Complex Polymeric Polyhydroxy Acids

PC Code 078503

Final Work Plan
Case Number 6320

Approved by: Le, Madison Digitally signed by Le, Madison Date: 2024.01.30 15:51:09 -05'00'

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Table of Contents

I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) Final Work Plan (FWP) for Complex Polymeric Polyhydroxy Acids (Case 6320) (hereafter referred to as CPPA) and is being issued pursuant to 40 CFR § 155.50. This document explains what EPA's Office of Pesticide Programs (OPP) knows about CPPA, highlights anticipated data and assessment needs, identifies types of information that would be especially useful to the Agency in conducting the review, and provides an anticipated timeline for completing the registration review process for CPPA. Additional information on CPPA can be found in the Agency's public docket (EPA-HQ-OPP-2022-0793) at www.regulations.gov.

A registration review decision is the Agency's determination of whether a pesticide meets, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, which mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States generally must be registered by the Agency based on scientific data showing that they will not cause unreasonable adverse effects to human health or to the environment when used as directed on product labeling. The registration review program is intended to ensure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to ensure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at www.epa.gov/pesticide-reevaluation.

In 2006, the Agency implemented the registration review program pursuant to FIFRA § 3(g). The Agency will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review are provided in 40 CFR part 155, subpart C. The public phase of registration review begins when the initial docket is opened for the case. The docket is the Agency's opportunity to inform the public what it knows about CPPA and what additional risk analyses and data or information it believes are needed to make a registration review decision on CPPA.

This document is organized into five sections: the *Introduction*, which includes this summary and CPPA case overview; *Updates Since the PWP was Issued*, which describes any notable use site changes since Preliminary Work Plan (PWP) issuance, *Use Information*, which describes how and why CPPA is used and summarizes data on its use, and associated pesticide products; *Scientific Assessments*, which summarizes the Agency's risk assessments, any revisions, risk conclusions, and any anticipated data needs that will help the Agency's decision-making process for CPPA; and, lastly, the *Next Steps* and *Timeline* which provides an anticipated timeline for the registration review process for CPPA.

Complex Polymeric Polyhydroxy Acids Registration Review Case Overview

Pursuant to 40 CFR § 155.50, the Agency initiates a pesticide's registration review by establishing a docket for registration review of CPPA (Case 6320) and opening it for public review.

The publication of the PWP marked the beginning of the current cycle of registration review for CPPA, with the opening of public docket EPA-HQ-OPP-2022-0793, which is available at www.regulations.gov. The following list highlights significant events that have occurred during the current cycle of registration review for this case:

- July 25, 2023 – The Agency published the *Complex Polymeric Polyhydroxy Acids Preliminary Work Plan* for a 60-day public comment period. The public comment period closed on September 25, 2023. The Agency received one public comment in support of CPPA's continued

use as an active ingredient in registered pesticide products. This comment was placed under the incorrect docket, however, the Agency is currently working to fix this.

- January 2024 – The Agency is now publishing the *Complex Polymeric Polyhydroxy Acids Final Work Plan.*

II. Updates Since the Preliminary Work Plan was Issued

There are no changes to the anticipated data needs, expected risk assessments, or registration review timeline since the PWP was issued.

III. Use Information

The first pesticide product containing CPPA as an active ingredient was registered by the Agency in 2013. Currently, there are nine registered products containing CPPA, one manufacturing-use product and eight end-use products, ranging from 0.018%-0.9% active ingredient.

CPPA is derived from natural organic matter (NOM) ubiquitously found in soils and ground and surface waters. NOM is formed resulting from the decomposition of plants, animals, and microbial materials in soil and water and is comprised of lignins, tannins, humic acids, and fulvic acids.[1] CPPA contains a complex mixture of these naturally occurring substances and is characterized specific to its intended use. CPPA is obtained by collecting water that has leached through forest soil and concentrating the organic substances found in the NOM via a manufacturing process. Products containing CPPA are intended for use as plant growth regulators, nematicides, fungicides, and insecticides for use on fields and/or in greenhouses on vegetables, fruits, nuts, vine crops, field crops, ornamentals, and turf. Currently all products are labeled for pre-harvest use only. CPPA elicit auxin-like responses in plants and, when applied to the soil or seeds, increase antioxidant activity in plants, reduce leaching and loss of nitrogen, buffer the soil solution to improve nutrient uptake and efficiency, and promote beneficial soil microbe activity (U.S. EPA, 2012a, 2012b, 2020). The exact modes of action for the nematicide, fungicide, and insecticide uses are unknown.

Table 1. CPPA Use Information

Ingredient Name	Complex Polymeric Polyhydroxy Acids
PC Code	078503
CAS Number	N/A
Pesticide Classification	Plant growth regulator, fungicide, nematicide, insecticide
Use Site Locations	Greenhouse indoor, agricultural outdoor
Application Types	Broadcast
No. of Registrations	9 FIFRA Section 3 products[2]
Physical Forms	Granule, liquid

IV. Scientific Assessments

A summary of the Agency's human health and ecological risk assessments for CPPA is presented below. Refer to the Appendices for a listing of product analysis, human health assessment, and nontarget organism data that support the scientific assessments for this registration review. For further information

[1] U.S. EPA, 2012a. CPPA is known to be made up of thousands of compounds. While exact percentages vary depending on chemical reactions occurring within the soil used to make CPPA, approximately 94% of CPPA are lignins (50%), tannins (30%), and condensed aromatics (including humic and fulvic acid) (14%).

