Male Sea Lamprey Mating Pheromone

PC Codes 000802 and 000803

Preliminary Work Plan
Case Number 6325

Approved by: MADISON LE Digitally signed by MADISON LE Date: 2024.09.11 16:43:16 -04'00'

Madison H. Le, Director
Biopesticides and Pollution Prevention Division

Table of Contents

I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) Preliminary Work Plan (PWP) for Male Sea Lamprey Mating Pheromone (Case 6325) and is being issued pursuant to 40 CFR § 155.50. This case includes the active ingredients 3-ketopetromyzonol sulfate and 3-ketopetromyzonol-24-sulfate, ammonium salt, hereafter referred to as male sea lamprey mating pheromone. These active ingredients were grouped into one registration review case pursuant to 40 CFR § 155.42(a). This document explains what EPA's Office of Pesticide Programs (OPP) knows about male sea lamprey mating pheromone, 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 male sea lamprey mating pheromone. As stated in 40 CFR § 155.50 the opening of this docket initiates the current cycle of registration review for male sea lamprey mating pheromone.

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, 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. This PWP marks the beginning of registration review for male sea lamprey mating pheromone. 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 male sea lamprey mating pheromone and what additional risk analyses and data or information it believes are needed to make a registration review decision on male sea lamprey mating pheromone.

The Agency encourages all interested stakeholders to review the PWP and to provide comments and additional information that will help the Agency's decision-making process for male sea lamprey mating pheromone. Interested stakeholders could include the following: environmental nonprofit or interest groups; pesticide manufacturers; agricultural labor or commodity groups; commercial, institutional, residential, and other users of pesticides; or the general public. In addition to general areas on which persons may wish to comment, there are some areas identified in the PWP about which the Agency specifically seeks comments and information.

After reviewing and responding to comments and data received in the docket during this initial comment period, the Agency will develop and commit to a Final Work Plan (FWP) and anticipated schedule for the registration review of the male sea lamprey mating pheromone case. Additional

information on male sea lamprey mating pheromone can be found in the Agency's public docket (EPA-HQ-OPP-2024-0382) at www.regulations.gov.

This document is organized into five sections: the *Introduction*, which includes this summary and the male sea lamprey mating pheromone case overview; *Use Information*, which describes how and why male sea lamprey mating pheromone 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 male sea lamprey mating pheromone; *Guidance for Commentors*, which highlights topics of special interest, additional information and data the Agency should consider prior to issuing a FWP; and, lastly, the *Next Steps* and *Timeline*, which provides an anticipated timeline for the registration review process for male sea lamprey mating pheromone.

Male Sea Lamprey Mating Pheromone Registration Review Case Overview

Pursuant to 40 CFR § 155.50, the Agency will initiate a pesticide's registration review by establishing a docket for registration review of male sea lamprey mating pheromone (Case 6325) and opening it for public review.

This PWP marks the beginning of the current cycle of registration review for male sea lamprey mating pheromone, with the opening of public docket EPA-HQ-OPP-2024-0382 available at www.regulations.gov. The following list highlights significant events that have occurred during the current cycle of registration review for this case:

- September 2024 – The Agency is now publishing the *Male Sea Lamprey Mating Pheromone Preliminary Work Plan* for a 60-day public comment period.

II. Use Information

The first pesticide products containing male sea lamprey mating pheromone as an active ingredient were registered by the Agency in 2015. Currently, there are two registered pesticide products containing male sea lamprey mating pheromone, consisting of one manufacturing-use product containing 98.5% active ingredient and one end-use product (EP) containing 1.10%-active ingredient.

Male sea lamprey mating pheromone is a sex pheromone excreted by sea lampreys; however, as an active ingredient, the compound (3-ketopetromyzonol-24-sulfate, ammonium salt) is produced synthetically for practical use on a commercial scale. In its concentrated form, the compound is a crystalline solid, but it readily dissociates in solvents, allowing for dispersal in aquatic environments. As a pesticide, male sea lamprey mating pheromone is intended for use as an attractant to lure and trap female sea lampreys (*Petromyzon marinus*) during their spawning season. The registered EP is time-released from traps that are placed directly into upstream portions of tributaries of the Great Lakes, Lake Champlain, and the Finger Lakes, where sea lampreys are an invasive species.

Label Recommendations

Exposure to swimmers and boaters is expected to be minimal. The registrant indicated that application timing is overnight during sea lamprey migration and spawning season. This overnight application timing information is included on the EP label.

Table 1. Male Sea Lamprey Mating Pheromone Use Information		
Ingredient Name	3-Ketopetromyzonol sulfate	3-Ketopetromyzonol-24-sulfate, ammonium salt
PC Code	000802	000803
CAS Number	N/A	435327-06-3
Pesticide Classification	Sex pheromone	
Use Site Locations	Woodland/Nature Areas/Animal Habitat (Outdoor)	
Application Types	Bait treatment	
No. of Registrations	2 FIFRA Section 3 products[1]	
Physical Forms	Solution and crystalline	

III. Scientific Assessments

A summary of the Agency's human health and ecological risk assessments for male sea lamprey mating pheromone 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 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 from exposure to the active ingredient in this case. Results from submitted scientific rationale and validated non-guideline *in vitro* studies show that the active ingredient is slightly toxic and slightly irritating (toxicity category III) for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation. Skin sensitization is not anticipated. EP application rates are not expected to exceed natural levels of male sea lamprey mating pheromone. Furthermore, male sea lamprey mating pheromone is not persistent in the environment.

Summary of Dietary Exposure and Risk Characterization

There are no food use sites for the EP with this active ingredient. Dietary risks from exposure to residues on food are not expected. Although the active ingredient is directly applied to water, dietary risks from exposure to residues in drinking water are not expected due to the low oral toxicity profile of male sea lamprey mating pheromone, low application rates that do not exceed natural levels, and low persistence in the environment. Exposure from drinking water is unlikely, as water from the targeted application streams is not used as source of municipal drinking water. Prolonged or repetitive exposure is not expected.

Food Tolerances

No registered pesticide products containing male sea lamprey mating pheromone are approved for food use. Therefore, EPA has not required a tolerance or an exemption from the requirement of a tolerance for residues of male sea lamprey mating pheromone found in or on food.

