STATE OF CONNECTICUT
DEPARTMENT OF PUBLIC HEALTH

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TOCOLOGY OVERVIEW AND ASSESSMENT FOR SELECTED HERBICIDES:
Procellacor within Drinking Water Watersheds
Environmental Health Section, October 2018

Through the Memorandum of Understanding between the Connecticut Department of Energy and Environmental Protection and the Drinking Water Section of the Connecticut Department of Public Health (CTDPH) regarding the use of pesticides in drinking water management areas, CTDPH's Environmental and Occupational Health Assessment program has reviewed the proposed use of Procellacor. This CTDPH evaluation is intended to inform the process by providing a toxicity and environmental fate review.

In summary, our findings are that Procellacor has low mammalian toxicity and no clear indication of carcinogenicity, mutagenicity or ability to cause reproductive effects, especially at the low environmental concentrations possible from its proper application. Procellacor's environmental degradation time is short, indicating that there is a low probability of detecting the parent compound in drinking water. Degradation time is longer however for hydroxyl acid breakdown product which also sequesters in plant sugars. Despite the uncertainty around the environmental persistence of Procellacor's degredates, the CTDPH does not believe that the use of this herbicide in watershed areas will adversely impact drinking water supplies or human health when used in accord with US EPA label instructions.

PRODUCT INFORMATION

Active Ingredient: Florpyrauxifen-benzyl (2.7%)
CAS #: 1390661-72-9
Trade Name: PROCELLACOR EC
EPA Reg # 67690-80 (February 27, 2018) Decision No. 534950
Application methods and rates:

- For in-water applications, the maximum single application rate is 80 fluid ounces product per acre-foot of water with a limit of three applications per year.
- For aquatic foliar applications, do not exceed 32 fluid ounces product per acre for a single application and do not apply more than 64 fluid ounces product total per acre per year.

Inactive Ingredients:

- Ethylhexanol (2.1 %)
- Methanol (0.9%)
- Unreported (94.3%)

Use Restrictions:

- There are no restrictions for recreational purposes, including swimming and fishing.
- Allow 14 days or greater between applications.

MECHANISM OF HERBICIDAL ACTIVITY

Procellacor belongs to the arylpicolinate group of synthetic auxin herbicides. This herbicide mimics the effect of a persistent high dose of the natural plant hormone auxin, causing over-stimulation of specific auxin-regulated genes which results in the disruption of several growth processes in susceptible plants.

ENVIRONMENTAL FATE AND PERSISTANCE

Water Column:
Procellacor has a low water solubility (about 15 µg/L) and is rapidly hydrolyzed in surface water with a half-life of 1.3 days at pH 9. When exposed to direct sunlight, the photolytic half-life approximately 0.1 days.

Soils and Sediments:
Procellacor log Koc values are approximately 5.4 to 5.5, indicating that the compound will bind to organic carbon of soils with high affinity. The compound degrades in aerobic soil with half-lives ranging from 2.5 to 34 days. Anaerobic soil metabolism rates are similar to the aerobic rates. The parent compound is thus not expected to accumulate in the sediments of treated lakes.

Environmental Degradants:
The primary degradation pathway in aerobic and anaerobic sediments and the water column is through cleavage of the benzyl ester parent to form the acid metabolite (X11438848). (The degradation scheme is outlined in the Appendix.) The acid metabolite exhibits moderate mobility potential, with an average Koc value of 115 mL/g. In acidic environments, the ester moiety is spared and the methyl-ether group cleaved to form an alcohol (X12300837). This compound has a low water leaching potential (Koc value is 2727 mL/g) as it binds tightly to soil. It is thus not expected to be a concern in surface water. Procellacor (XDE-848 benzyl ester) is also degraded by sunlight. The dechlorinated acid degradant of photolysis, X12393505 and the aforementioned primary hydrolysis product have similar leaching potentials. Both the acid and the alcohol compounds are further degraded to a hydroxyl acid (X11966341). This hydroxyl acid metabolite has a geometric mean water/organic carbon partition coefficient (Koc) of 61.2 (Volume 3 – Annex CA - B.8 – Page 147), indicating that this compound is mobile in the aquatic environment. The hydroxyl metabolite is also moderately persistent in the environment. The water half-life (DT50) in a water/sediment system ranged from 37.3 to 87.9 days (Volume 3 – Annex CA - B.8 – Page 237). The list of Procellacor degradants that could be present in surface waters therefore includes; X11438848 (XDE-848 acid), X12131932 (dechlorinated XDE-848 BE), X12393505 (dechlorinated XDE-848 acid), and X11966341 (hydroxyl acid).

Degradation times for the first three aforementioned degradants are short, while the degradation time for the hydroxyl acid is greater and may be prolonged. The prolonged effect is likely due to sequestration with plant sugars (e.g.; cellulose) via conjugation of the hydroxyl acid with glucose. Significant portions of the hydroxyl acid metabolite were converted to either a glucose conjugate (X12431091) or a glucose-malonic acid conjugate (X12431475) in treated crops (Volume 1 – Level 1 – Page 41).

The X11966341 (hydroxyl acid) degradant is formed in significant quantities relative to the applied dose. When radiolabeled Procellacor was applied to the water layer in aerobic flooded soil systems, the maximum total system concentration of X11966341 was 64% of the applied radioactivity (Volume 1 – Level 1 – Page 44).