[2] FIFRA labels can be obtained from the Pesticide Product Label System (ordspub.epa.gov/ords/pesticides/f?p=PPLS:1)

on the human health and environmental risk assessments, including a summary of data and literature search findings, please see Appendices B and C.

A. Human Health Assessment

Hazard Characterization

The toxicological database is considered complete for characterizing hazard and assessing risk from the active ingredient in this case. CPPA can be classified as toxicity category IV for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation and primary dermal irritation. CPPA is not a dermal sensitizer according to the available data (U.S. EPA, 2012a). Subchronic toxicity studies on CPPA itself are not available. The available studies in the toxicity database for CPPA were conducted using humic, fulvic, and tannic acids, which are acceptable analogs since they comprise the majority of CPPA's components.[3] Results from a 90-day (non-guideline) oral study on fulvic and humic acid demonstrate a lack of concern to human health as the no observed adverse effect level (NOAEL) is 2,000 mg/kg/day (highest dose tested), which is two times the recommended limit dose for this data requirement. Adequate rationales to address the 90-day dermal and 90-day inhalation toxicity data requirements are on file and include the following considerations: natural occurrence, no adverse effects noted from exposure to fulvic and humic acid in a 90-day oral toxicity study up to 2,000 mg/kg/day, and the mitigation from personal protective equipment (PPE) when worn by applicators and handlers. No maternal or developmental effects were noted up to the highest dose tested in either of the prenatal developmental (non-guideline) studies with humic or tannic acid. An Ames test and in vitro mammalian cell assay (non-guideline) performed with a humic and fulvic acid preparation were negative for genotoxicity. Currently, the Agency does not anticipate the need for additional studies for the CPPA registration review case. All data requirements, per 40 CFR §158.2050, have been fulfilled for CPPA.

Dietary Exposure and Risk Characterization

Human exposure to CPPA may occur via dietary exposure to treated commodities. A qualitative risk assessment was conducted for the chemical to assess potential risks (if any) from dietary exposure. Although dietary and drinking water exposure to humans may occur, the Agency has determined that there is reasonable certainty of no harm to humans when exposed to residues of the active ingredient from pesticidal use when label instructions are followed. This conclusion is based on the following: 1) available toxicology data and information indicate that the active ingredient is of low toxicity and is not likely to be a developmental toxicant, a mutagen, or toxic via repeated oral exposure; 2) humans are already exposed to CPPA in the diet as CPPA is derived from NOM, which is ubiquitous in soil and water; 3) CPPA is volatile, is applied at low application rates (approximately 0.0064 lbs ai/acre), and is not directly applied to water; and 4) maximum expected estimated environmental concentrations (EEC's) following application of CPPA according to the maximum proposed seasonal application rate are expected to be < 2 ppm on all terrestrial matrices and < 0.0004 ppm in aquatic matrices (U.S. EPA, 2012a). Based on the low toxicity and ubiquity in the environment, no dietary risks of concern have been identified.

Food Tolerances

Considering the available toxicity and exposure data discussed above, EPA concluded that there was a reasonable certainty that no harm would result to the U.S. population from aggregate exposure to residues of CPPA when used according to label directions. Therefore, EPA established a tolerance exemption for residues of the active ingredient. The current tolerance exemption is stated as follows:

[3] Preliminary analysis MRID 48427402

40 CFR §180.1321 Complex Polymeric Polyhydroxy Acids (CPPA); exemption from the requirement of a tolerance.

An exemption from the requirement of a tolerance is established for residues of the pesticide complex polymeric polyhydroxy acids (CPPA) in or on all food commodities, when used in accordance with label directions and good agricultural practices. [87 FR 29050 May 12, 2022]

Residential and Non-Occupational Exposure and Risk Characterization

Exposure to CPPA is not expected in residential and non-occupational settings, as the end-use products containing this active ingredient are intended for use in commercial settings only. Significant spray drift from the use of products containing CPPA is not anticipated as no aerial equipment is used. Although minimal spray drift may occur as ground spray equipment may be used to apply CPPA products, no unreasonable adverse effects to the human population will result from this exposure when label directions are followed.

Occupational Exposure and Risk Characterization

Significant occupational exposure is not expected when CPPA is used according to label instructions with the appropriate PPE. Although some dermal exposure may occur to applicators/handlers, all product labels require long sleeve shirt and long pants, shoes and socks, waterproof gloves, and protective eyewear that would mitigate the exposure. Inhalation exposure is also possible with spraying equipment; however, the risk is considered minimal as CPPA is a naturally occurring, ubiquitous substance in water and soil, and no systemic toxicity has been identified in the toxicity database. Post-application inhalation exposure is expected to be minimal based on a relatively low application (approximately 0.0064 lbs ai/acre). Post-application dermal exposure is expected to be low as much of the substance would have been volatilized into the air before someone would come in contact with a surface with a pesticidal residue. More importantly, based on the active ingredient's low toxicity and ubiquity in the environment, no occupational risks of concern have been identified.