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

Summary of Residential and Non-Occupational Exposure and Risk Characterization

The product is not for residential use; therefore, residential handler exposure is not expected. Non-occupational post-application exposures are also not expected. The EP is only applied to the tributaries of the Great lakes, Finger Lakes, and Champlain lakes during spawning season (April through June) at low rates that fall below natural levels. Exposure from swimming and boating activities are not expected during time of application. Timing of applications occurs overnight at 12 to 16 °C water temperature during lamprey migration at spawning season.

Summary of Occupational Exposure and Risk Characterization

Risks from occupational exposure are expected to be minimized by protective personal equipment (PPE) label requirements. Occupational handler exposure is mitigated by baseline attire (long sleeved shirt, long pants and socks) and PPE requirements (coveralls, and chemical resistant footwear and chemical resistant gloves (nitril or butyl), goggles and face shield, and respirator). Therefore, considering the low toxicity demonstrated in the hazard data for male sea lamprey mating pheromone, as well as baseline attire and PPE required on the EP label, risks from occupational exposure during product applications is expected to be minimal. According to use instructions on the EP label, the product is applied directly to water where spawning sea lamprey and traps are present. The sealed vial is opened, and the pheromone is mixed with water from the stream to be applied at the desired application rates ranging from 0.0472 – 4.72 ppt, which are below natural levels (33.4 to 120.9 ppt).

Human Incidents

A search of the OPP Incident Data System conducted on March 1, 2023, revealed no reported incidents associated with male sea lamprey mating pheromone. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

B. Summary of Environmental Risk Assessment

All nontarget organism data for male sea lamprey mating pheromone are addressed with scientific rationale. Effects are not anticipated for nontarget aquatic, or terrestrial organisms exposed to male sea lamprey mating pheromone when the EP is used according to the proposed label use directions. The male sea lamprey mating pheromone is not toxic to the target pest as it is a pheromone used to attract sea lamprey into traps. Exposure of nontarget organisms to the active ingredient is anticipated to fall within natural background levels emitted by sea lamprey during the spawning season. Thus, adverse effects on wildlife and aquatic organisms are not expected. Based on the available safety information and lack of adverse effects reported in the published literature for nontarget organisms, male sea lamprey mating pheromone does not pose any significant safety concerns and does not contain any ingredients that may be toxic to nontarget organism. For details see Appendix C.

Ecological Incidents

A search of OPP's Incident Data System conducted on March 1, 2023, revealed no reported incidents associated with male sea lamprey mating pheromone. This database contains information dating back to the 1970s and is continuously updated as incidents are reported.

Endangered Species Assessment

Based on male sea lamprey mating pheromone's lack of known direct toxic effects to nontarget organisms, no expected effects to the prey, pollination, habitat or dispersal (PPHD) of listed species, its limited use pattern, and low application rate that are at concentrations below natural background levels, the EPA has determined there is no reasonable expectation for any registered use of male sea lamprey mating pheromone to cause discernible direct effects to endangered (listed) species or their designated critical habitats. Due to non-toxic modes of action (pheromone) and low exposure to nontarget species, EPA is making a "No Effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitats for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

IV. Guidance for Commentors

Preliminary Work Plan

During the comment period, anyone may submit relevant data or information for the Agency's consideration. The public is invited to comment on the Agency's PWP. The areas below highlight topics of special interest to the Agency where comments, information and data, or reference to sources of additional information could be of particular use. The Agency will carefully consider all comments, as well as any additional information or data provided in a timely manner, prior to issuing a FWP for this case.

Additional Information

Stakeholders are also specifically asked to provide information and data that will assist the Agency in refining the risk assessments, including the ESA assessment. The Agency is interested in obtaining the following information regarding male sea lamprey mating pheromone:

i. Confirmation on the following label information:
   - *Sites of application*
   - *Formulations*
   - *Application methods and equipment*
   - *Maximum application rates*
   - *Frequency of application, application intervals, and maximum number of applications*
   - *Geographic limitations on use*
ii. Use or potential use distribution (e.g., acreage and geographical distribution of relevant use sites)
iii. Median and 90th percentile reported use rates from usage data – national, state, and county
iv. Application timing (date of first application and application intervals) – national, state, and county
v. Usage/use information for agricultural and nonagricultural uses
vi. Typical application interval (days)
vii. State or local use restrictions
viii. Monitoring data
ix. Foreign technical registrants not listed above who supply pesticide products containing male sea lamprey mating pheromone to the U.S. market

Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues related to registration review decisions, the Agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to male sea lamprey mating pheromone compared to the general population or who may otherwise be disproportionately affected by the use of male sea lamprey mating pheromone as a pesticide. Please comment if you are aware of any such issues and can provide information to help the Agency to more fully consider and address potential environmental justice issues.

V. Next Steps and Timeline

A Federal Register Notice will announce the docket opening for the current cycle of registration review for male sea lamprey mating pheromone and a 60-day comment period for this *Preliminary Work Plan* to provide comments and additional information that will help the Agency's decision-making process for male sea lamprey mating pheromone. After the 60-day comment period closes, the Agency will review and respond to any comments received in a timely manner, then issue a Final Work Plan for male sea lamprey mating pheromone. The Agency's final decision on the male sea lamprey mating pheromone registration review case will occur following satisfaction of the Endocrine Disruptor Screening Program (EDSP) obligations under FFDCA § 408(p).

Table 2. Anticipated Registration Review Schedule for Male Sea Lamprey Mating Pheromone

Anticipated Activity	**Estimated Month/ Year**
Opening the Docket	
Open Docket and 60-Day Public Comment Period for Preliminary Work Plan	September 2024
Close Public Comment Period	November 2024
Case Development	
Final Work Plan	January 2025
Registration Review Decision and Implementation	
Open 60-Day Public Comment Period for Proposed Registration Review Decision	June 2025
Close Public Comment Period	August 2025
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).

Appendix A –Product Characterization

The available product chemistry data for male sea lamprey mating pheromone (otherwise known as 3-ketopetromyzonol-24- sulfate ammonium salt; 3-kPMZS; 3-kPZS) are acceptable to support the current registration review case. The current product chemistry data requirements and results supporting registration are summarized in Table 3 per product data requirements in 40 CFR 158.2030. All product chemistry data requirements have been addressed with guideline studies on the Technical Grade Active Ingredient (TGAI) and have been found acceptable.