While the parent compound is unlikely to be a contaminant of concern in drinking water, this has not been demonstrated for the X11966341 (hydroxyl acid) degradant. Further work should investigate this degradant's fate and persistence in the aquatic environment.
Furthermore, as the hydroxyl degradant is known to sequester in plant sugars, the possibility that decomposition could release this degradant into the water column should be evaluated.

TOXICOKINETICS

Mammalian absorption and elimination:
Excretion is primarily via feces (> 51%) and urine (8-42%) with the majority eliminated within 24 hr. Plasma elimination of Procellacor is biphasic with a rapid declining plasma alpha phase ($t_{1/2\alpha}$=~2 hours) and a more slowly declining beta phase plasma half-life ($t_{1/2}$= 27-51 hours) in both male and female rats. The fraction eliminated in the urine was higher in the lower dose groups, consistent with higher absorption at lower doses. This kinetic non-linearity is consistent with either reduced absorption or higher biliary elimination at the high dose, as possible reasons for reduced renal elimination at the high dose. Based on relatively low percent recoveries in the liver and in bile samples the non-linearity appears to be a result of reduced absorption of Procellacor at higher dose levels.

Mammalian metabolism:
The kinetic profile of Procellacor was consistent across the species in rats, mice, dogs and rabbits, with a rapid systemic absorption and complete hydrolysis of the absorbed fraction to the acid metabolite (X11438848) and other minor metabolites. There was no Procellacor detected in the urine, blood or liver samples across species suggesting that the systemic exposure is primarily to the acid metabolite (X11438848). The hydroxyl acid metabolite (X11966341) is a small percentage of the dose and is eliminated through conjugation. As a percentage of the dose, the sum of the hydroxyl acid and its conjugate is less than 5%.

The European Union, in their assessment, considered the hydroxyl acid (X11966341) toxicity to be covered by the toxicological database of the parent compound (Volume 1 – Level 1 – Page 33). Though this assumption cannot presently be refuted, the lack of toxicity data for this specific degradant represents a significant gap in the toxicology database because, as per the discussion in the section on environmental degradants, the hydroxyl acid (X11966341) is the contaminant of greatest concern for surface water.

Results from in vitro comparative metabolism study have shown that Procellacor was highly metabolized in liver microsomes from rat, mouse, dog, rabbit, and human donors. No unique metabolites were formed in human microsomal incubations compared to rat, mouse, rabbit or dog microsomal incubations.

Mammalian distribution:
Procellacor is well metabolized primarily in to a single metabolite XDE-848 acid (X11438848), and readily eliminated in urine and feces from the rat, with almost no tissue residues. In necropsied test animals, the concentrations of Procellacor were highest, by far, in the GI tract, followed by urinary bladder, plasma, kidney and liver.

When goats were dosed with radiolabeled Procellacor at 10 mg/kg dry feed in the diet for 7 consecutive days, approximately 80% of applied test material was recovered. Of the radioactivity recovered, > 99% was eliminated from the animals through the feces and urine. Less than 1% of recovered radioactivity was detected in the edible tissues and milk. Only the liver and kidney tissues contained > 0.010 mg/kg. Edible tissues and milk contained < 0.010 mg/kg. Parent compound distribution is thus limited primarily to within the portal of entry and primary excretion tissues.

Maximum Tolerated Dose:
The inflection point for onset of a sublinear relationship between administered dose and systemic concentration is a benchmark which represents the kinetically derived maximum dose (KMD). In test animals exposed to Procellacor, this inflection point is between 300 and 1000 mg/kg*day. The highest dose tested in registration studies is within this range and justifiably represents the practical limit on administered dose.

TOXICOLOGY DATABASE

Tumor Effect:
In a long-term study, the incidence of adenocarcinoma of the rat mammary gland was 0/50, 0/6, 1/11, and 2/50 in males given 0, 10, 50 or 300 mg/kg/day, respectively (Two-Year Chronic Toxicity/Oncogenicity Study in F344/DuCrl Rats. In Volume 3 – Annex CA - B.3 – Page 222). This dose response has been identified as possibly indicative of a data gap and has led some reviewers to consider 50 mg/kg*day the NOAEL for an endocrine effect. (European Food Safety Authority (2018) https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5378) Others however have noted that the minimally higher incidence of mammary gland adenocarcinomas in males given the high-dose of 300 mg/kg/day was not statistically significant, and while effects on mammary gland including mammary tumors are most commonly seen in female rats, study, there were no treatment-related effects on the mammary gland of females at any dose in this study, and no females from either the control or treatment groups had an adenocarcinoma of the mammary gland.

While this response to Procellacor may represent a data gap, the response was positive in just a single test animal in the 50 mg/kg group, and the effect is not dose-dependent. Though the result is most likely an artifact, the small number of test animals in the 10 and 50 mg/kg*day groups highlights a weakness in the study.

TUMOR EFFECT OR THRESHOLD							
*LOAEL (mg/kg*day)*	*NOAEL (mg/kg*day)*	*Doses (mg/kg*day)*	*Route of Exposure*	*Tumor Endpoint*	*N (initial)*	*# Dosing Days*	*Model*
none	>300	0,10,50,300	Diet	no significant tumor result *	50/(sex* group)	760	Rat
none	>800(F),>1000(M)	0,50,200,800(F), 1000(M)	Diet	no significant tumor result	50/(sex* group)	547	Mouse

* Dose response for interstitial cell adenomas of the testes was within the range of historical controls.