Human Incidents

A search of the OPP Incident Data System conducted on May 8, 2023, revealed no reported incidents associated with CPPA. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Environmental Risk Assessment

All nontarget organism and environmental fate data necessary to meet the standard for CPPA were satisfied through studies that were cited from open literature, with the exception of the honeybee study, the laboratory study referenced for wild mammals, and rationale for nontarget plants. The Agency is currently working with its federal partners and other stakeholders to improve the consultation process for listed species and their designated critical habitats under the Endangered Species Act (ESA). The Agency has not yet fully evaluated CPPA's effects to listed species. However, EPA will complete its listed-species assessment and any necessary consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services) before completing the CPPA registration review case. See the Endangered Species Assessment section below for more details. As such, only potential risks for nontarget species generally are described below.

Humic acids, fulvic acids, and tannins are ubiquitous in the environment and nontarget organisms are regularly exposed to them. CPPA can comprise 0.74% to 9.9% of mineral soils, tannins are widely present in plants, aquatic plants are continually exposed to CPPA, and when plants decompose large

amounts of CPPA is released into soil and aquatic habitats (U.S. EPA, 2012a and 2012b). The estimated environmental concentration (EEC) is less than 2 parts per million (ppm) based on the Terrestrial Residue Exposure model (T-REX) for terrestrial nontarget organisms and it is based on the application rate of 0.0064 lbs active ingredient/acre (U.S. EPA, 2012a, 2012b, and 2022). CPPA is naturally present in the environment and has been measured at between 7400 ppm and 99,000 ppm (0.74-9.9%) in mineral soils (U.S. EPA, 2012b and 2022). The activity of CPPA-like substances on plants depends on several factors including the dosage, molecular size, origin, and hydrophobicity and aromaticity of the molecular substances (Nardi et al., 2021). The activity for aquatic plants is considered to be between 0.3 ppm and 3 ppm (U.S. EPA, 2012a), while for terrestrial plants, like corn, the activity varies between 0.01 ppm to 100 ppm (Cannellas et al., 2020). These values are higher than the amount expected in the environment after application at the highest rate (U.S. EPA, 2012a). Additionally, exposure to CPPA for aquatic plants is expected to be less than 0.0004 ppm, which is also below natural exposure levels.

Nontarget terrestrial plants were addressed via rationale and lack of anticipated adverse effects to plants at the proposed application rates (U.S. EPA, 2012a). An acute oral toxicity study for honeybees was submitted which showed no effects. The provided study and rationales demonstrate no adverse effects will occur for any nontarget organisms. The avian oral toxicity study using red winged blackbirds exposed to gallic acid reported a lethal dose $(LD)_{50}$ >100 mg/kg but did not use high enough concentrations to achieve a definitive endpoint. The dietary studies on avian taxa suggest that the compounds are practically non-toxic to birds. Slight toxicity was reported for one of the five fish studies when exposed to extract of Norway Spruce bark, which had a lethal concentration $(LC)_{50}$ of 50 ppm, classifying it as slightly toxic while four additional fish studies had LC_{50}'s that were classified as practically non-toxic. No toxicity was reported for aquatic invertebrates and honeybees. The risk quotients (RQs) are well below any level of concern (LOC) for nontarget organisms and are all less than 0.01. Additionally, in the most recent ecological risk assessment it was concluded that no adverse effects will occur for nontarget organisms from the use of pesticide products containing CPPA when applied in accordance with approved labeling (U.S. EPA, 2022). Because CPPA is a plant growth regulator, positive effects may occur to listed plants if exposed similar to the positive effects anticipated on the treated crop. An endangered species assessment will be conducted to examine the exposure of CPPA on threatened and endangered species and their designated critical habitat and if any positive effects are anticipated as part of registration review, which will include the potential positive effects on nontarget plants.

Ecological Incidents

A search of OPP's Incident Data System conducted on May 8, 2023, revealed no reported incidents associated with CPPA. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

Endangered Species Assessment

This section provides general background about the Agency's assessment of the effects of pesticides on listed species and designated critical habitats under the Endangered Species Act (ESA).