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

Data Requirement	Guideline No.	Results / Findings	MRIDs
Product identity and composition	880.1100	Confidential Business Information	48936201
Description of Starting Materials, Production and Formulation Process	880.1200	Confidential Business Information	48936201
Discussion of Formation of Impurities	880.1400	Confidential Business Information	49614503
Preliminary Analysis	830.1700	Confidential Business Information	49614501
Certified Limits	830.1750	Confidential Business Information	--
Enforcement Analytical Method	830.1800	Submitted data satisfy the data requirement	49614501 49614502
Color	830.6302	White	48936203
Physical State	830.6303	Solid	48936203
Odor	830.6304	Odorless	48936203
Stability to Normal and Elevated Temperatures, Metals, and Metal Ions	830.6313	Stable in the presence of aluminum (Al), iron (Fe), zinc (Zn) and their acetate salts. Stable at 54 ±2°C.	48936204
pH	830.7000	6.92 in 1% deionized water solution @ 25°C	48936203
UV/Visible Light Absorption	830.7050	No significant absorption observed.	48936204
Melting Point/Melting Range	830.7200	185.1°C	48936204
Boiling Point/Boiling Range	830.7220	N/A; TGAI is a solid.	48936203
Density/Relative Density/Bulk Density	830.7300	1305.6 kg/m^3	48936204
Particle Size, Fiber Length, and Diameter Distribution	830.7520	N/A; TGAI is soluble in water and not fibrous with diameter ≥0.1 µm	48936203
Partition Coefficient	830.7550	N/A; TGAI is soluble in water	48936203
Water Solubility	830.7840	46.41 mg/mL distilled water 12.89 mg/mL pH 4 20.46 mg/ml pH 10	48936204
Vapor Pressure	830.7950	N/A; TGAI is a salt.	N/A

Appendix B – Human Health Risk Assessment

Summary of Mammalian Toxicology Data

All human health data requirements per 40 CFR § 158.2050 have been satisfied with submission of non-guideline *in vitro* studies on the TGAI and rationale in lieu of animal studies. All studies and rationales have been jointly reviewed by EPA and Pesticides Management Regulatory Agency of Canada (PMRA) and found acceptable to support the current registration. These data are summarized in Table 4. No data gaps are identified.

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

Data Requirement	Guideline OCSPP No.	Results / Findings[1]	Toxicity Category/ Description	MRIDs[3]
Acute Oral Toxicity - Rat	870.1100	Satisfied with a weight of evidence (WOE) approach considering a lack of exposure[2] and an estimated LD_{50} > 2,000 mg/kg from *in vitro* testing. The *in vitro* test[3, 4] used H4IIE model (rat hepatoma-derived H4IIE cells) for assessing cytotoxicity. Values generated from 24 hours exposure to a series of concentrations in the presence of 20% serum are ranked to determine sustained concentration at which toxicity is predicted to occur after 14 days of repeated dosing. Results showed very low cytotoxicity based on intracellular adenosine triphosphate (ATP) concentration > 3,000 µM. Acceptable.	III	48936205
Acute Dermal Toxicity	870.1200	Satisfied with a WOE approach considering a lack of exposure[2] and *in vitro* toxicity data. The *in vitro* data include the cytotoxicity study submitted to satisfy the acute oral toxicity data requirement (MRID 48936205) and a guideline *in vitro* dermal absorption test (OECD 428)[3] (MRID 48936206). Abdominal skin from human cadavers was used to assess dermal absorption potential. Although the data are considered limited[6], results show very low percutaneous absorption and permeability. Acceptable.	III	48936206
Acute Inhalation Toxicity	870.1300	Satisfied using a WOE approach considering a lack of exposure[2], *in vitro*	III	48936207

Table 4. Summary of Toxicology Data (40 CFR § 158.2050)				
Data Requirement	**Guideline OCSPP No.**	**Results / Findings[1]**	**Toxicity Category/ Description**	**MRIDs[3]**
		toxicity data and physical/chemical properties of the active ingredient. The results from an *in vitro* test (no OCSPP or OECD guideline) using the MatTek Airway model, a 3-dimensional human airway epithelial model derived from human tracheal/bronchial epithelial cells cultured to imitate pseudo-stratified epithelial tissue of the respiratory tract, show a reduction in cell viability with increases in two pro-inflammatory markers. However, the active ingredient is not a volatile substance, and the intended use pattern[2] is not anticipated to result in inhalation exposure. Acceptable.		
Primary Eye Irritation – Rabbit	870.2400	Satisfied with a WOE approach considering lack of exposure [2] and *in vitro* toxicity data. In the *in vitro* test [3, 4] (OECD 492) using the MatTek EpiOcular model, stratified squamous epithelium is used, which is similar to the human corneal epithelium. Ocular tissue is exposed to multiple exposure periods to determine the ET_{50} (exposure time to reduce cell viability 50% relative to control). The ET_{50} value is converted to a Draize score. Cell viability of ocular tissues treated with 5% solution of male sea lamprey mating pheromone was 59.6%, 68.6%, 47.6%, 35.2% and 36.3% after 5-, 10-, 20-, 40- and 60-minute exposures, respectively. ET_{50} = 19.7 minutes corresponds to an *in vivo* Draize score of 18.2, and a ET_{50} score of toxicity category III [ET_{50} score ≥4 and ≤70 minutes, according to EPA Alternate Testing guidelines (U.S. EPA, 2015a)]. Results show the TGAI as being a mild ocular irritant. Acceptable.	III [5]	48936208
Primary Dermal Irritation	870.2500	Satisfied with a WOE approach considering lack of exposure[2] and *in vitro*	III	48936209

Table 4. Summary of Toxicology Data (40 CFR § 158.2050)				
Data Requirement	**Guideline OCSPP No.**	**Results / Findings[1]**	**Toxicity Category/ Description**	**MRIDs[3]**
		toxicity data. Results from an *in vitro* test[3] (OECD 439) using the MatTek Epiderm model, which mimics the human epidermis. Exposure to the controls and test material lasted 60 minutes. Tissues were analyzed after 42 hours recovery period. Average percent cell viability for the negative control was 100%; average percent cell viability for the positive control was 7%, and average percent cell viability in tissues treated with male sea lamprey mating pheromone was 111%. Acceptable.		
Dermal Sensitization	870.2600	Satisfied based on WOE approach considering lack of exposure[2] and likelihood of low percutaneous absorption and permeability (MRID 48936206)[6]. Acceptable.	___	48936210
Hypersensitivity Incidents		No sensitivity incidents have been reported	___	___
90-Day Oral	870.3100	Data requirement addressed with acceptable rationale based on lack of repetitive exposure. The product is not registered for food use. Acceptable.	___	48936211
90-Day Dermal	870.3250	Data requirement addressed with acceptable rationale based on lack of repetitive exposure.[2] Acceptable.	___	48936211
90-Day Inhalation	870.3465	Data requirement addressed with acceptable rationale based on lack of repetitive exposure[2]. The TGAI is a salt, soluble in water and non-volatile. Acceptable.	___	48936211
Prenatal Developmental	870.3700	Data requirement addressed with acceptable rationale based on lack of repetitive exposure. Repeated exposure through oral, dermal or inhalation routes to human females is highly unlikely. The TGAI is not registered for food use, and repeated exposure during post-	___	48936211

