Humates (as derived from Leonardite)

PC Code 021818

Final Work Plan
Case Number 6323

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Table of Contents

I. Introduction 3
II. Updates Since the Preliminary Work Plan was Issued 4
III. Use Information 4
IV. Scientific Assessments 4
A. Human Health Assessment 4
B. Summary of Environmental Risk Assessment 6
V. Next Steps and Timeline 8
Appendix A – Product Characterization 9
Appendix B – Human Health Risk Assessment 11
Summary of Mammalian Toxicology Data 11
Hazard Characterization 12
Dietary Exposure and Risk Assessment 13
Residential and Occupational Exposure and Risk Assessment 13
Literature and Incident Search Findings 13
Appendix C – Environmental Risk Assessment 15
Summary of Nontarget Organism Data 15
Risk Characterization 15
Literature and Incident Search Findings 16
Appendix D – Endocrine Disruptor Screening Program (EDSP) 17
References 20

I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) Final Work Plan (FWP) for Humates as derived from Leonardite (Case 6323) and is being issued pursuant to 40 CFR § 155.50. This case includes the active ingredient humates as derived from leonardite, hereafter referred to as "humates". This document explains what EPA's Office of Pesticide Programs (OPP) knows about humates, 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 humates. In accordance with 40 CFR § 155.50, the opening of this docket initiates the current cycle of registration review for humates.

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 humates and what additional risk analyses and data or information it believes are needed to make a registration review decision on humates.

This document is organized into five sections: the *Introduction*, which includes this summary and humates case overview; *Use Information*, which describes how and why humates 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 humates; *Updates Since the PWP was Issued*; and, lastly, the *Next Steps and Timeline* which provides an anticipated timeline for the registration review process for humates.

Humates (as derived from Leonardite) Registration Review Case Overview

Pursuant to 40 CFR § 155.50, the Agency initiated this pesticide's registration review by establishing a docket for registration review of humates (Case 6323) and opening it for public review.

The publication of the Preliminary Work Plan (PWP) marked the beginning of the current cycle of registration review for humates, with the opening of public docket EPA-HQ-OPP-2024-0017 available at www.regulations.gov. The following list highlights significant events that have occurred during the current cycle of registration review for this case:

- March 2024 – The Agency published the *Humates (as derived from Leonardite) Preliminary Work Plan* for a 60-day public comment period. The Agency received no public comments during this time.
- September 2024 – The Agency is now publishing the *Humates (as derived from Leonardite) 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 humates as an active ingredient was registered by the Agency in 2014. Currently, there are two registered products containing humates: one manufacturing-use product and one end-use product, ranging from 12.0%-18.5% active ingredient.

Humates are naturally occurring substances formed by the biodegradation of dead organic matter, and are often associated with deposits of coal, lignite, and mudstone. Humates are ubiquitous in the environment in soil and water, including agricultural areas where crops are grown for human and animal consumption. Humates are to be used as plant growth regulators to control the vegetative growth and maturation of agricultural and greenhouse crops. Treatment of plants with humates enhances root growth, improves the uptake of nitrogen, potassium, and phosphate, increases the treated plants' ability to resist plant disease, and reduces the need to add soil nutrients and fertilizers during the growing season.

Table 1. Humates (as derived from Leonardite) Use Information

Ingredient Name	Humates (as derived from Leonardite)
PC Code	021818
Pesticide Classification	Plant Growth Regulator
Use Site Locations	Agricultural (Outdoors & Indoors)
Application Types	Soil incorporated, spray drench, dip treatment
No. of Registrations	2 FIFRA Section 3 products[1]
Physical Forms	Liquid Solution

IV. Scientific Assessments

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

Summary of Hazard Characterization

The toxicological database is considered complete for characterizing hazard and assessing risk for the active ingredient in this case. The human health requirements were met via submission of data and scientific rationales. Humates can be classified as Toxicity Category IV for the acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation;

