additive by FDA, and 5) thyme and thyme oil recognized as GRAS (EPA, 2021).

Developmental Toxicity

EPA granted a waiver of this data requirements due to 1) there are no adverse effects applicable to humans from thymol, 2) overall low oral toxicity, 3) natural occurrence and long history of thymol in human diet, 4) rapidly biodegradable, and 5) thyme and thyme oil recognized as GRAS (EPA, 2021).

3.1.2. Dietary and Occupation Exposure and Risks

Dietary and Drinking Water Exposure and Risk Characterization: A quantitative dietary (food & drinking water) exposure and risk assessment has not been conducted at this time because risk attributed to dietary exposure to residues of thymol in food is not expected to be a concern based on the following: (1) low toxicity profile and (2) thymol is naturally occurring and has long been part of the normal human diet.

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

Occupational Exposure and Risk Characterization: Occupational handler exposure and post-application exposure to thymol from the use of the EPs may occur, but the risk is not expected to be a concern based on low toxicity of the AIs, ready biodegradation in the environment and Personal Protective Equipment (PPE) requirements due to the potential corrosivity of thymol (long-sleeved shirt and long pants, waterproof or chemical-resistant gloves, shoes plus socks, and goggles, face shield, or safety glasses). Therefore, a qualitative risk assessment rather than a quantitative risk assessment would be most appropriate for these end-use products. No risks of concern have been identified.

3.1.3. Cumulative Risk

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as thymol does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that thymol has a common mechanism of toxicity with other substances.

3.1.4. Human Health Conclusions

EPA concludes that the use of thymol will not result in unreasonable adverse effects tohumans or the environment 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 thymol. EPA does not expect dietary (food and drinking water) or other non-occupational risks of concern

from use of thymol as an active ingredient in products for food use. Data demonstrated that thymol is of low toxicity through all routes of exposure and no toxicological end points have been identified.

Any potential occupational exposures to individuals handling thymol are not expected to be of concern and would be further reduced by use of the PPE required on the label.

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 thymol please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0521" 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 thiscombined 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 bedone 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 thymol, all nontarget toxicology data requirements have been satisfied per 40 CFR 158.2060 through rationales, data from publicly available scientific literature, and guideline studies.

Adequate non-target toxicology data/information submitted and reviewed by the Agency satisfies the non-target toxicology data requirements for thymol (MP). A combination of guideline studies and scientifically supported rationales demonstrate that thymol is practically non-toxic to birds, not expected to have adverse effects on non-target insects, mammals and is slightly toxic to freshwater fish (rainbow trout) and moderately toxic to freshwater aquatic invertebrate (*Daphnia*). Furthermore, the data indicate that thymol has phytotoxic properties to plants. To allay any concerns regarding phytotoxicity, labeling mitigation measures such as a buffer zone and prohibition of aerial applications will be applied to limit potential exposure via spray drift. Therefore, based on the minimal toxicity, low application rates, high volatility, rapid dissipation from the environment, and the incorporation of mitigation measures, the Agency does not anticipate any adverse effects as a result of the labeled EP applications of thymol.

3.2.1 Terrestrial Animals and Plants

Birds and Mammalian Species (850.2100 & 850.2200 and Nontarget Insects Testing (880.4350):
A quantitative risk assessment was not conducted for birds, mammals, and non-target insects due to lack of effects and low exposure of the pesticide. Thymol is regularly incorporated in avian feed without adverse effects, is classified as practically non-toxic to birds with an acute oral LD50 of EP > 10,000 mg/kg. Tests with mammals also do not show adverse effects. Minimal exposure is expected due to thymol being readily biodegradable and volatile which would result in transitory exposure. Moreover, thymol naturally occurs in at least 163 plant species and thus is not expected to adversely affect non-target insects.

Nontarget Plants (850.4100 & 850.4150):

Risk to plants is based on both the understood toxicity of thymol to plants and the anticipated exposure of plants off the treated field.

Modeling with Terrplant v1.2.2, based on the toxicity of thymol, indicated that non-listed plants may be at risk if exposed to Cedroz at the maximum application rate of 0.34 lb a.i./A. Since there is no drift from the proposed drip irrigation application method for Cedroz, ground application was assumed in the model to generate the most conservative risk scenario. Modeling a ground application, that overestimates off-site exposure compared to drip irrigation, resulted in risk quotients (RQs) that ranged from <0.1 to 1.02 for non-listed plants. These values slightly exceeded the level of concern (LOC) of 1.0, where risk cannot be discounted. While RQs were similar to the LOC, the assumed exposure in the model from ground applications overestimates exposure. Furthermore, drip irrigation uses are not parameterized in the model and are not expected to result in drift off the treated field.

Additionally, exposure is expected to be lower than modeled because thymol is volatile and readily biodegradable in nature. This is supported by a study conducted to mimic application of mixed geraniol/eugenol/thymol in a dry system and dry/wet system. In the study, thymol was below the limit of detection in the gaseous phase after 73 hours in the dry system, and below the limit of detection after 96 hours in the wet/dry system. The rapid dissipation of thymol on the field due to its volatility suggests that thymol will not be present in quantities sufficient to run off the treated field. Therefore, due to the lack of drift off the treated field and thymol's high volatility, risks of concern to listed and non-listed plants is not expected off the treated field from the proposed applications of Cedroz.