Table 4. Summary of Toxicology Data (40 CFR § 158.2050)				
Data Requirement	**Guideline OCSPP No.**	**Results / Findings[1]**	**Toxicity Category/ Description**	**MRIDs[3]**
		application and handling the product is highly unlikely[2]. Acceptable.		
Bacterial Reverse Mutation Test	870.5100	Data requirement addressed with acceptable rationale based on lack of repetitive exposure. The TGAI is not related to known mutagens. Unlikely repeated exposure during handling the product[2]. Acceptable.	___	48936211
In vitro Mammalian Cell Assay	870.5300 870.5375	Data requirement addressed with acceptable rationale based on lack of repetitive exposure. The TGAI is not related to known mutagens. Unlikely repeated exposure during handling the product[2]. Acceptable.	___	48936211

[1] LD_{50} = Lethal Dose causing 50% mortality in the sample

[2] Rationale for lack of exposure to TGAI: The EP is placed directly in the water near traps which are placed in waters of tributaries where female sea lampreys are present during spawning season from April to July. Male sea lamprey pheromone is released out of traps at trace amounts ranging from 0.0472 to 4.72 ppt, below natural concentrations. Natural concentrations range from 33.4 to 120.9 ppt in places where sea lampreys are found during spawning season. Exposure from drinking water is unlikely; water from the targeted application streams is not used as source of municipal drinking water. The only EP containing the active ingredient is registered for non-food use; therefore, dietary exposure is not expected. Post-application residential exposure is not expected because the EP is not for residential use and not applied to residential areas. Exposure from swimming and boating activities are unlikely during time of application (timing of applications occurs overnight at 12 to 16 °C water temperature when sea lampreys migrate during spawning season). Occupational handler exposure is mitigated by baseline attire and PPE requirements (coveralls, long sleeved shirt and long pants; socks and chemical resistant footwear and chemical resistant gloves (nitril or butyl), goggles and face shield, and respirator).

[3] Alternative *in vitro* tests were conducted due to extremely high cost of manufacturing the pheromone in large quantities required for limit dose testing to satisfy Tier I human health data requirements. Human health data from alternative *in vitro* tests were jointly reviewed and accepted by EPA and PMRA.

[4] Acute oral and primary eye irritation *in vitro* tests were conducted on human-derived cell cultures to evaluate toxicity effects over a range of exposure periods and concentrations. Toxicity or irritation was predicted from the *in vitro* data using proprietary algorithms developed by CeeTox, Inc. The *in vitro* toxicity modeling was peer reviewed and validated in the scientific literature (Refer to U.S. EPA, 2015c for a complete list of references for validation studies).

[5] Mild ocular irritant according to Alternate Testing Framework for Classification of Eye Irritation Potential of EPA Pesticide Products (U.S. EPA 2015a) https://www.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa.

[6] To assess dermal penetration, the Office of Pesticide Programs usually requires more than one assay. Therefore, the results from only one test (MRID 48936206) are not fully reliable for precluding low percutaneous exposure.

Human Health Risk Assessment

The data generated show that the active ingredient, male sea lamprey mating pheromone, is expected to be of low toxicity to humans and poses no risks of concern from exposure. No further testing is needed. All data requirements have been met and the database is complete, no new uses are

proposed, and no additional information has been found in the literature or incident database that would alter the Agency's previous risk conclusions. The Agency has determined that human exposure profile has not changed, and risks of concern are not anticipated. Therefore, the Agency's previous risk assessments are still applicable. Hazard and exposure data, Agency's risk assessments, and other information on this active ingredient were evaluated against standards established by FIFRA and the Agency's regulations and scientific policies.

Hazard Characterization

All data requirements, per 40 CFR § 158.2050, have been fulfilled for male sea lamprey mating pheromone. The toxicological database is considered complete for characterizing hazard and assessing risk from exposure to the active ingredient in this case. Results from submitted scientific rationale and validated non-guideline *in vitro* studies show that the active ingredient is classified as toxicity category III for acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary eye irritation, and primary dermal irritation. Skin sensitization is not anticipated.

Much of the WOE submitted to satisfy the mammalian toxicology data requirements is based on a lack of exposure to the active ingredient. Lack of acute and prolonged exposure is attributed to baseline attire and PPE requirements on the product label, application rate, time and place of application, and low persistence in the environment. Baseline attire and PPE requirements include coveralls, long sleeved shirt and long pants, socks, chemical resistant footwear and chemical resistant gloves (nitril or butyl), goggles and face shield, and respirator.

Male sea lamprey mating pheromone is naturally present at concentrations ranging from 5.3 ± 1.4 ppt to peak concentrations of 33.4 ppt and 120.9 ppt where sea lampreys are found during spawning season (Wang et al., 2013). The active ingredient is effective at concentrations ranging from approximately 0.0472 to 4.72 ppt. Application rates range from 11.0 to 13.0 mL/minutes, depending on stream flow. EP application rates are not expected to exceed natural levels (33.4 to 120.9 ppt) of male sea lamprey mating pheromone. Furthermore, male sea lamprey mating pheromone is not persistent in the environment. Estimated half-life of male sea lamprey mating pheromone is 5 days at 4°C (MRID 47805202). A much shorter half-life is reported in Wang et al. (2013) using an innovative extraction method employing Ultra-high Performance Liquid Chromatography with Mass Spectrometer (UPLC-MS/MS) analysis to quantify pheromone concentration. Pheromone concentrations were measured from triplicated water samples collected from five tributaries of Lake Ontario from April thru June. Pheromone concentrations were influenced by lamprey abundance (natural concentration of male sea lamprey mating pheromone increases downstream during spawning season when spawning sea lampreys are more abundant), discharge (dilution caused by rainfall), and water temperature. The reported average half-life for male sea lamprey mating pheromone was of 26.1 ± 1.8 hours at average water temperature of 18.2 ± 2.5^{o}C, and pH = 8.2 ± 0.2. Compared to migratory pheromones with average half-life of 3 days at water temperature of 15^{o}C, the faster degradation rate of male sea lamprey mating pheromone in the Wang et al. (2013) study is attributed to higher water temperature (18.2 ± 2.5^{o}C in Wang et al. (2013) versus 4°C in MRID 47805202), and the male sea lamprey mating pheromone's biological function. In contrast to migratory pheromones which must remain stable until the river enters the ocean or the Great Lake, which could be long distance (tens of kilometers downstream), male sea lamprey mating pheromone only needs to activate areas in its immediate proximity to lure female sea lampreys to nests occupied by males.