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

furthermore, the active ingredient is not a dermal sensitizer. In addition, the current use patterns (i.e., soil drench, trunk injection, chemigation, and bare root dip) requires that all handlers wear personal protective equipment (PPE). Required PPE includes long-sleeve shirts, long pants, shoes plus socks, and protective eyewear. There is a long history of use and occupational exposure to humate substances with no reported incidents or any significant toxicological concerns. No risks of concern have been identified from the use of humates as a pesticide due to the lack of toxicity, lack of significant exposure, and its natural presence in the environment. The Agency does not anticipate the need for additional studies for this registration review. All data requirements, per 40 CFR § 158.2050, have been fulfilled for humates at this time. Please see Appendix B for additional information.

Summary of Dietary Exposure and Risk Characterization

Humates have a low overall toxicity profile according to the available data, as there were no noted adverse effects in the submitted studies or studies found in the literature. Humates are naturally occurring in soil and water and show a lack of toxicity as demonstrated in the submitted studies, and therefore there are no anticipated risks of concern to potential exposure to residues in drinking water. Based on the available information, the Agency has concluded that there are no dietary risks of concern for the pesticidal uses of this active ingredient. Additionally, humans are already exposed to humates because they are ubiquitous in the environment and a component of soil and water. Exposure to residues of humates when used as a pesticide is expected to be negligible when compared to the existing levels humans are exposed to in the environment. Please see Appendix B for additional information.

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 humates when used according to label directions.

Residues resulting from the use of humates (including: humic acid; humic acids, potassium salts; humic acids, sodium salts) as either an inert or an active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempt from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices (40 CFR part 180.950 (e)). Exposure to the active ingredient is expected to be low since the product is applied using sprinkler and drip irrigation systems, soil injections, and foliar spray; moreover, it is a natural component of soil and water with no known adverse effects to humans and the environment.

Summary of Residential and Non-Occupational Exposure and Risk Characterization

Residential and non-occupational exposure from humates is not expected. Currently, there are no residential (non-occupational) uses; moreover, it is a natural component of soil and water with no known adverse effects to humans and the environment. Therefore, residential handlers (non-occupational) and post-application risks of concern are not expected. Please see Appendix B for additional information.

Summary of Occupational Exposure and Risk Characterization

Occupational exposure to humates is expected to be low since the product is applied using sprinkler and drip irrigation systems, soil injections, and foliar spray all at a low application rate; moreover, it is a natural component of soil and water with no known adverse effects to humans and the environment. Based on current product labeling, PPE is required (i.e., long-sleeve shirt, long pants, shoes plus socks,

and protective eyewear) for applicators and handlers, and since the product is for commercial use only occupational handler and post-application risks of concern are not expected. Please see Appendix B for additional information.

Human Incidents

A search of the OPP Incident Data System conducted on February 26, 2024, revealed no reported incidents associated with humates. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Summary of Environmental Risk Assessment

All non-target organism and environmental fate data necessary to meet the standard for humates risk assessments were satisfied through the acceptance of scientific rationales and data submissions. Scientific rationales were based on lack of any reports of adverse effects to humans, other mammals, insects or the environment despite it being applied to crops and soil historically. Since humates are ubiquitous in soil and water, birds, fish, and other living organisms are already naturally exposed. The major component of humates, humic acids, enriches the soil and stimulates root growth and uptake of nutrients by the treated plants and the end-use product label application rates would result in little net increase in the background amount of humates already present in the environment. Therefore, the use of humates does not result in risk to the environment, nontarget plants, nontarget organisms, and/or threatened or endangered species. Based on this information in conjunction with the label, the Agency believes that when used in accordance with the label directions, the use of humates should not result in adverse effects to birds, fish, aquatic invertebrates or nontarget insects. However, due to its use as a plant growth regulator, an endangered species assessment will be needed in order to support a determination under the Endangered Species Act (ESA).

The use and exposure from humates have not changed and the Agency's existing risk assessments are sufficient to evaluate the use of humates in the current registrations. Additionally, the Agency conducted a literature search for the active ingredient in this case, which returned with no open literature studies and no incident reports. Hazard and exposure data, Agency risk assessments, and other information on the active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. For further information, please see Appendix C.