Sub-Chronic Exposure Studies

Short-term dietary toxicity studies in F344 rats, CD-1 mice, and Beagle dogs were conducted. There were no treatment-related effects on clinical signs, body weights, body weight gains, feed consumption, ophthalmology, hematology, prothrombin time, clinical chemistry parameters, urinalysis, organ weights, and gross or histopathologic observations. There was no evidence of short-term toxicity when Procellacor was administered up to a limit dose of 1000 mg/kg/day for 28 days or 90 days in rats, mice or dogs.

SYSTEMIC EFFECT OR THRESHOLD (SUBCHRONIC)								
*HDT (mg/kg*day)*	*LOAEL (mg/kg*day)*	*NOAEL (mg/kg*day)*	*Doses (mg/kg*day)*	*Effect*	*Route of Exposure*	*# Dosing Days*	*Model*	*N (initial)*
1000	none	>1000	0,250,500,1000	No effect	Diet	28	Rat	5 each sex/grp
1000	none	>1000	0,250,500,1000	No effect	Diet	28	Mouse	5 each sex/grp
1000	none	>1000	500, 1000	5% d bw, hd	Diet	28	Dog	2 male, 4 female
1000	none	>1000	0,100, 300, 1000	No effect	Diet	90	Rat	5 each sex/grp
1000	none	>1000	0,100,300,1000	F HDT: 9.6% d bw & 31% d bwg	Diet	90	Mouse	10 each sex/grp
1008	none	>1008	0,106,336,1008	No effect	Diet	90	Dog	4 each sex/grp

Chronic Exposure Studies

In the rat study there were no statistically significant or treatment-related changes in final body weights or any of the organ weights of males or females at any dose level as compared to the respective controls. There were no treatment-related histopathological observations in any of the organs/tissues examined.

In the mouse study there were no treatment-related differences in body weights/body weight gains of males or females between any of the treatment groups as compared to their respective controls. There were no treatment-related histopathologic observations in males or females at any dose level.

SYSTEMIC EFFECT OR THRESHOLD (CHRONIC)							
*HDT (mg/kg*day)*	*LOAEL (mg/kg*day)*	*NOAEL (mg/kg*day)*	*Doses (mg/kg*day)*	*Effect*	*Route of Exposure*	*# Dosing Days*	*Model*
300	none	>300	0,10,50,300 *	none	Diet	365	Rat
800(F),1000(M)	none	>800(F), >1000(M)	0,50,200,800(F), 1000(M)	none	Diet	547	mouse

* Above kinetically derived maximum dose

Reproductive

There were no treatment-related effects in clinical observations, body weights, feed consumption, reproductive function, litter size, prenatal/early neonatal growth and survival of the offspring, organ weights, gross pathology or histopathology in either sex at all dose levels tested.

REPRODUCTIVE EFFECT OR THRESHOLD								
*Doses (mg/kg*day)*	*Parental LOAEL, devel/repro (mg/kg*day)*	*Parental NOAEL, devel/repro (mg/kg*day)*	*Offspring LOAEL, devel/repro (mg/kg*day)*	*Offspring NOAEL, devel/repro (mg/kg*day)*	*Route of Exposure*	*Subject N*	*Note*	*Model*
0,100,300, 1000	none	1000	none	1000	Diet	10/(sex*group)	Screening study	Rat
0,10,50,300	none	300	none	300	Diet	25/(sex*group)	Dietary Two-Generation Reproduction	Rat

Developmental

In rats, administration of Procellacor in the diet at 975 mg/kg*day, the KMD, produced no treatment-related maternal toxicity and no indication of embryo/fetal toxicity or teratogenicity.

In rabbits, administration of Procellacor in the diet at 1042 mg/kg*day, the KMD, produced no treatment related maternal toxicity and no indication of embryo/fetal toxicity or teratogenicity.

DEVELOPMENTAL EFFECT OR THRESHOLD										
*HDT (mg/kg*day)*	*Doses (mg/kg*day)*	*Maternal LOAEL (mg/kg*day)*	*Maternal NOAEL (mg/kg*day)*	*Effect, maternal*	*Offspring LOAEL (mg/kg*day)*	*Offspring NOAEL (mg/kg*day)*	*Effect, developmental*	*Route of Exposure*	*Model*	*Study N*
975	0,975	none	975	none	none	975	none	Diet	Rat	24/(group)
1042	0,1042	none	1042	none	none	1042	no sig ef treat *	Diet	Rabbit	24/(group)

* The effect on percent postimplantation loss was above historical controls but statistically insignificant