Exposure from swimming and boating activities are unlikely during time of application (timing of applications occur overnight at 12 to 16 °C water temperature when sea lampreys migrate during spawning season (MRID 48936212 with references therein)). The EP, containing 1.06 % w/w of male sea lamprey mating pheromone, is contained in sealed vials. Prior to application, the sealed vial containing the pheromone is opened and the pheromone is diluted with water from the stream to be applied at the desired concentration, ranging from 0.0472 to 4.72 ppt, depending on stream discharge at the application site. Rates of application (ranging from 0.0472 –4.72 ppt) are below natural levels (33.4 to 120.9 ppt) during spawning season. The EP is only intended for localized and timed applications. The pheromone is applied to upstream portions of tributaries of the Great Lakes, Lake Champlain, and Finger Lakes (the Great Lakes Basin) where spawning sea lampreys are present during spawning season from April to June, in conjunction with traps that are placed in the waters of the tributaries. According to label directions, male sea lamprey mating pheromone is diluted with stream water at the desired concentration, and released directly into water where traps are located to draw sea lampreys to the traps. According to use instructions on the EP label, applications are conducted at night from sunset to sunrise only during sea lamprey migratory and mating season.

The acute oral toxicity data requirement was satisfied with a WOE approach considering lack of exposure and an estimated LD_{50} > 2,000 mg/kg from *in vitro* testing (MRID 48936205) showing very low cytotoxicity based on an intracellular ATP concentration > 3,000 µM. The acute dermal toxicity data requirement was satisfied with a WOE approach considering a lack of exposure and combination of the *in vitro* cytotoxicity study (MRID 48936205) and a guideline *in vitro* dermal absorption test (OECD 428) (MRID 48936206). Although results from this test show very low percutaneous absorption and permeability, the data are considered supplemental. In general, OPP requires more than one assay for assessing dermal penetration. Therefore, the results from only one test (MRID 48936206) are not fully reliable for precluding low percutaneous exposure. However, due to the lack of exposure and the use of PPE, no acute dermal risk is expected and the data requirement is satisfied. The acute inhalation data requirement was satisfied with a WOE approach considering a lack of exposure, *in vitro* toxicity data (MRID 48936207) and physical/chemical properties of the active ingredient showing negligible volatility. Sea lamprey mating pheromone is a salt that dissolves in water, and the intended use pattern is not anticipated to result in inhalation exposure. The primary eye irritation data requirement was satisfied with a WOE approach considering lack of exposure and *in vitro* toxicity data (MRID 48936208) using the MatTek EpiOcular model (OECD 492). The ET_{50} value (exposure time to reduce cell viability 50% relative to control) generated from the MatTek EpiOcular model was converted to a Draize score. The ET_{50} of 19.7 minutes corresponds to an *in vivo* Draize score of 18.2. According to EPA Alternate Testing guidelines (U.S. EPA, 2015a), the ET_{50} score falls within ≥4 and ≤70 minutes. Based on these results male sea lamprey mating pheromone is classified a mild ocular irritant. The primary dermal irritation data requirement was satisfied with a WOE approach considering lack of exposure and *in vitro* toxicity data from a guideline (OECD 439) *in vitro* test (MRID 48936209) using the MatTek Epiderm model, which mimics the human epidermis. Based on these data, male sea lamprey mating pheromone was considered non-irritating. The dermal sensitization data requirement was satisfied with satisfied with a WOE approach considering lack of exposure and likelihood of low percutaneous absorption and permeability (MRID 48936206). All subchronic toxicity data requirements were satisfied with rationale based on lack of repetitive exposure and the non-food use pattern of the active ingredient.

Dietary Exposure and Risk Characterization

The only EP containing the active ingredient is registered for non-food use; therefore, dietary risks from exposure to residues on food are not expected. Although the active ingredient is directly applied to water, dietary risks from exposure to residues in drinking water are not expected due to the low oral toxicity profile of male sea lamprey mating pheromone, low application rates that do not exceed natural levels (See Hazard Characterization section), and low persistence in the environment (MRID 47805202) (Wang et al. 2013). It is applied to the tributaries of the Great lakes, Finger Lakes, and Champlain lakes during spawning season (April through June) at low rates that fall below natural levels. Exposure from drinking water is unlikely; water from the targeted application streams is not used as source of municipal drinking water. Prolonged or repetitive exposure is not expected.

Residential and Non-Occupational Exposure and Risk Characterization

The product is not for residential use; therefore, residential handler exposure is not expected. Non-occupational post-application exposures are also not expected. The EP is only applied to the tributaries of the Great lakes, Finger Lakes, and Champlain lakes during spawning season (April through June) at low rates that fall below natural levels. Exposure from swimming and boating activities are not expected during time of application. Timing of applications occurs overnight at 12 to 16 °C water temperature during lamprey migration at spawning season (references are attached to MRID 48936212).

Occupational Exposure and Risk Characterization

Risks from occupational exposure are expected to be minimized by PPE label requirements. Occupational handler exposure is mitigated by baseline attire (long sleeved shirt, long pants and socks) and PPE requirements (coveralls, and chemical resistant footwear and chemical resistant gloves (nitril or butyl), goggles and face shield, and respirator). Therefore, considering the low toxicity demonstrated in the hazard data for male sea lamprey mating pheromone, as well as baseline attire and PPE required on the EP label, risks from occupational exposure during product applications is expected to be minimal. According to use instructions on the EP label, the product is applied directly to water where spawning sea lamprey and traps are present. The sealed vial is opened, and the pheromone is mixed with water from the stream to be applied at the desired application rates ranging from 0.0472 – 4.72 ppt, which are below natural levels (33.4 to 120.9 ppt).