Ecological Incidents

A search of OPP's Incident Data System conducted on February 26, 2024, revealed no reported incidents associated with humates. 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). Additional background specific to humates appears at the conclusion of Appendix C. The Agency will conduct an assessment of humates on listed species, in order to support a determination under the 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[2] for assessing the effects of pesticides to 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.[3]

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.[4]

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[5] from FWS in February 2022 and a final biological opinion from NMFS on malathion, chlorpyrifos and diazinon in June 2022.[6] 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[7] to evaluate potential effects of new conventional pesticide active ingredients on 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

[2] https://www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.
[3] https://www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.
[4] https://www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.
[5] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[6] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[7] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.

jeopardizing listed species or adversely modifying their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

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*.[8] 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*.[9] 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.

V. Next Steps and Timeline

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

Table 2. Anticipated Registration Review Schedule for Humates (as derived from Leonardite)

Anticipated Activity	**Estimated Month/ Year**
Opening the Docket	
Open Docket and 60-Day Public Comment Period for Preliminary Work Plan	March 2024
Close Public Comment Period	May 2024
Case Development	
Final Work Plan	September 2024
Registration Review Decision and Implementation	
Open 60-Day Public Comment Period for 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).

[8] https://www.epa.gov/endangered-species.
[9] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.

Appendix A – Product Characterization

The product chemistry database is considered complete for characterizing and assessing the physical chemical properties of the active ingredient in this case. Humates (as derived from leonardite) are naturally occurring substances derived from the biodegradation of dead organic matter. Leonardite is a form of soft coal that is found at shallow depths throughout the world that is a rich source of humic acids and is the main source of organic matter used for humate-based fertilizers in the United States. Leonardite has been described as being a salt of humic acids and fulvic acids mixed with mineral matter such as gypsum, silica, and clay (Fowkes et.al., 1973). Therefore, the more technical description of the active ingredient is *Organic acids derived from leonardite* because the aqueous solubilized extract of leonardite contains several classes of organic acids to include humic acids, fulvic acid, and other discrete low-molecular weight organic acids. Humates are equivalent to other humic substances i.e., humates, humic acids-potassium salts, humic acids-sodium salts, and humin (U.S. EPA, 2014).

The product chemistry database supporting the humates is acceptable and complete. Table 3 summarizes the current product chemistry data requirements and results supporting registration review of this active ingredient.

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

Data Requirement	Guideline No.	Results / Findings	MRIDs
Product identity and composition	880.1100	Submitted data to satisfy the data requirement. Confidential Business Information (CBI) ACCEPTABLE/GUIDELINE	48711101
Description of Starting Materials, Production and Formulation Process	880.1200	Submitted data to satisfy the data requirement. CBI ACCEPTABLE/GUIDELINE	48711101
Discussion of Formation of Impurities	880.1400	Submitted data satisfy the data requirement. CBI ACCEPTABLE/GUIDELINE	48711101
Preliminary Analysis	830.1700	Submitted data to satisfy the data requirement. CBI ACCEPTABLE/GUIDELINE	48711101
Certified Limits	830.1750	Submitted data to satisfy the data requirement. CBI ACCEPTABLE/GUIDELINE	48711101
Enforcement Analytical Method	830.1800	Submitted data to satisfy the data requirement. CBI ACCEPTABLE/GUIDELINE	48711101
Color	830.6302	Black	48711103
Physical State	830.6303	Liquid	48711103
Odor	830.6304	Mild, alcoholic	48711103
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Stable for 14 days at normal and elevated temperatures (54°C) in high-density polyethylene (HDPE) containers. Stability to metals and metal ions is not applicable since the product is not stored or packaged in metal containers.	48711103 48711104
pH	830.7000	10.67 +/- 0.005 (1% solution in carbon dioxide (CO_2) free water at 21.1°C)	48711103
UV/Visible Light Absorption	830.7050	No absorbance maximum was observed in the wavelength range 200-750 nm.	48711103
Viscosity	830.7100	3.01 mm^2/s (cSt) at 19.8°C 2.53 mm^2/s (cSt) at 39.9°C	48711103