TOXICOLOGY SUMMARY

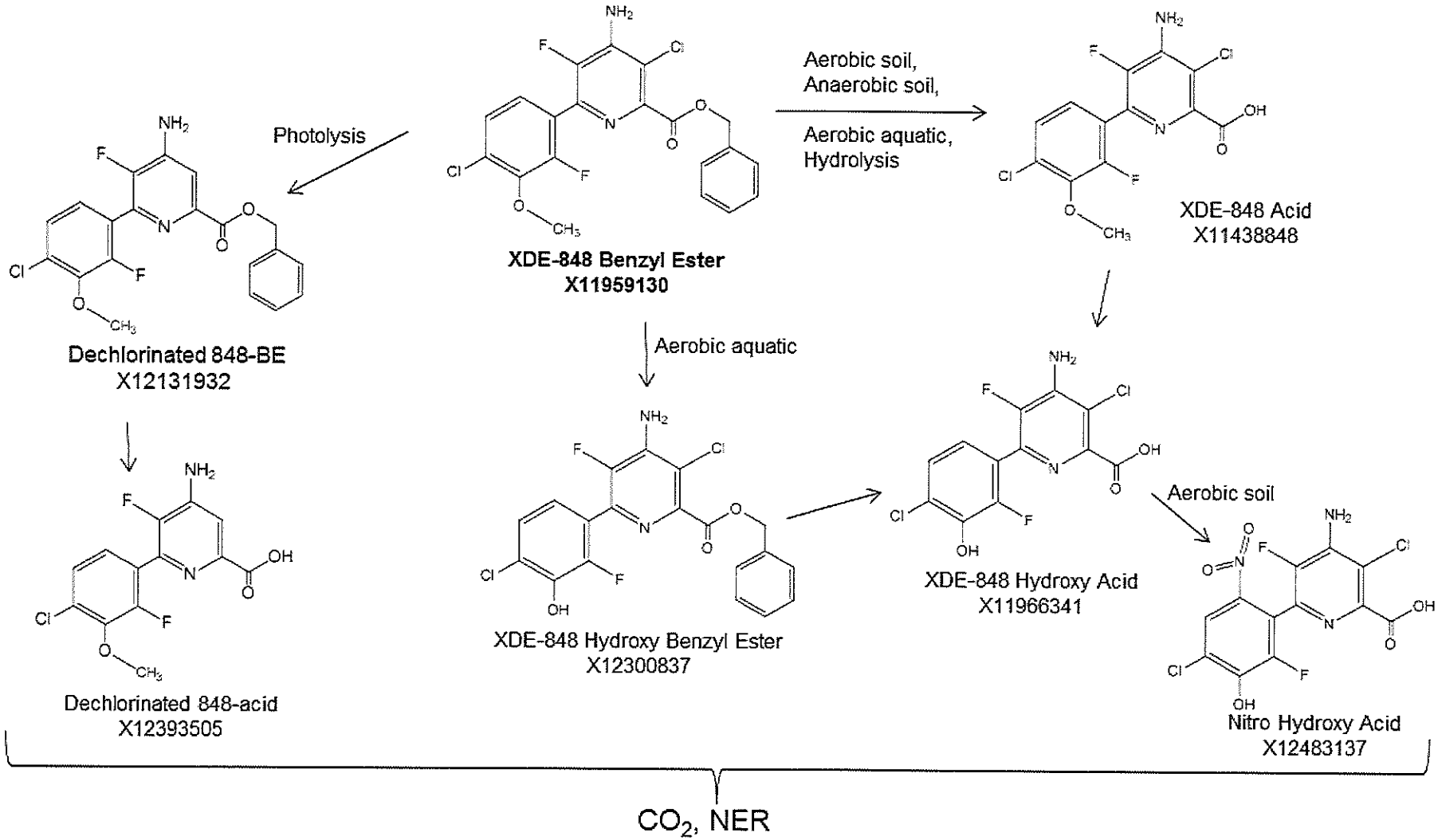
The toxicology database for the parent compound, Procellacor (XDE-848 benzyl ester), is nearly complete with the exception of some uncertainty focused at the low denominators in the 10 and 50 mg/kg*day groups in the long-term toxicity study. (See the section on tumor effect.) Overall, the parent compound is poorly absorbed in mammalian systems, and distribution is limited to the organs of excretion.

The available mammalian toxicology database for this herbicide understandably focuses almost exclusively on the parent compound. Within this report's scope (use around drinking water supplies), this is a limitation because the parent compound is not the most persistent in the aquatic environment. The hydroxyl acid degradant (X11966341) therefore presents the greatest exposure potential within the drinking water exposure scenario.

SOURCES

The information referenced in this report was obtained from the European Food Safety Authority; "Public consultation on the active substance florpyrauxifen-benzyl - Updated: 28 July 2017", available at https://www.efsa.europa.eu/en/consultations/call/170705. Information from the relevant US EPA docket was also reviewed (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0560).

Appendix: Route of Degradation of Procellacor (XDE-848 BE) in the Environment (Volume 1 – Level 1 – Page 82)



Final Registration Decision on the New Active Ingredient Florpyrauxifen-benzyl

Approved by: Richard P Keigwin, Jr

Richard P. Keigwin, Jr., Acting Director

Office of Pesticide Programs

Date: 9/8/2017

Summary

This document announces that the U.S. Environmental Protection Agency (EPA) is granting an unconditional registration under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for the new active ingredient florpyrauxifen-benzyl (XDE-848 benzyl ester or Rinskor™; 2-Pyridinecarboxylic acid, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro-, phenylmethyl ester).