Overall Human Health Risk Characterization and Conclusion

There is ample information indicating that the use of male sea lamprey mating pheromone will not result in any meaningful exposure above natural background levels. The compound is expected to be of low toxicity and does not pose risks of concern through any route of exposure. Risk is mitigated by precautionary statements and baseline attire and PPE requirements on MP and EP labels. In conclusion, given the existing information regarding the low toxicity of male sea lamprey mating pheromone, the specific use pattern of the registered product containing this active ingredient, low application rates, infrequent and localized applications to specific sites, low persistence in the environment, and low volatility, no risks of concern are expected to occur via any route of exposure. The MP and the EP are manufactured in small batches. No new uses have been registered that justify the need for a new risk assessment. No adverse effects have been identified. Previous risk assessments are still applicable, and additional risk assessments are not needed.

One update has been made to the toxicity categories since the last risk assessment. Male sea lamprey mating pheromone was previously assigned toxicity category IV for primary dermal irritation. The toxicity classification has been changed to toxicity category III as a more conservative measure due to lack of robust data on the active ingredient. Currently, OPP does not have a policy for assigning toxicity categories for the primary dermal irritation data requirement supported by *in vitro* toxicity data.

With respect to labeling recommendations, according to the registrant, application timing is overnight during sea lamprey migration and spawning season. This information should be included on the product label.

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 male sea lamprey mating pheromone. Searches conducted for male sea lamprey mating pheromone are described below.

Human Health Results:

The male sea lamprey mating pheromone is also referred to by the chemical name 3-ketopetromyzonol-24-sulfate ammonium salt, and the acronym 3-KPZS in the scientific literature. A literature search was conducted with Google Scholar, PubMed, PMRA, ResearchGate, SciDirect, National Institute of Health (NIH), Sage Publications, and search engines using the terms “male sea lamprey mating pheromone,” “3-KPZS,” “3-ketopetromyzonol-24-sulfate ammonium salt” alone and in combination with the following terms: “mammalian toxicity.” The search under “male sea lamprey mating pheromone” alone or in combination with the terms “mammalian toxicity” and “pathogenicity” yielded a total of 55 results, none of which were related to human or mammalian pathogenicity or toxicity. Most of the search results were associated with management and control of sea lamprey, their physiology and behavior, and chemoreception mechanisms for intra specific communication. The terms “3-KPZS” and “3-ketopetromyzonol-24- sulfate ammonium salt” alone and in combination with “mammalian toxicity” and “pathogenicity” yielded zero results. An additional search was performed using PubMed, Sci Direct, and Google Scholar data bases with the terms “3-ketopetromyzonol-24-sulfate ammonium salt” or “3-KPZS and “male sea lamprey mating pheromone” in combination with “androgen,” “estrogen,” “hormone,” “cytotoxicity,” “thyroid,” and “endocrine disruptor.” The search yielded no results for endocrine effects of male sea lamprey mating pheromone on mammalian endocrine system. Most of the research results are associated to chemistry and physiological effects of male sea lamprey mating pheromone on sea lampreys. In conclusion, 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 male sea lamprey mating pheromone on humans or other mammals. An incident search performed for “male sea lamprey mating pheromone” using the Agency’s pesticide incident database system returned no incident reports.

Appendix C – Environmental Risk Assessment

Summary of Nontarget Organism Data

All nontarget organism data for male sea lamprey mating pheromone are addressed with scientific rationale to support the current registration review because effects are not anticipated for nontarget aquatic or terrestrial organisms exposed to male sea lamprey mating pheromone when the EP is used according to the proposed label use directions. The active ingredient male sea lamprey mating pheromone is not toxic to the target pest as it is a pheromone used to attract sea lamprey into traps. Exposure of nontarget organisms to the active ingredient is anticipated to fall within natural background levels emitted by sea lamprey during the spawning season. Thus, adverse effects on wildlife and aquatic organisms are not expected. Based on the available safety information and lack of adverse effects reported in the published literature for nontarget organisms, male sea lamprey mating pheromone does not pose any significant safety concerns and does not contain any ingredients that may be toxic to nontarget organisms. Table 5 summarizes the current nontarget organism data requirements and results supporting registration of male sea lamprey mating pheromone.

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 exposure to the male sea lamprey mating pheromone via drinking water or consuming contaminated prey is not expected to exceed exposure via these routes from the naturally occurring form of the active ingredient released into natural waters by male sea lampreys during the normal spawning periods. ACCEPTABLE	48936212 48936407
Avian Dietary Toxicity	850.2200	Data requirement is addressed with scientific rationale. Avian dietary toxicity is not anticipated because exposure to the male sea lamprey mating pheromone via drinking water or consuming contaminated prey is not expected to exceed exposure via these routes from the naturally occurring form of the active ingredient released into natural waters by male sea lampreys during the normal spawning periods. ACCEPTABLE	48936212 48936407
Fish Acute Toxicity, Freshwater	850.1075	Data requirement is addressed with scientific rationale. Fish acute toxicity is not anticipated because exposure to the male sea lamprey mating pheromone is not expected to exceed exposure from the naturally occurring form of the active ingredient released into natural waters by male sea lampreys during the normal spawning periods. ACCEPTABLE	48936212 48936407
Aquatic Invertebrate	850.1010	Data requirement is addressed with scientific rationale. Aquatic invertebrate acute toxicity is not anticipated	48936212 48936407