Melting Point/Melting Range	830.7200	Not applicable because the technical grade active ingredient (TGAI) is a liquid	48711104
Boiling Point/Boiling Range	830.7220	102.6 +/- 0.1°C	48711103
Density/Relative Density/Bulk Density	830.7300	1.14 g/mL	48711103
Particle Size, Fiber Length, and Diameter Distribution	830.7520	Not applicable because the TGAI is not water insoluble and it is not a fibrous material.	48711104
Partition Coefficient	830.7550-.7570	Not applicable. The TGAI is 70% water, and the components are not expected to partition in octanol.	48711104
Water Solubility	830.7840	The TGAI is soluble because it is comprised of more than 70% water.	48711104
Vapor Pressure	830.7950	The TGAI is 70% water and contains non-volatile solutes, therefore, the vapor pressure is not anticipated to be much lower than pure water.	48711104

Appendix B – Human Health Risk Assessment

Summary of Mammalian Toxicology Data

All human health toxicity data available for humates are acceptable and support the current registration review. Table 4 summarizes the current mammalian toxicology data requirements and the acute toxicity results supporting registration of the TGAI are from the manufacturing product, PM-4300.

Table 4. Human Health Toxicological Profile (40 CFR § 158.2050)

Study/OCSPP Guideline No.	Results	Toxicity Category/ Description	MRID
Acute oral toxicity (870.1100)	LD_{50} > 5,000 mg/kg (rats) ACCEPTABLE/GUIDELINE	IV	48711105
Acute dermal toxicity (870.1200)	LD_{50} > 5,000 mg/kg (rats) ACCEPTABLE/GUIDELINE	IV	48711106
Acute inhalation toxicity (870.1300)	LC_{50} > 2.05 mg/kg (rats) ACCEPTABLE/GUIDELINE	IV	48711107
Primary eye irritation (870.2400)	Minimal effects clearing in less than 24 hours in rabbits. ACCEPTABLE/GUIDELINE	IV	48711108
Primary dermal irritation (870.2500)	Slight irritation resolved within 72 hours in rabbits. ACCEPTABLE/GUIDELINE	IV	48711109
Dermal sensitization (870.2600)	Not a dermal sensitizer (guinea pigs) ACCEPTABLE/GUIDELINE	N/A	48711110
90-day oral toxicity (870.3100)	Rationale was submitted to address the data requirements. A weight of evidence (WOE) approach was used due to the low acute toxicity of the TGAI, low active ingredient concentrations in the registered pesticide products, its natural ubiquity in the environment, and data published in the literature show humic acids have low oral toxicity, are poorly absorbed after oral administration, and are not toxic after subchronic exposures. ACCEPTABLE/ NON-GUIDELINE	N/A	48711115
90-day dermal toxicity (870.3200)	Rationale was submitted to address the data requirements. A WOE approach was used due to the low acute toxicity of the TGAI, its natural ubiquity in the environment, and data published in the literature show humic acids exhibited no significant toxicological effects in the repeat oral toxicity studies, and due to their physical chemical properties dermal absorption is expected to be low. ACCEPTABLE/ NON-GUIDELINE	N/A	48711115
90-day inhalation toxicity (870.3465)	Rationale was submitted to address the data requirements. A WOE approach was used due to the low acute toxicity of the TGAI, its natural ubiquity in the environment, and data published in the literature show humate substances did not produce any systemic toxicity via repeat dose oral studies. ACCEPTABLE/NON-GUIDELINE	N/A	48711115
Developmental toxicity (870.3700)	Rationale was submitted to address the data requirements. A WOE approach was used due to the low acute toxicity of the TGAI, its natural ubiquity in the environment, and data published in the literature show humates exhibited no signs of toxicity or developmental effects in pregnant rats.	N/A	48711115