Florpyrauxifen-benzyl, an herbicide, is for use on rice (pre- and post-flooding) for post-emergence grass, sedge, and broadleaf weed control in Arkansas, Florida, Louisiana, Mississippi, Missouri, South Carolina, Tennessee and Texas; and for national use on freshwater aquatic sites, including foliar application to emergent aquatic vegetation (foliar-aquatic) or direct application to water body (in-water) use sites. The aquatic use is intended for management of freshwater aquatic vegetation in slow-moving/quiescent waters with little or no continuous outflow in ponds, lakes, reservoirs, freshwater marshes, wetlands, bayous, drainage ditches, and non-irrigation canals, including shoreline and riparian areas in or adjacent to these sites, as well as, management of invasive freshwater aquatic vegetation in slow-moving/quiescent areas of rivers (coves, oxbows or similar sites). Target plants for the aquatic use include invasive species such as hydrilla (*Hydrilla verticillata*), Eurasian watermilfoil *(Myriophyllum spicatum*), and crested floating heart (*Nymphoides cristata*). Tolerances on rice, freshwater fish, and shellfish (crustacean and mollusc) are being proposed to support these uses.

Florpyrauxifen-benzyl will be formulated as one technical product (Rinskor™ Technical) and four end-use products. GF-3480, GF-3206, and GF-3565 are proposed for use on rice only and GF-3301 is proposed for use on the rice and aquatic uses. The Rinskor™ Technical contains 94.6% florpyrauxifen-benzyl. The end-use product GF-3206 contains 2.7% florpyrauxifen-benzyl. The end-use product GF-3301 contains 26.5% florpyrauxifen-benzyl. The end-use product GF-3565 contains 1.3% florpyrauxifen-benzyl and 2.1% penoxsulam. The end-use product GF-3480 contains 2.13% florpyrauxifen-benzyl and 10.64% cyhalofop-butyl.

Although florpyrauxifen-benzyl is a new active ingredient, penoxsulam and cyhalofop-butyl, the co-formulated active ingredients in GF-3565 or GF-3480, respectively, are both currently registered active ingredients with labeled use on rice. Since penoxsulam and cyhalofop-butyl will be co-formulated in products only proposed for use on rice, no new exposures for these active ingredients are being considered with this registration action, and no new assessments were performed for penoxsulam and cyhalofop-butyl. Therefore, this document discusses the results of the EPA's findings on the assessment of the new active ingredient florpyrauxifen-benzyl and its use in rice and aquatic (in-water and foliar) use sites.

Background

On September 15, 2015, the EPA received an application from Dow AgroSciences (DAS) to register products containing the new active ingredient florpyrauxifen-benzyl (CAS No. 1390661-72-9), a post emergence herbicide, for use on rice fields (Labeled for use only in Arkansas, Florida, Louisiana, Mississippi, Missouri, South Carolina, Tennessee and Texas) and for aquatic applications (in-water and foliar) for management of freshwater aquatic vegetation. The application also requested the establishment of tolerances for residues resulting from these uses.

Florpyrauxifen-benzyl is a new synthetic auxin (plant hormone) and belongs to the arylpicolinate class of herbicides (WSSA Group 4; HRAC Group O). Florpyrauxifen-benzyl, like other synthetic auxins, mimics the plant growth hormone auxin, resulting in the disruption of growth processes in susceptible plants. Florpyrauxifen-benzyl undergoes de-esterification to its corresponding free acid florpyrauxifen (also known as XDE-848 acid). Alternatively, depending on the environmental conditions, florpyrauxifen-benzyl can undergo demethylation to yield XDE-848 benzyl hydroxy, which then can hydrolyze to form XDE-848 hydroxy acid.

The product labels specify that florpyrauxifen-benzyl is to be applied as a post-emergent herbicide on rice with a maximum single application rate of 0.027 lb a.i./A. Two foliar spray applications for rice are allowed per year, with a maximum yearly rate of 0.0525 lb a.i./A. The preharvest interval (PHI) is 60 days. One end use product (GF-3301) can be applied directly to water or sprayed into emergent foliage of aquatic plants for purposes of freshwater aquatic vegetation management. For the in-water aquatic use, the concentration of the active ingredient in the volume of water must be calculated. Three applications a year are permitted, with a maximum active ingredient concentration of 50 ppb per application. For the aquatic foliar application, the maximum single application rate is 0.0527 lb a.i./A, with a maximum of two applications per year (maximum of 0.1054 lbs a.i./A/year). For both the rice and aquatic uses, applications can be made using aerial or ground equipment. A 14-day interval is required between treatments.

On February 8, 2016, florpyrauxifen-benzyl was granted Reduced Risk status for both the rice and aquatic uses based predominantly on reduced risk to human health when compared to registered alternatives.

Evaluation of Risk to Human Health and the Environment

In evaluating a pesticide registration application, the EPA assesses a wide variety of exposure information *(i.e.,* where and how the pesticide is used), environmental fate studies *(i.e.,* how the chemical will move in the environment) and toxicity studies *(i.e.,* effects on humans and other non-target organisms) to determine the likelihood of adverse effects (*i.e.,* risk) from exposures

associated with the proposed use of the product. Risk assessments are developed to evaluate the environmental fate of the compound as well as how it might affect a wide range of non-target organisms including humans, terrestrial and aquatic wildlife and plants. On the basis of these assessments, the EPA evaluates and, as appropriate, approves language for each pesticide label to ensure the directions for use and safety measures are appropriate to mitigate any potential risk. The pesticide's label helps to communicate essential limitations and mitigations that are necessary for public safety. It is a violation of federal law to use a pesticide in a way that conflicts with the label.