Table 5. Summary of Nontarget Organism Data (40 CFR § 158.2060)			
Data Requirement	**Guideline No.**	**Results / Findings**	**MRIDs**
Acute Toxicity, Freshwater		because exposure to the male sea lamprey mating pheromone is not expected to exceed exposure from the naturally occurring form of the active ingredient released into natural waters by male sea lampreys during the normal spawning periods. ACCEPTABLE	
Terrestrial Plant Toxicity, Seedling Emergence	850.4100	Data requirement is addressed with scientific rationale. Terrestrial plant toxicity is not anticipated because exposure to the male sea lamprey mating pheromone would only occur via irrigation with water treated with the EP. The concentration in treated water is not expected to exceed concentrations in natural waters found during the normal lamprey spawning periods. Toxicity of the male sea lamprey mating pheromone to plants has not been observed in any waters containing naturally occurring pheromone or experimental uses of the active ingredient. ACCEPTABLE	48936212
Terrestrial Plant Toxicity, Vegetative Vigor	850.4150	Data requirement is addressed with scientific rationale. Terrestrial plant toxicity is not anticipated because exposure to the male sea lamprey mating pheromone would only occur via irrigation with water treated with the EP. The concentration in treated water is not expected to exceed concentrations in natural waters found during the normal lamprey spawning periods. Toxicity of the male sea lamprey mating pheromone to plants has not been observed in any waters containing naturally occurring pheromone or experimental uses of the active ingredient. ACCEPTABLE	48936212
Nontarget Insect Testing	880.4350	Data requirement is addressed with scientific rationale. Nontarget insect toxicity is not anticipated because exposure to the male sea lamprey mating pheromone would only occur through contact with treated waters. The concentration in treated water is not expected to exceed concentrations in natural waters found during the normal lamprey spawning periods. Toxicity of the male sea lamprey mating pheromone to terrestrial insects has not been observed in any waters containing naturally occurring pheromone or experimental uses of the active ingredient. ACCEPTABLE	48936212

Risk Characterization

All nontarget organism and environmental fate data necessary to meet the standard for male sea lamprey mating pheromone risk assessments were satisfied through the acceptance of scientific rationale. The scientific rationale was based on petromyzonol sulfate being a naturally occurring substance produced by sea lamprey larvae. The chemical is part of compounds known as bile acid (Li et. al. 2002 and Yun et. al. 2002). Sea lampreys produce the substance throughout the year, and it is a naturally occurring substance already present in waters where invasive species control efforts will be made. The concentration of male sea lamprey mating pheromone is not anticipated to exceed the amount that is already present in the environment. During the spawning season, the natural concentrations range between 33.4 to 120.9 ppt (Johnson et. al., 2009; Siefkes et al., 2005) (references are attached to MRID 48936406). Also, the active ingredient is not toxic to the target pest as it is a pheromone used to attract sea lamprey into traps. When applied as a pesticide in traps, exposure of male sea lamprey mating pheromone to nontarget organisms is lower than the natural background levels of male sea lamprey mating pheromone emitted by sea lamprey. The addition of male sea lamprey mating pheromone from pesticides is not expected to increase ambient levels due to the short half-life and localized proximity to traps. Male sea lamprey mating pheromone does not persist in the environment and had an average half-life across three sample reservoirs of 26.1 ± 1.8 hours (Wang et. al., 2013—see Human Health Hazard Characterization section for more study details). In more than 60 years that sea lamprey and their mating pheromones have been in the target streams, no toxic effects from exposure to these compounds has ever been observed or reported. In addition, efficacy studies demonstrated that nontarget species were not more likely to be captured in male sea lamprey mating pheromone-baited traps compared to unbaited traps. Thus, adverse effects on wildlife and aquatic organisms are not expected.

The use and expected exposure of male sea lamprey mating pheromone have not changed, and the Agency's existing risk assessment (U.S. EPA, 2015b) concluded that there are no concerns for nontarget aquatic or terrestrial organisms resulting from the use of the EP according to the label use directions, which is sufficient to evaluate the use of male sea lamprey mating pheromone in the currently registered EP. 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 male sea lamprey mating pheromone should not result in adverse effects to birds, mammals, amphibians, reptiles, fish, aquatic invertebrates, nontarget insects, or plants.

Literature Search Findings

To support registration review, 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 male sea lamprey mating pheromone. Searches conducted for male sea lamprey mating pheromone 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 “male sea lamprey mating pheromone AND avian,” “male sea lamprey mating pheromone AND plants,” “male sea lamprey mating pheromone AND insects,” “male sea lamprey mating pheromone AND aquatic organisms”. These terms resulted zero relevant result (accessed on 8/17/2023). Incident searches performed for male sea lamprey mating pheromone using the Agency’s pesticide incident database system returned no incident reports.

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 male sea lamprey mating pheromone 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 initiatives 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 adverse estrogen, androgen, or thyroid effect. If EPA finds, based on that data, that the pesticide has an adverse endocrine-related 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))[2].

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.[3]

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*

[2] For additional details of the EDSP, please visit https://www.epa.gov/endocrine-disruption.
[3] 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

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)*;
- *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, considering its current focus on developing a comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[4] and November 2022 ESA Workplan Update[5]). However, EPA notes that for 35 of the List 1 chemicals (33 active ingredients and 2 inert ingredients), Tier 1 WoE memoranda[6] indicate that available data were sufficient for FFDCA section 408(p) assessment and review for potential adverse 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 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 the chemical's potential to interact with estrogen, androgen, and/or thyroid pathways and EPA will generally not need to obtain any additional data to reevaluate those pathways, if in registration review, or to provide an initial evaluation for new active ingredient applications. For instance, EPA has endocrine-related data for numerous conventional pesticide active ingredients through either a two-generation reproduction toxicity study performed in accordance with the current guideline (referred to here as the updated two-generation reproduction toxicity 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 reevaluate the available data for the conventional active ingredient during registration review to determine what additional data, if any, might be needed to confirm EPA's assessment of the potential for impacts to estrogen,

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

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 with a two-generation reproduction toxicity study performed under a previous guideline (i.e., an updated two-generation reproduction toxicity study or an EOGRT is not available), 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 EDSP Strategies Notice as Group 1 active ingredients). For these cases, although EPA has not reevaluated the existing endocrine-related data, EPA has sought additional data and information in response to the 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 to confirm the sufficiency of data to support EPA's assessment of potential adverse effects to the estrogen, androgen, and/or thyroid pathways in humans and to inform FFDCA 408(p) data decisions. For the remaining conventional pesticides (described in EPA's EDSP Strategies Notice as Group 2 and 3 conventional active ingredients), EPA committed to reevaluating the available data to determine what additional studies, if any, might be needed to confirm EPA's assessment of 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 male sea lamprey mating pheromone. Such issues will be addressed in future updates by EPA on its strategies for implementing FFDCA section 408(p).

References

Johnson, N. S., Yun, S., Thompson, H. T., Brant, C. O., and Li, W. 2009. A synthesized pheromone induces upstream movement in female sea lamprey and summons them into traps. PNAS. 2009, 106 (4) 10-21.