	ACCEPTABLE/ NON-GUIDELINE		
Bacterial reverse mutation test (870.5100)	The TGAI did not cause gene mutations by base pair changes or frame shifts; no evidence of cytotoxicity at highest doses tested; Negative for reverse gene mutations in *Salmonella typhimurium* TA 1535, TA 1537, TA98, and TA100 in the presence or absence of a metabolic system. Non-mutagenic. ACCEPTABLE/GUIDELINE	N/A	49080301
In vitro mammalian cell assay (870.5300-5375)	Rationale was submitted to address the data requirements. A WOE approach was used due to the low acute toxicity of the TGAI, its natural ubiquity in the environment, and data published in the literature show humates are non-mutagenic and non-genotoxic. ACCEPTABLE/ NON-GUIDELINE	N/A	48711115

Hazard Characterization

The toxicological database is considered complete for characterizing hazard and assessing risk from the active ingredient in this case. Humates are naturally occurring substances derived from the biodegradation of dead organic matter and are similar to other organic acids i.e., humates, humic acids, potassium salts and humic acids, sodium salts (U.S. EPA, 2014). The humates can be classified as Toxicity Category IV for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation; in addition, the TGAI is not a dermal sensitizer (U.S. EPA, 2012; 2014). The scientific rationales submitted for subchronic toxicity, developmental toxicity, and genotoxicity were acceptable based on the lack of exposure, low application rates, low overall toxicity profile, the physical chemical properties, its natural presence in the environment, the currently approved use pattern of the products containing humates is only for commercial use and require that all handlers wear appropriate personal protective equipment (PPE), and the availability of previously generated data found in the public literature. According to the public literature, no adverse or toxic effects were observed in repeat oral dose studies in rats given humic acids derived from leonardite at 1000 mg/kg bw, in dogs fed humic acid at 300 mg/kg bw, or in rabbits fed humic acids at 1000 mg/kg bw (EAEMP,1999; NICNAS, 2010; Van Rensburg et al., 2007). Humates are expected to have low dermal penetration due to their high molecular weight (>1000 Da), high water solubility, and low partition coefficient. Studies showed that absorption of humic acid across the gastrointestinal tract of rats was less than 0.7% (EAEMP,1999; NICNAS, 2010). Repeat human exposure by the inhalation route is not expected to be of concern because there will be minimal exposure for the current use patterns (i.e., soil drench, trunk injection, chemigation, and bare root dip), low acute inhalation toxicity (Toxicity category IV), and there is a long history of use and occupational exposure to humate substances with no reported incidents or any significant toxicological concerns. End-use products are diluted in water and applied as a foliar spray, soil drench, trunk injection, soil incorporation, or bare root dip at a maximum rate of 1.1 lbs AI/A (0.11 lbs AI/gallon solution). Unintentional exposures to the TGAI are anticipated to be mitigated because according to the product label, applicators and handlers are required to wear PPE such as long-sleeve shirts, long pants, shoes plus socks, and protective eyewear. The Agency may reevaluate these rationales and additional data may be required if the use pattern or use rates change in future end-use products, or if new toxicity information becomes available. The Agency does not anticipate the need for additional studies for this registration review. All data requirements, per 40 CFR § 158.2050, have been fulfilled for humates.

Dietary Exposure and Risk Assessment

The Agency considers the current assessments (U.S. EPA, 2012; 2014) to be sufficient to support the dietary (food and drinking water) risk assessment. Hazard and exposure data, Agency risk assessments, and other information on this active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. There are no risks of concern anticipated for humates. Humans are already exposed to humates because they are ubiquitous in the environment in soil and water, including agricultural areas where crops are grown for human and animal consumption. Humates have a low overall toxicity profile according to the available data, as there were no noted adverse effects in the repeat oral toxicity studies or genotoxicity study found in the literature. Because humates are naturally occurring in soil and water and show a lack of toxicity as demonstrated in the submitted studies, there are no anticipated risks of concern to potential exposure to residues in drinking water. Based on the available information, the Agency has concluded that there are no dietary risks of concern for the pesticidal uses of this active ingredient.