Assessment of Risk to Human Health

The EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. The EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. The toxicology database for florpyrauxifen-benzyl is considered complete and no additional data are required at this time.

Toxicological Profile

One of the unique features for this herbicide is that, with oral administration, the maximum absorption occurs at approximately 300 mg/kg, above which the blood level of the test material remains constant. Hence, 300 mg/kg is considered as the kinetically-derived maximum dose. The absorbed florpyrauxifen-benzyl was rapidly metabolized, and the parent compound was essentially undetectable in the majority of blood samples, but it was found in large quantities in feces indicating much of the administered dose is not absorbed. The majority of the administered dose was eliminated within the first 24 hours post-dosing.

Single or repeated dose studies performed by any routes and durations of exposure produced no adverse effect following florpyrauxifen-benzyl treatment at or above the limit dose (1000 mg/kg/day) or the kinetically derived maximum dose. Chronic administration of florpyrauxifen-benzyl did not show any carcinogenicity potential in rats and mice, and it was not genotoxic. Florpyrauxifen-benzyl is of very low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an irritant to eyes or skin but demonstrated only a weak dermal sensitization potential in mouse local lymph node assay.

Since no adverse toxicity was found in the available toxicology database, toxicity endpoints and points of departure for risk assessment were not selected for florpyrauxifen-benzyl exposure scenarios, and a quantitative risk assessment was not conducted. Instead, a qualitative human health risk assessment has been conducted to support the proposed uses of florpyrauxifen-benzyl.

Residues in Food and Drinking Water

The submitted residue chemistry studies are adequate for establishing appropriate tolerance levels for enforcement and for purposes of risk assessment. The recommended residues of concern for the risk assessment and tolerance expression in crops are the parent florpyrauxifen-benzyl and its acid metabolite, florpyrauxifen (XDE-848 acid) only.

There is potential for exposure to florpyrauxifen-benzyl from food and drinking water based on the proposed uses. Florpyrauxifen-benzyl reaching water bodies by drift or applied directly to water (aquatic use) is expected to degrade rather quickly, forming into degradates that are structurally similar to the parent compound and are expected to have the same or lesser toxicity and similar hazard to florpyrauxifen-benzyl. Therefore, the degradates are not expected to cause any human health adverse effects and the EPA does not have any hazard concern for metabolites and/or degradates of florpyrauxifen-benzyl that may be found in food or drinking water.

Aggregate Exposure Assessment

Potential exposure to florpyrauxifen-benzyl residues in food (including fish and shellfish) could occur because florpyrauxifen-benzyl may be applied directly to growing rice and aquatic sites. These applications can also result in florpyrauxifen-benzyl reaching surface and groundwater, both of which can serve as sources of drinking water. There are no proposed uses in residential settings and there are no anticipated residential exposures.

Based on the lack of toxicity in the florpyrauxifen-benzyl toxicological database, the EPA has determined that a quantitative risk assessment is not needed at this time for dietary (food and drinking water), residential, aggregate, or cumulative exposure. Since no adverse toxicity is found in any of the available toxicological studies, and no toxicity endpoints and points of departure are established for risk assessment, no quantitative risk assessment was conducted. Therefore, the FQPA safety factor to protect infants and children is not necessary. The EPA concludes that there is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to florpyrauxifen-benzyl.

Occupational Exposure Assessment

Occupational handler and post-application short and intermediate term exposures to florpyrauxifen-benzyl may occur as a result of the proposed agricultural uses. Applicators might be exposed while handling the pesticide prior to application, mixing/loading the pesticide, and during application. Also, there is a potential for post-application exposure for workers re-entering treated fields.

No adverse effects were observed in the submitted toxicological studies for florpyrauxifen-benzyl regardless of the route of exposure; therefore, a quantitative occupational exposure assessment was not conducted. Thus, no quantitative occupational exposure assessments are

needed for the EPA to conclude with reasonable certainty that occupational exposures to florpyrauxifen-benzyl do not pose a significant human health risk. Technical florpyrauxifen-benzyl is of low acute toxicity by oral, dermal, and inhalation routes of exposure, since all acute studies were in the lowest toxicity category (Category IV). The acute studies showed that the four end-use products were also in toxicity Category IV except for the eye irritation study which was toxicity Category III for all end-use products. Based on the low acute toxicity, baseline personal protective equipment (PPE) is required which includes a long sleeved shirt, long pants, shoes, socks, protective eyewear, and waterproof gloves. The restricted entry interval (REI) is 12 hours.

Assessment of Ecological Risk

Environmental Fate

Florpyrauxifen-benzyl has a relatively low potential for volatility from water, moist soils, and dry surfaces, due to its low vapor pressure. Florpyrauxifen-benzyl shows low mobility in soils and readily binds to soil or sediment. The dominant routes of degradation of florpyrauxifen-benzyl are through aerobic aquatic metabolism and aqueous photolysis. When applied to rice, florpyrauxifen-benzyl is expected to reach paddy water and soil from labeled uses, but is expected to partition to the soil where it is strongly bound to sediment. The parent compound is expected to degrade via aerobic flooded soil metabolism (half-lives of 12 – 31 days), anaerobic soil metabolism (half-lives of 15 – 46 days), and aqueous photolysis (half-life of < 1 day). When applied directly to aquatic sites, florpyrauxifen-benzyl is expected to dissipate much more quickly, with rapid photolysis (<1 day) and aerobic aquatic metabolism (4-6 days) as the major routes of degradation.