Li, W., Scott, A.P., Siefkes, M.J., Yan, H., Liu, Q., Yun, S., and Gage, D.A. (2002). Bile Acid Secreted by Male Sea Lamprey That Acts as a Sex Pheromone. Science, 296(5565), 138–141.

Siefkes, M.J., Winterstein SR and Li WM 2005. Evidence that 3-keto petromyzonol sulphate specifically attracts ovulating female sea lamprey, *Petromyzon marinus*. Animal Behaviour 70: 1037-1045.

US EPA. 2015a. Alternate Testing Framework for Classification of Eye Irritation Potential of EPA Pesticide Products. https://www.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa

US EPA. 2015b. Science Review in Support of the Registration of Male Seal Lamprey Pheromone Technical and Male Sea Lamprey Mating Pheromone Respectively Containing 99.3% and 1.06% 3-Ketopetromyzonal Sulfate as Their Active Ingredient. Tier I Non-Target Organism Hazard Assessment. BPPD Concurrence of Review by CANADA PMRA. Endangered Species Assessment Addendum.

US EPA. 2015c. Registration Decision for the New Active Ingredient Male Sea Lamprey Mating Pheromone. Signed 12/14/2015.

Wang, H., Johnson, N. Bernardi, J. Terry, H and Li, W. 2013. Sea Lamprey Pheromones and their Degradation Using Rapid Streamside Extraction Coupled with UPLC-MS/MS. Journal of Separation Science. Vol. 36: Issue 9-10, pp. 1612-1620.

Yun, S.S., Scott, A. P., Siefkes, M.J., and Li, W.M. 2002. Development and application of ELISA for the sex pheromone released by the male sea lamprey (*Petromyzon marinus).* General and Comparative Endocrinology. 129(3): 163-170.

Cited MRIDs

MRID 48936201. Hessler, E.; Johnson, N. (2009) Product Identity and Composition, Description of Starting Materials, Production and Formulation Process, and Discussion of Formation of Impurities for 3-Keptopetromyzonol-24-sulfate, Ammonium Salt. Project Number: 3KPZS/TGAI/09/ID/COMP/02. Unpublished study prepared by Great Lakes Fishery Commission. 14p.

MRID 48936203. Johnson, N. (2011) Physical and Chemical Characteristics of 3-Ketopetromyzonol-24-sulfate, Ammonium Salt Technical Grade Active Ingredient. Project Number: 3KPZS/TGAI/11/PHYSCHEM/2. Unpublished study prepared by U.S. Dept. of The Interior. 5p.

MRID 48936204. Leslie, S.; Moseley, R. (2010) Male Sea Lamprey Mating Pheromone (3-Ketopetromyzonol-24-Sulfate, Ammonium Salt) Evaluation of Selected Physical Chemical Properties: Final Report. Project Number: 1001827 8222236. Unpublished study prepared by Covance Laboratories, Ltd. 138p.

MRID 48936205. Wilga, P. (2012) Acute Systemic Toxicity (LD50) Panel: 24 and 72 Hr. Project Number: 9195/100512/ACUTE. Unpublished study prepared by CeeTox, Inc. 35p.

MRID 48936206. Burton, P. (2012) In vitro Percutaneous Absorption of 3-Keptopetromyzonol-24-sulfate, Ammonium Salt in a Cadaver Skin Model. Project Number: 9195/100512. Unpublished study prepared by CeeTox, Inc. 16p.

MRID 48936207. Willoughby, J. (2012) In vitro Prediction of Acute Airway Irritation Using the MatTek EpiAirway Model. Project Number: 9195/100512AIR. Unpublished study prepared by CeeTox, Inc. 32p.

MRID 48936208. Willoughby, J. (2012) In vitro Prediction of Acute Ocular Irritation Using the MatTek EpiOcular Model: (Male Sea Lamprey Pheromone Technical). Project Number: 9195/100512OCL. Unpublished study prepared by CeeTox, Inc. 25p.

MRID 48936209. Willoughby, J. (2012) In vitro Prediction of Acute Dermal Irritation Using the MatTek EpiDerm Model: (Male Sea Lamprey Pheromone Technical). Project Number: 9195/100512SIT. Unpublished study prepared by CeeTox, Inc. 23p.

MRID 48936210. Wilga, P. (2012) Skin Sensitization in 3-D Model: 1 Test Article: (Male Sea Lamprey Pheromone Technical). Project Number: 9195/100512SENS. Unpublished study prepared by CeeTox, Inc. 26p.

MRID 48936211. Hubert, T. (2012) Waivers Requests for Tier 1 Human Health Assessment Subchronic Testing, Developmental Toxicity, Mutagenicity Testing for 3-Ketopetromyzonol-24-sulfate, Ammonium Salt Technical-grade Active Ingredient. Project Number: 3KPZS/11/HUMANTOXWAIVERS/02. Unpublished study prepared by Great Lakes Fishery Commission. 8p.

MRID 48936212. Hubert, T. (2012) Waivers Requests for Tier 1 Nontarget Avian and Aquatic Organisms, Plants and Insect Testing for 3-Ketopetromyzonol-24-sulfate, Ammonium Salt Technical-grade Active Ingredient. Project Number: 3KPZS/11/NONTARGETWAIVERS/02. Unpublished study prepared by Great Lakes Fishery Commission. 7p.

MRID 48936407. Rivera, J. (2011) Acute, Avian and Aquatic Organisms Toxicity Guideline Waiver Requests for the Male Sea Lamprey Mating Pheromone End-Use Product. Project Number: GLFC/10/VISCOSITY/01. Unpublished study prepared by Upper Midwest. 8p.

MRID 49614501. Shen, H.; Arndt, T. (2015) Preliminary Analysis of Technical Grade 3-Ketopetromyzonol-24-sulfate, ammonium salt (3KPZS). Project Number: 2653W. Unpublished study prepared by PTRL West, Inc. 46p.

MRID 49614502. Shen, H.; Arndt, T. (2015) Method Validation of 3-Ketopetromyzonol-24-sulfate, Ammonium Salt (3KPZS) Assay in Technical Grade 3KPZS. Project Number: 2652W. Unpublished study prepared by PTRL West, Inc. 45p.

MRID 49614503. Hessler, E. (2015) Impurity Discussion for the Preparation of Ammonium 3-Ketopetromyzonol-24-sulfate. Unpublished study prepared by Bridge Organics Co. 4p.