Developing Approaches for ESA Assessments and Consultation for FIFRA Actions

In 2015, EPA, along with the Services—the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) (referred to as "the agencies") released their joint Interim Approaches[4] for assessing the effects of pesticides to

[4] www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.

listed species. The agencies jointly developed these Interim Approaches in response to the 2013 National Academy of Sciences' recommendations that discussed specific scientific and technical issues related to the development of assessments of pesticides' effects to listed species. Since that time, the agencies have been continuing to work to improve the approaches for assessing effects to listed species. After receiving input from the Services and USDA on proposed revisions to the interim method and after consideration of public comments received, EPA released an updated *Revised Method for National Level Listed Species Biological Evaluations of Conventional Pesticides* ("Revised Method") in March 2020.[5]

The agencies also continue to work collaboratively through a FIFRA Interagency Working Group (IWG). The IWG was created under the 2018 Farm Bill to recommend improvements to the ESA section 7 consultation process for FIFRA actions and to increase opportunities for stakeholder input. This group is led by EPA and includes representatives from NMFS, FWS, USDA, and the Council on Environmental Quality (CEQ). The IWG outlines its recommendations and progress on implementing those recommendations in reports to Congress.[6]

Consultation on Chemicals in Registration Review

EPA initially conducted biological evaluations (BEs) using the interim method on three pilot chemicals representing the first nationwide pesticide consultations (final pilot BEs for chlorpyrifos, malathion, and diazinon were completed in January 2017). These initial pilot consultations were envisioned as the start of an iterative process. Later that year, NMFS issued a final biological opinion for these three pesticides. In 2019, EPA requested to reinitiate formal consultation with NMFS on malathion, chlorpyrifos and diazinon to consider new information that was not available when NMFS issued its 2017 biological opinion. EPA received a final malathion biological opinion[7] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[8] The Agency plans to implement both biological opinions according to the 18-month timeframes specified in the biological opinions.

In 2020, EPA released draft BEs for the first two chemicals conducted using the 2020 Revised Method—carbaryl and methomyl. Subsequently, EPA has used the Revised Method to complete final BEs for carbaryl, methomyl, atrazine, simazine, glyphosate, clothianidin, imidacloprid, and thiamethoxam. EPA is currently in consultation with the Services on these active ingredients.

EPA's New Actives Policy and the 2022 Workplan

In January 2022, EPA announced a policy[9] to evaluate potential effects of new conventional pesticide active ingredients to listed species and their designated critical habitat and initiate consultation with the Services, as appropriate, before registering these new pesticides. Before the Agency registers new uses of pesticides for use on pesticide-tolerant crops, EPA will also continue to make effects determinations. If these determinations are likely to adversely affect determinations, the Agency will not register the use unless it can predict that registering the new use would not have a likelihood of jeopardizing listed species or adversely modifying their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

[5] www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.
[6] www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.
[7] www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[8] www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[9] www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.

In April 2022, EPA released a comprehensive, long-term approach to meeting its ESA obligations, which is outlined in *Balancing Wildlife Protections and Responsible Pesticide Use*.[10] This workplan reflects the Agency's most comprehensive thinking to date on how to create a sustainable ESA-FIFRA program that focuses on meeting EPA's ESA obligations and improving protection for listed species while minimizing regulatory impacts to pesticide users and collaborating with other agencies and stakeholders on implementing the plan.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[11] As part of this update, EPA announced its plan to consider and include, as appropriate, a menu of FIFRA Interim Ecological Risk Mitigation intended to reduce off-target movement of pesticides through spray drift and runoff in its registration review and other FIFRA actions. These measures are intended to reduce risks to nontarget organisms efficiently and consistently across pesticides with similar levels of risks and benefits. EPA expects that these mitigation measures may also reduce pesticide exposures to listed species.

ESA Assessments or Biological Opinions Impacting Complex Polymeric Polyhydroxy Acids

An assessment will be conducted on impacts of CPPA on threatened and endangered species and their designated critical habitat as part of registration review.

V. Next Steps and Timeline

The Agency has created the following estimated timeline for the completion of the registration review for CPPA. The Agency's final decision on the CPPA registration review case will occur following satisfaction of the Endocrine Disruptor Screening Program (EDSP) obligations under FFDCA § 408(p) and completion of an ESA determination and any necessary consultation with the Services.

Table 2. Anticipated Registration Review Schedule for CPPA

Anticipated Activity	Estimated Month/ Year
Opening the Docket	
Open Docket and 60-Day Public Comment Period for Preliminary Work Plan	July 2023
Close Public Comment Period	September 2023
Case Development	
Final Work Plan	January 2024
Registration Review Decision and Implementation	
Open 60-Day Public Comment Period for the Proposed Registration Review Decision	TBD
Close Public Comment Period	TBD
Final Decision*	TBD

*The anticipated schedule will be revised as necessary (e.g., need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

[10] www.epa.gov/endangered-species.
[11] www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.

Appendix A – Summary of Existing Product Analysis Data

In evaluating product chemistry for registration review, the Agency is focused on the active ingredient (for practical purposes, the technical grade active ingredient or TGAI) and not the individual end- and manufacturing-use products. Provided in the table below are the Biochemical Pesticides Product Chemistry Data Requirements (40 CFR § 158.2030) and how they are met. All are satisfied and support the registration review for CPPA. All product chemistry were performed on the TGAI, CPPA.