The degradation of parent florpyrauxifen-benzyl results in the following major transformation products: XDE-848 acid, XDE-848 benzyl hydroxy, and XDE-848 hydroxy acid. These degrade more slowly than the parent compound, with half-lives ranging from 6.3 – 18 days for the acid, 6 – 14 days for the benzyl hydroxy, and 127-729 days for the hydroxy acid.

Exposures to florpyrauxifen-benzyl are expected through spray drift (from rice and foliar applications), direct contact with treated water (aquatic applications), or from runoff from treated areas (rice soil applications). Florpyrauxifen-benzyl and its degradates may reach surface waters due to run-off or release of paddy waters into receiving surface water bodies, or may move downstream after direct application to water. Thus, exposure to florpyrauxifen-benzyl and its degradates may occur to terrestrial organisms (from spray drift and runoff), and aquatic organisms (from direct exposure and downstream movement of treated water) from the proposed uses.

Ecological Hazard

Florpyrauxifen-benzyl is practically non-toxic on an acute basis to bird, mammals, and bees. Toxicity to fish and aquatic organisms was not observed, in most cases, at the highest levels tested, which approach the limit of solubility of the compound. Chronic toxicity to birds and mammals was not observed in the available data; however, chronic tests with the midge and mysid both showed toxicity at all levels tested. The parent compound as well as the three degradates demonstrate some toxicity to plants, however, the degradates show lower toxicity than the parent compound. For terrestrial plants, dicots are far more sensitive than monocots, and for aquatic plants, vascular plants are more sensitive than non-vascular species. Bioaccumulation data in fish showed low bioconcentration factors and rapid depuration, suggesting extensive metabolism of florpyrauxifen-benzyl. Metabolism data for mammals also demonstrates extensive metabolism, indicating bioaccumulation of florpyrauxifen-benzyl is unlikely. Additionally, florpyrauxifen-benzyl is relatively short lived in aquatic metabolism systems (2-6 days), which further limits its potential for bioaccumulation in the environment.

Ecological Risk Characterization

Ecological risk characterization integrates the results of the exposure analysis and ecotoxicity data to evaluate the likelihood of adverse ecological effects. The means of integrating the results of exposure and ecotoxicity data is called the quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposures/Toxicity). RQs are then compared to the EPA's levels of concern (LOCs). The LOCs are criteria used by the EPA to indicate potential risk to non-target organisms. The criteria indicate whether a pesticide, when used as directed, has the potential to cause adverse effects to non-target organisms.

The originally proposed labels for the aquatic use instructed the applicator to achieve a target water concentration of 150 ppb. Due to risk concerns to certain taxa at that rate, a lowered target concentration of 50 ppb was also assessed. This level, which is still efficacious for aquatic weed control, results in significantly lower exposure, and therefore risk, to non-target organisms and has been implemented on the proposed labels. Additional details for the comparison of the two rates and ecological risk characterization can be found in the document *"Florpyrauxifen-benzyl Environmental Fate and Ecological Risk Assessment for the Section 3 New Chemical Registration"* at http://www.regulations.gov, docket ID number EPA-HQ-OPP-2016-0560.

Risks to Aquatic Animals

Acute

For the proposed use on rice, acute risks to freshwater and estuarine/marine fish (which are also surrogates for aquatic-phase amphibians), and freshwater and estuarine/marine aquatic

invertebrates do not exceed the EPA's LOCs. For the proposed aquatic uses, the acute risks to freshwater and estuarine/marine fish and invertebrates (water column) slightly exceed the EPA's LOC (with RQs ranging from <0.56 to <3.7). However, acute toxicity was not observed at any level in the submitted studies, which were conducted up to the limit of solubility for florpyrauxifen-benzyl. Additionally, acute toxicity data for typical end-use products (TEP) and degradates show that the levels where toxicity was demonstrated are well above the levels of the chemicals in aquatic environments expected from the proposed use. Therefore, the potential for acute risk to fish and invertebrates from the proposed aquatic uses is expected to be low.

Chronic

Chronic RQs did not exceed the EPA's LOC for freshwater fish or freshwater invertebrates (water column) for either the rice or aquatic uses. Likewise, the chronic RQs did not exceed the LOC's for freshwater (benthic) invertebrates. For freshwater benthic invertebrates, the submitted study showed toxicity at all of the levels tested, resulting in uncertainty regarding what level of florpyrauxifen-benzyl residues in the environment would be below the threshold for toxicity. Using the lowest level tested in that study and comparing it to the expected environmental concentration of florpyrauxifen-benzyl, the RQ was below the LOC; however, risk to these organisms cannot be entirely precluded due to the uncertainty regarding what level of florpyrauxifen-benzyl would be non-toxic. Any potential toxicity of concern would be due to the parent compound and is likely to be short lived due to dissipation in the environment. Therefore, chronic risks of concern are not expected for these taxa.