Modeling based on the toxicity of thymol from maximum applications of Mevalone (0.237 lb a.i./A) indicated that non-listed plants off the treated field were not at risk. While application via hand-held sprayer is anticipated to be minimal and not result in off-field exposure, the proposed boom and aerial spray application methods may result in off-site drift for Mevalone. However, because the toxicity of thymol was not sufficient to predict adverse impacts to non-listed plants at concentrations that would drift off the treated field, risk to non-listed plants off the treated field is also not expected from ground and aerial spray applications of Mevalone at the maximum application rates on the proposed labels.

A full Endangered Species Assessment (ESA) was not conducted for the new uses of thymol. However, in conducting the risk analysis to non-listed species, modeling information suggests that there are potential risks to listed species from some of the proposed methods of application for Mevalone. The Agency arrived at this conclusion using a no observed adverse effect concentration (NOAEC) of 0.034 lb a.i./A and identified potential risks of concern to listed plant species off the treated field from both aerial and ground applications. As a result, the Agency is prohibiting aerial application on the Mevalone label. Boom spray/ground applications are permitted; however, the Agency is requiring a droplet size restriction on the Mevalone label to a medium or coarser droplet. Due to these mitigations and thymol's high volatility, the Agency concludes that risks of concern to listed plants off the treated field is not expected for the proposed uses of Mevalone.

3.2.2. Aquatic Organisms

Freshwater Fish and Aquatic Invertebrates (850.1075 & 850.1010):

Thymol is moderately toxic to invertebrate and freshwater fish. In a conservative approach, worst case aquatic Estimated Environmental Concentrations (EECs) were calculated based on direct application to a 6-inch water column for standard farm pond used in EPA models using the maximum application rate for each product, even though neither product is intended for application to water. This resulted in water column concentrations between 55 and 402 times less than the ecotoxicity endpoints for fish and invertebrates. The highest Risk Quotient (RQ) that would result from a worst-case exposure scenario is 0.02, which is well below the listed species Level of Concern (LOC) of 0.05 and the non-listed species LOC of 0.5.

Since the thymol manufacturing use product is intended to allow for formulation into end-use products that will be applied to grapevines, actual aquatic EECs would be dependent on spray drift and runoff into nearby waterbodies and would result in aquatic concentrations substantially less than calculated for direct application to water. Thus, the RQs are anticipated to be less than 0.02 and risk to both non-listed and listed aquatic organisms from use of the end-use product is not anticipated. Aquatic exposure will also be additionally limited because applications via aerial equipment will be prohibited and ground application with boom sprayers will restrict droplet size to medium or coarse droplets that will reduce drift off the treated field.

The database of studies required to support the hazard assessment to the environment is complete. For more information on the environmental hazard assessment of thymol, please see the supporting documentation provided in the associated regulatory docket (search for "EPA-HQ-OPP-2018-0521" at http://www.regulations.gov).

4. Benefits

Thymol provides control of a variety of fungal and nematode pests with an overall toxicity profile that is more favorable than that of traditional conventional pesticides for the same use patterns. Moreover, its long history of safe use in foods and its rapid biodegradability of in the environment is another factor that contributes to the attractiveness of thymol as a pesticide. To that end, the new food use registration of thymol would be a valuable addition to the pesticide

tool kit as a viable alternative to conventional broad-spectrum fungicides and nematicides.

5. Public Comments

On September 12, 2018, EPA announced receipt of two applications in the *Federal Register* to register, a manufacturing-use product (MP)/technical grade of the active ingredient (TGAI), Thymol Technical (EPA File Symbol 92331-E); and two end-use products (EP), Cedroz (EPA File Symbol 92331-U) and Mevalone (EPA File Symbol 92331-R), containing the active ingredient thymol. No significant comments were received in response to this Notice of Receipt.

On September 12, 2018, 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 thymol in or on all agricultural commodities. No significant comments were received in response to this Notice of Filing.

6. Regulatory Decision

The thymol 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 thymol meets the regulatory standard under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Therefore, the EPA is proposing to grant the unconditional registration of thymol under Section 3(c)(5) of FIFRA to add food use sites and to amend the tolerance exemption at 40 CFR 180. 1240 to cover to residues of thymol in or on all food commodities. Three products are proposed to be registered: One manufacturing-use product (MP)/technical grade of the active ingredient (TGAI), Thymol Technical (EPA File Symbol 92331-E), and two end-use products (EP), Cedroz (EPA File Symbol 92331-U) to control nematodes on fruiting vegetables & cucurbits and Mevalone (EPA File Symbol 92331-R), to control grey mold **(***Botrytis cinerea***)** on grapevine.

The risk assessments supporting this decision can be found in the associated regulatory docket regulatory docket (search for “EPA-HQ-OPP-2018-0522” at http://www.regulations.gov).

References Cited

EPA, 2021. Summary of Hazard and Science Policy Council (HASPOC) Meeting on April 29, 2021: Recommendations on the Appropriateness of a Qualitative Dietary and Occupational Risk Assessment, and the Need for a 90-day Oral Toxicity, 90-Day Dermal Toxicity, 90-day Inhalation Toxicity, and Prenatal Developmental Toxicity Study. Memorandum from Victoria Kurker to Sadaf Shaukat and Shannon Borges. 04/29/2021.