Table 3. Summary of Product Analysis Data (40 CFR §158.2030)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Product identity and composition	880.1100	*Common Name*: Complex Polymeric Polyhydroxy Acid *CAS RNs*: N/A *PC Code*: 078503 *CPPA is derived from natural organic matter (NOM) in soils and ground and surface waters.*	BRAD, 2012a.
Description of Starting Materials, Production and Formulation Process	880.1200	Confidential Business Information (CBI)	48436901
Discussion of Formation of Impurities	880.1400	CBI; No impurities of toxicological concern were identified.	48436901
Preliminary Analysis	830.1700	CBI.	48427402
Color	830.6302	Dark brown	48456501
Physical State	830.6303	Liquid	48456501
Odor	830.6304	Mild	48456501
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Product will not normally contact metal ions during manufacture, use, or storage; stable at ambient and elevated temperatures	48456501 48105301
pH	830.7000	6.75	48456501
UV/Visible Light Adsorption	830.7050	Neutral: 0.748 (maximum absorbance; molar absorptivity = 27,800 m^{-1}/M) Acidic: 0.722 (maximum absorbance; molar absorptivity = 27,800 m^{-1}/M) Basic: 0.788 (maximum absorbance; molar absorptivity = 27,800 m^{-1}/M)	48456501
Melting Point/Melting Range	830.7200	N/A; TGAI is a liquid	48456501
Boiling Point/Boiling Range	830.7220	100ºC	48456501
Density/Relative Density/Bulk Density	830.7300	1.010 g/cm^3 @ 25ºC 1.002 g/cm^3 @ 41ºC	48456501
Particle Size, Fiber Length, and Diameter Distribution	830.7520	N/A; only required for water insoluble substances or fibrous test substances; the test substance is neither water insoluble or fibrous	48456501
Partition Coefficient (n-Octanol/Water)	830.7550 830.7560 830.7570	N/A; test substance is soluble in water	N/A
Water Solubility	830.7840	100% soluble	48456501
Vapor Pressure	830.7950	Approximately equal to water	48456501

N/A = not applicable

Appendix B – Summary of Mammalian Toxicology Data

The toxicology data for this active ingredient are acceptable and the database is complete. Table 4 summarizes the current mammalian toxicology data requirements and results supporting registration review of CPPA. The available subchronic toxicity studies were performed with fulvic acid, humic acid, tannins, or a combination of these three major components of CPPA. The relative concentrations of each are influenced by environmental conditions, such as climate, soil types, vegetation, and hydrology, but the data on these components are considered adequate for assessing toxicity to CPPA.

The Agency's existing risk assessment is sufficient to evaluate the use of CPPA in the currently registered manufacturing and end-use products.

Table 4. Summary of Toxicology Data (40 CFR §158.2050)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Acute Oral Toxicity - Rat	870.1100	LD_{50} > 5,000 mg/kg body weight in rats; Toxicity Category IV; ACCEPTABLE/GUIDELINE (TGAI)	47916001
Acute Dermal Toxicity	870.1200	LD_{50} > 5,050 mg/kg body weight in rats: Toxicity Category IV; ACCEPTABLE/GUIDELINE (TGAI)	47916002
Acute Inhalation Toxicity	870.1300	LC_{50} > 2.16 mg/L in rats: Toxicity Category IV ACCEPTABLE/GUIDELINE (TGAI)	47916003
Primary Eye Irritation – Rabbit	870.2400	Non-irritating; Toxicity Category IV; ACCEPTABLE/GUIDELINE (TGAI)	47916004
Primary Dermal Irritation	870.2500	Non-irritating; Toxicity Category IV; ACCEPTABLE/GUIDELINE (TGAI)	47916005
Dermal Sensitization	870.2600	Not a sensitizer; ACCEPTABLE/GUIDELINE (TGAI)	47916006
Hypersensitivity Incidents	N/A	None reported	--
90-Day Oral - Rat	870.3100	NOAEL = 2,000 mg/kg/day (highest dose tested) of a fulvic and humic acids preparation* ACCEPTABLE/NON-GUIDELINE	Murbach, T. et al., 2020
90-Day Dermal – Rat	870.3250	CPPA is naturally occurring and has a long history of human exposure without known adverse effects based on the available data. The AI is not a dermal irritant nor is it acutely toxic via the dermal route. Registered uses do not involve purposeful application to human skin and are not expected to result in prolonged human exposure to the product. Although applicators/handlers may be exposed, exposure would be mitigated by personal protective equipment (PPE) on all product labels with this AI (i.e., long sleeve shirt and long pants, shoes and socks, waterproof gloves, and protective eyewear).	--
90-Day Inhalation – Rat	870.3465	Although applicators/handlers may be exposed when CPPA is used in spray applications, CPPA is a naturally occuring substance with a long history of human exposure without known adverse effects. In addition, no adverse effects were seen in the toxicity database. The 90-day oral toxicity study on a mixture of humic and fulvic acids showed no adverse effects up to 2,000 mg/kg/day. In addition, the AI is not a dermal or ocular irritant nor is it acutely toxic via the inhalation route.	--
Prenatal Developmental	870.3700	Maternal and Developmental NOAEL = 4% in the diet (40,000 ppm/highest dose tested) tannic acid in diet (prairie voles) ACCEPTABLE/NON-GUIDELINE Maternal NOAEL = 0.8 g/L humic acid (800 ppm, highest dose tested; dietary study administered via drinking water for dams and via oral intubation for pups from day 6-21, and via drinking water for pups from day 21-41) (rats)	Meyer and Richardson, 1993 Smith et al., 1986