Food Tolerances

The active ingredient consists of the humic substance's humic acid and fulvic acid which could be identified as potential residues. Humic acid and fulvic acid resulting from the use of humates as an inert or active ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemicals, are exempt from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices (40 CFR 180.950 (e)).

Residential and Occupational Exposure and Risk Assessment

The Agency's existing risk assessments are sufficient to evaluate the use of humates in the currently registered end-use product (U.S. EPA, 2012; 2014). Hazard and exposure data, Agency risk assessments, and other information on the active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. No risks of concern have been identified. The active ingredient is a natural component of soil and water with no known adverse effects to humans and the environment. Based on current product labeling that requires PPE (i.e., long-sleeve shirt, long pants, shoes plus socks, and protective eyewear) for applicators and handlers, the product is for commercial use only, so occupational handler and post-application risks of concern are not expected. There are no anticipated residential (non-occupational) uses and significant residential exposure is not expected; therefore, residential handler and post-application risks of concern are not expected.

Literature and Incident 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 humates. Searches conducted for humates are described below.

<u>Human Health Results</u>:

A literature search was conducted with the PubMed, PubChem, Google Scholar, and Researchgate search engines using the term "humates" or "humic acids" paired with "toxicity", "oral toxicity", "dermal toxicity", "inhalation toxicity", "sensitizer", "sensitization", "allergenicity", "subchronic toxicity", "developmental toxicity", and "mutagenicity". The search returned 762 results. Based on the

search results, the available toxicity information concerning human health did not identify any significant adverse effects. Incident searches performed for humates using the Agency's pesticide incident database system returned no incident reports.

EPA CompTox Chemicals Dashboard (U.S. EPA, 2023) indicates there are no endocrine disruption relevant data available. A search was also performed using PubMed with the terms "humates" paired with "endocrine", "endocrine system", "endocrine disruptor", and "endocrine effects". The search terms produced no relevant results. However, in January 2023, a literature search was conducted using the terms "fulvic acid" and "humic acid" paired with "endocrine", "endocrine system", "endocrine disruptor", "endocrine effects", "estrogen", "androgen", and "hormone" and three relevant documents were found for this registration review case. The first article 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 (Gu, 2016). The second article shows the 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 (Rosenmai, 2018). The third article discusses the anti-androgenic activity of humic substances (Bittner et. al., 2015). These study results indicate that further research is needed to accurately characterize the potential endocrine-disruption activities of humates.

Appendix C – Environmental Risk Assessment

Summary of Nontarget Organism Data

All nontarget organism data for humates are addressed with data and scientific rationales to support the current registration review. No adverse effects are anticipated for nontarget species exposed to humates when used as plant growth regulators in agricultural settings. Humates are naturally occurring substances formed by the biodegradation of dead organic matter, and are often associated with deposits of coal, lignite, and mudstone. They are ubiquitous in the environment in soil and water, including agricultural areas where crops are grown for human and animal consumption. Humates are used to condition the soil and are widely regarded as being beneficial to plants and have historically been applied to soil with no reports of adverse effects to humans, other mammals, or the environment. In addition, treatment of plants with humates enhances root growth, improves the uptake of nitrogen, potassium, and phosphate, increases the treated plants' ability to resist plant disease, and reduces the need to add soil nutrients and fertilizers during the growing season.

Based on the available safety information and lack of adverse effects reported in the published literature for non-target organisms, humates do not pose any significant safety concerns and do not contain any ingredients that may be toxic to non-target organisms. Table 5 summarizes the current non-target organism data requirements and results supporting registration of humates.