		Developmental NOAEL = 1.0 g/L humic acid (1,000 ppm, highest dose tested) ACCEPTABLE/NON-GUIDELINE**	
Bacterial Reverse Mutation Test	870.5100	Not mutagenic up to 5,000 µg/plate (highest dose tested) (fulvic and humic acids preparation)* ACCEPTABLE/NON-GUIDELINE	Murbach, T. et al, 2020
In vitro Mammalian Cell Assay	870.5300 870.5375	No genotoxic effects observed up to 5,000 µg/mL (fulvic and humic acids preparation)* ACCEPTABLE/NON-GUIDELINE	Murbach, T. et al, 2020

* A specific fulvic and humic acids preparation (Trade name: blk. 333) derived from a lignite deposit in Alberta, Canada.
**This was a non-guideline reproductive toxicity study; not a prenatal developmental toxicity study.

Literature Search Findings

To support registration review, the Biopesticides and Pollution Prevention Division (BPPD) conducts searches of the literature and incident databases to determine if there are any reports of adverse effects that might change risk conclusions or change knowledge of the state of the science for CPPA. Searches conducted for CPPA are described below.

Human Health Results:

A literature search was conducted using Google Scholar and PubMed for "complex polymeric polyhydroxy acid," "humic acid," "fulvic acid", "tannins," and "NOM" in combination with "toxicity", "endocrine," "estrogen," "androgen," and "hormone" and five relevant documents were found for this registration review case. The first article[12] is an investigation on the pharmacology and toxicology of tannins and provides an overview of the antioxidant, anti-inflammatory, anti-cancer, neuroprotective, antimicrobial and anti-diabetic properties of tannins along with their toxicology. The second article[13] demonstrates that dissolved organic matter (DOM) containing "lake fulvic acid" and "lake humic acid" had a very important accelerating effect on the degradation of 17-B estradiol, confirming DOM as an important source of energy for microbes that promote the biodegradation of steroid estrogens. The third article[14] indicates that tannic acid has the potential to become an anti-estrogen receptor positive breast cancer treatment or preventative agent. The fourth article[15] shows that Nordic Aquatic fulvic acid (NA-FA) and Nordic reservoir natural organic matter (NR-NOM) inhibited androgen receptor activity and NA-FOM induced estrogen receptor activity in *in vitro* bioactivity assays. The fifth article[16] discusses the anti-androgenic activity of humic substances. These study results indicate that further research is needed to accurately characterize the potential endocrine-disruption activities of CPPA.

[12] Maugeri, et. al, 2022.
[13] Gu, et. al, 2016.
[14] Booth, et. al, 2013.
[15] Rosenmai, et al., 2018.
[16] Bittner, et al., 2012.

Appendix C – Summary of Nontarget Organism Data

Data cited from the open literature were submitted to satisfy data requirements for avian oral and dietary, freshwater fish, freshwater invertebrates, and nontarget aquatic plant toxicity testing. Data was submitted for nontarget insect (honeybee) testing, and the acute oral toxicity testing for rats was used to satisfy the data requirement for wild mammals. No data for nontarget terrestrial plants was provided, however rationale within the cited risk assessment describes that terrestrial plants are naturally exposed to complex polymeric polyhydroxy acids (CPPA) at amounts higher than CPPA application amounts. The testing cited from the open literature has been conducted with components of CPPA such as humic acids, tannins, gallic acid, and plant extracts. These surrogates were considered acceptable because they are integral parts of CPPA.

The information provided is sufficient to satisfy the Tier I nontarget organism data requirements for ecological risk assessment for the active ingredient. Further testing of nontarget organisms at higher tiers was not required for the proposed label uses.

Table 5. Summary of Nontarget Organism Data (40 CFR §158.2060)

Data Requirement	Guideline No.	Results / Findings	MRIDs
Avian oral toxicity	850.2100	Red winged blackbird (*Agelaius phoeniceus*) exposed to gallic acid had an LD_{50} >100 mg/kg [1].	Schafer et al., 1983
Avian dietary toxicity	870.2200	LD_{50}>30,000 ppm (tannins) Practically nontoxic to poultry (*Gallus gallus domesticus*) 5,000 ppm (tannins) depressed egg and growth production. Practically nontoxic to poultry 1500-2500 ppm for 42 days (humic acid) increased broiler weight.	Cornell Univ., 2009 Cornell Univ., 2009 Islam et al., 2005
Wild mammal toxicity	885.4150	Acute oral toxicity to rats (*Rattus norvegicus*) >5000 mg/kg. Toxicity Category IV. This was a guideline study that was considered acceptable.	47916001
Freshwater fish toxicity	850.1075	96-hour LC_{50}= 50 ppm[2] (*Cyprinus carpio* L.) Slightly toxic 96-hour LC_{50}= 5.8 ppm[3] (*Cyprinus carpio* L.) Practically non-toxic 96-hour LC_{50}= 5.6 ppm[3] (*Poecilia reticulate*) Practically non-toxic 96-hour LC_{50}= 7 ppm[3] (*Beta splendens*) Practically non-toxic 96-hour LC_{50}= 30 ppm[4] and 107.2 ppm[5] (*Oreochromis mossabica*) Slightly toxic and practically non-toxic, respectively	Temmink et al., 1989 Chansue and Assawawong-kasem, 2008 Saha and Kaviraj, 1996.
Freshwater invertebrate toxicity	850.1010	EC_{50}= 248 ppm (immobilization) NOEC=175 ppm in *Daphnia magna*, Practically non-toxic.	Nicola et al., 2004
Nontarget plant testing	850.4100-4150	Algae treated with 0.03 ppm to 30 ppm tannins[6] growth stimulation occurred at up to 0.3 ppm (*S. capricornutum*) or up to 3 ppm (*D. tertiolecta*). Growth was inhibited at approximately 5 ppm to 20 ppm respectively, with no observed mortality.	Nicola et al., 2004
Nontarget insect testing	850.4350	LD_{50}>25 ug/bee NOEC= 2.5 ug/bee, for *Apis mellifera*, categorized as practically non-toxic.	48795201

[1] Gallic acid, [2] Extract of Norway Spruce bark (50-60% tannins, 35% sugars, 10% non-tannin monomers, 5% resins), [3] Water extract of Indian almond leaves (*Terminalia catappa* L.), [4] Extract of Cinchona bark, [5] Analytical grade Tannic acid, [6] Fresh tannin water extract of Mimosa

Literature Search Findings

To support registration review, the BPPD conducts searches of the literature and incident databases to determine if there are any reports of adverse effects that might change risk conclusions or change knowledge of the state of the science for Complex Polymeric Polyhydroxy Acids. Searches conducted for CPPA are described below.

Ecological Results:

A literature search was conducted using the Web of Science Core Collection, the default database within the Web of Science system, with the terms " Complex Polymeric Polyhydroxy Acids" and "avian," "mammals," "plants," "insects," and "aquatic organisms," which returned 22 results. The results discussed the use of CPPA as nematicides, plant growth regulators, and as soil conditioners. None of the results discussed any adverse effects for nontarget organisms.

A search of OPP's Incident Data System on May 8, 2023, revealed no reported incidents associated with CPPA. No additional information was gained from these searches that would alter the BPPD's understanding of the current state of the science for any potential effects of CPPA pesticides on nontarget organisms.

Appendix D – Endocrine Disruptor Screening Program (EDSP)

The Federal Food Drug and Cosmetic Act (FFDCA) § 408(p) requires EPA to develop a screening program to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." (21 U.S.C. 346a(p)). In carrying out the Endocrine Disruptor Screening Program (EDSP), FFDCA section 408(p)(3) requires that EPA "provide for the testing of all pesticide chemicals," which includes "any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), including all active and pesticide inert ingredients of such pesticide." (21 U.S.C. 231(q)(1) and 346a(p)(3)). However, FFDCA section 408(p)(4) authorizes EPA to, by order, exempt a substance from the EDSP if the EPA "determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen." (21 U.S.C. 346a(p)(4)).

The EDSP developed by EPA in 1998 includes human and wildlife testing for estrogen, androgen, and thyroid pathway activity and employs a two-tiered approach. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid pathways. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship for any estrogen, androgen, or thyroid effect. If EPA finds, based on that data, that the pesticide has an endocrine effect on humans, FFDCA § 408(p)(6) also requires EPA, "as appropriate, [to] take action under such statutory authority as is available to the Administrator … as is necessary to ensure the protection of public health." (21 U.S.C. 346a(p)(6))[17].

Between October 2009 and February 2010, EPA issued Tier 1 test orders/data call-ins (DCIs) for its first list of chemicals ("List 1 chemicals") for EDSP screening and subsequently required submission of EDSP Tier 1 data for a refined list of these chemicals. EPA received data for 52 List 1 chemicals (50 pesticide active ingredients and 2 inert ingredients). EPA scientists performed weight-of-evidence (WoE) analyses of the submitted EDSP Tier 1 data and other scientifically relevant information (OSRI) for potential interaction with the estrogen, androgen, and/or thyroid signaling pathways for humans and wildlife.[18]

For FIFRA registration, registration review, and tolerance-related purposes, EPA collects and reviews numerous studies to assess potential adverse outcomes, including potential outcomes to endocrine systems, from exposure to pesticide active ingredients. Although EPA has been collecting and reviewing such data, EPA has not been explicit about how its review of required and submitted data for these purposes also informs EPA's obligations and commitments under FFDCA section 408(p). Consequently, on October 27, 2023, EPA issued a Federal Register Notice (FRN) providing clarity on the applicability of these data to FFDCA section 408(p) requirements and near-term strategies for EPA to further its compliance with FFDCA section 408(p). This FRN, entitled *Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation' Notice of Availability and Request for Comment* (88 FR 73841) is referred to here as EPA's EDSP Strategies Notice. EPA also published three documents supporting the strategies described in the Notice:

- *Use of Existing Mammalian Data to Address Data Needs and Decisions for Endocrine Disruptor Screening Program (EDSP) for Humans under FFDCA Section 408(p)*;

[17] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[18] Summarized in *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions*; EPA-HQ-OPP-2023-0474-0001; https://www.regulations.gov/document/EPA-HQ-OPP-2023-0474-0001

- *List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed*; and,
- *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions* (referred to here as List 1 Screening Conclusions).