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

Data Requirement	Guideline No.	Results / Findings	MRIDs
Avian Acute Oral Toxicity	850.2100	Data requirement is addressed with scientific rationale. Avian oral toxicity is not anticipated because humates are ubiquitous in soil and water, and birds are already naturally exposed. ACCEPTABLE	49080302
Avian Dietary Toxicity	850.2200	LC_{50} > 5620 ppm of PM-4300 (MP), Classified as practically nontoxic. ACCEPTABLE	48711112
Fish Acute Toxicity, Freshwater	850.1075	LC_{50} > 100 mg PM-4300 (MP)/L. Classified as practically nontoxic. ACCEPTABLE	48711113
Aquatic Invertebrate Acute Toxicity, Freshwater	850.1010	EC_{50} > 100 mg PM-4300 (MP)/L. Classified as practically nontoxic. ACCEPTABLE	48711114
Terrestrial Plant Toxicity, Seedling Emergence	850.4100	Data requirement is addressed with scientific rationale. Humates have historically been applied to crops with no reports of adverse effects to the environment. Humates provide benefits to soils and plants and are considered to have a nontoxic mode of action. ACCEPTABLE	48711116
Terrestrial Plant Toxicity, Vegetative Vigor	850.4150	Data requirement is addressed with scientific rationale. Humates have historically been applied to crops with no reports of adverse effects to the environment. Humates provide benefits to soils and plants and are considered to have a nontoxic mode of action. ACCEPTABLE	48711116
Nontarget Insect Testing	880.4350	Data requirement is addressed with scientific rationale. Humates are intended for application to growing crops. There have been no reports in the public literature of deleterious effects to honeybees and other non-target insects from exposures to humic acid or other humic substances. ACCEPTABLE	48711116

Risk Characterization

All non-target organism and environmental fate data necessary to meet the standard for humates risk assessments were satisfied through the acceptance of scientific rationales and data submissions. Scientific rationales were based on the lack of any reports of adverse effects to humans, other

mammals, insects or the environment despite it being applied to crops and soil historically. Since humates are ubiquitous in soil and water, birds, fish, and other living organisms are already naturally exposed. The major component of humates, humic acids, enriches the soil and stimulates root growth and uptake of nutrients by the treated plants, and the end-use product label application rates would result in little net increase in the background amount of humates already present in the environment.

In addition, the data submission for Avian Dietary toxicity (MRID 48711112; LC_{50} > 5620 ppm), Freshwater Fish Acute Toxicity (MRID 48711113; LC_{50} > 100 mg/L) and Aquatic Invertebrate Acute Toxicity (MRID 48711114; EC_{50} > 100 mg/L), classify humates as practically non-toxic.

The use and exposure of humates have not changed and the Agency's existing risk assessments (U.S. EPA, 2014) are sufficient to evaluate the use of humates in the currently registered end use product. Additionally, the Agency conducted a literature search for the active ingredients in this case which returned with no open literature studies and no incident reports. Hazard and exposure data, Agency risk assessments, and other information on the active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies. Based on this information in conjunction with the label, the Agency believes that when used in accordance with the label directions, the use of humates should not result in adverse effects to birds, fish, aquatic invertebrates or nontarget insects. However, due to its use as a plant growth regulator, an endangered species assessment will be needed in order to support a determination under the Endangered Species Act (ESA).

Literature and Incident 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 humates as derived from leonardite. Searches conducted for humates are described below.

Ecological Results:

Databases were searched, including PubChem, U.S. National Library of Medicine (National Institute of Health), Researchgate, PubMed, European Food Safety Authority (EFSA), and Google Scholar. Search terms included "humates", humic acid", "fulvic acid" paired with "avian" "plants" "insects," and "aquatic organisms". These terms resulted in zero relevant results (Accessed on 12/14/2023). Incident searches performed for humates using the Agency's pesticide incident database system returned no incident reports.

No additional information was gained from these searches that would alter BPPD's understanding of the current state of the science for any potential effects of humates 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))[10].

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.[11]

In addition, 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*

[10] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[11] 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

Screening Program (EDSP) for Humans under FFDCA Section 408(p);

- *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[12] and November 2022 ESA Workplan Update[13]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[14] 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 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

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

identify a group of chemicals with the highest priority for potential data collection (described in EPA's 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 humates**.** Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

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