The EDSP Strategies Notice and the support documents are available on www.regulations.gov in docket number EPA-HQ-OPP-2023-0474. As explained in these documents, EPA is prioritizing its screening for potential impacts to the estrogen, androgen, and thyroid systems in humans, focusing first on conventional active ingredients. Although EPA voluntarily expanded the scope of the EDSP to screening for potential impacts to the estrogen, androgen, and thyroid systems in wildlife, EPA announced that it is not addressing this discretionary component of the EDSP at this time, taking into account its current focus on its comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[19] and November 2022 ESA Workplan Update[20]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[21] indicate that available data were sufficient for FFDCA section 408(p) assessment and review for potential effects to the estrogen, androgen, or thyroid pathways for wildlife. For the remaining 17 List 1 chemicals, Tier 1 WoE memoranda made recommendations for additional testing. EPA expects to further address these issues taking into account additional work being done in concert with researchers within the EPA's Office of Research and Development (ORD).

As discussed in EPA's EDSP Strategies Notice and supporting documents, EPA will be using all available data to determine whether or what additional data are needed to meet EPA's obligations and discretionary commitments under FFDCA section 408(p). For some conventional pesticide active ingredients, the toxicological databases may already provide sufficient evaluation of endocrine potential for estrogen, androgen, and/or thyroid pathways and EPA will generally not need to obtain any additional data to evaluate those pathways. For instance, EPA has data for numerous conventional pesticide active ingredients on mammalian estrogen and androgen effects through either an acceptable two-generation reproductive study in accordance with the current guideline (referred to here as the updated two-generation reproduction study; OCSPP 870.3800 - Reproduction and Fertility Effects) or an extended one-generation reproductive toxicity (EOGRT) study (OECD Test Guideline 443 - Extended One-Generation Reproductive Toxicity Study). In these cases, EPA expects to make FFDCA 408(p)(6) decisions for humans without seeking further estrogen or androgen data. However, as also explained in the EPA's EDSP Strategies Notice, where these data do not exist, EPA will assess available data for the conventional active ingredient to determine what additional data, if any, might be needed to assess the potential for impacts to estrogen, androgen, and/or thyroid pathways in humans. For more details on EPA's approach for assessing these endpoints, see EPA's EDSP Strategies Notice and related support documents.

Also described in the EPA's EDSP Strategies Notice is a framework that represents an initial approach by EPA to organize and prioritize the large number of conventional pesticides in registration review. For conventional pesticides that lack an updated two-generation reproduction study or an EOGRT study, EPA has used data from the Estrogen Receptor Pathway and/or Androgen Receptor Pathway Models to identify a group of chemicals with the highest priority for potential data collection (described in EPA's

[19] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf
[20] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf
[21] https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-tier-1-screening-determinations-and

EDSP Strategies Notice as Group 1 active ingredients). For these cases, EPA sought in the FRN data and information in response to issuance of EPA's EDSP Strategies Notice to better understand the positive findings in the ToxCast™ data for the Pathway Models and committed to issuing DCIs to require additional EDSP Tier 1 data. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to assessing the available data to determine what additional studies, if any, might be needed to assess the potential for impacts to endocrine pathways in humans.

Although EPA has prioritized conventional active ingredients as presented in EPA's EDSP Strategies Notice, EPA is planning to develop similar strategies for biopesticide and antimicrobial pesticide (*i.e.*, nonconventional) active ingredients and will provide public updates on these strategies, when appropriate. At this time, EPA is making no findings associated with the implementation of EDSP screening of CPPA. Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

References

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U.S. EPA. 2012a. Biopesticide Registration Action Document (BRAD), Complex Polymeric Polyhydroxy Acids (CPPA).

U.S. EPA 2012b. Memorandum. Science Review in Support of the Second Resubmission of the Registration of Carbon Power Concentrate, a Manufacturing Use Product (MP) and Carbon Power, an End-Use Product (EP), Respectively Containing 4% and 0.4 % of the New Active Ingredient, Complex Polymeric Polyhydroxy Acids; and a Tolerance Exemption. Review of Tier I Toxicity Data, Information, and Waiver Requests.

U.S. EPA. 2022. Memorandum. Revised Science Review in Support of Adding a New Uses as a Fungicide and Insecticide for the End-Use Product (EP) FBS Defense 500 with 0.9% Complex Polymeric Polyhydroxy Acid (CPPA) as its Active Ingredient.