Chronic risk potential to estuarine/marine invertebrates, both water-column and benthic, is also uncertain. There was toxicity observed at all levels of the submitted mysid chronic toxicity study, resulting in uncertainty regarding what level of florpyrauxifen-benzyl residues in the environment would be below the threshold for toxicity to these organisms. In the case of water-column estuarine/marine invertebrates, using the lowest level tested in that study and comparing it to the expected environmental concentration of florpyrauxifen-benzyl, the RQ was slightly above the LOC (>2.5). The marine/estuarine benthic RQ did not exceed the LOC; however, risk to these organisms cannot be entirely precluded due to the uncertainty regarding what level of florpyrauxifen-benzyl would be non-toxic. In addition, chronic risks to estuarine/marine fish could not be evaluated due to the lack of toxicity data for both the rice and aquatic uses. However, the proposed uses are not expected to result in significant residues of florpyrauxifen-benzyl or its degradates in saltwater/brackish water environments. Rice is not grown in salt or brackish water, and the proposed aquatic uses are for freshwater sites only. Additionally, the label specifically prohibits direct application to salt or brackish waters. The proposed rice use requires a 60-day pre-harvest interval (PHI), which means that the product cannot be applied within 60 days of rice harvest. Since the typical practice for rice cultivation in the eight states listed on the label is to hold flood water until very close to harvest, there will be a substantial built-in holding period between the time of the last application and when the paddy water is

released, allowing ample time for florpyrauxifen-benzyl to degrade into compounds that do not demonstrate toxicity to aquatic animals. The proposed aquatic uses are limited to slow-moving/quiescent waters, again allowing time for parent florpyrauxifen-benzyl to degrade. Furthermore, due to the likelihood that significant dilution will also occur, concentrations are not expected to reach estuarine/marine waters in concentrations high enough to reach levels of concern in estuarine/marine environments.

Risks to Terrestrial Animals

Florpyrauxifen-benzyl is considered "practically non-toxic" to bees, birds, reptiles, terrestrial-phase amphibians and mammals on an acute basis. The acute RQs for these species do not exceed the EPA's LOC. Additionally, chronic RQs for birds (which are also surrogates for reptiles and amphibians) and mammals also did not exceed the EPA's LOC. Therefore, EPA has no chronic risks of concern for terrestrial animals.

Risks to Plants

As would be expected for an herbicide, florpyrauxifen-benzyl is toxic to plants, and there are some risks of concern for both terrestrial and aquatic plant species. When assessing risk to non-target aquatic plants, the EPA used a Total Toxic Residues (TTR) approach, since the parent compound, as well as the major degradates, all demonstrate some level of toxicity to aquatic plants at environmentally relevant levels. The TTR approach assumes the parent and degradates have the same fate and toxicity characteristics. Although two of the most persistent degradates (benzyl hydroxyl and hydroxyl acid) are considered toxicologically relevant to aquatic plants based on the proposed uses, their toxicity to aquatic plants is several orders of magnitude less than the parent compound. Therefore, the resulting RQ derived from the TTR approach is considered a conservative (e.g., "worst case") approach. Actual RQs would be lower when considering differential toxicity of the parent and relevant degradates.

Aquatic Plants

When considering total toxic residues, the resulting RQs for non-target aquatic vascular plants are 410 for the rice use, and 3,090 for the aquatic use, which exceed the LOC. However, these are based on conservative assumptions, assuming exposure at the applied rate. For the rice use, the label prohibits applications within 60 days of harvest. As described above, since the flood water is held in the paddy until close to the time of harvest, there is ample time for the parent compound and the XDE-848 acid to degrade prior to release of the paddy water into receiving waters. Additionally, the labels prohibit application to ratoon crops, because these would have a shorter holding time prior to release of paddy water.

For aquatic uses, florpyrauxifen-benzyl would be at or below the target concentration of 50 ppb in the treatment area at the time of application. The label limits the treatments to slow-moving, quiescent waters, thus reducing potential exposure to non-target aquatic plants. Additionally, the most toxic components of the TTR (parent compound and acid degradate) degrade relatively rapidly (e.g., within days to a few weeks), further reducing the risk that would be expected downstream from the treated area. Other degradates degrade more slowly but are shown to be much less toxic.

Terrestrial Plants

When considering just the parent compound and the XDE-848 acid residues, exposure may occur from spray drift, runoff, either individually or in combination from the proposed rice or aquatic uses. Exposure could also potentially occur if treated water was used to irrigate crops or other plants. The maximum RQs for non-target terrestrial monocots ranged were 0.65 for parent, and 0.91 for the acid, which did not exceed the LOC. For dicots, maximum RQs were 29 for parent, and 12.6 for the acid, which do exceed the LOC. Though the RQ values range widely based on the type of plant exposed, the EPA assumes the highest risk scenario when determining mitigation measures in order to protect the most sensitive species. To reduce non-target terrestrial plant risk, label elements for both the rice and aquatic uses such as prohibiting use of treated water for irrigation and language to reduce the potential for spray drift have been added to the product labels. These are further explained in the "Mitigation and Labeling Requirements" section of the document.

Compost

Residues of other chemicals belonging to the synthetic auxin class of chemistry have been detected in finished compost derived from the composting of auxin-treated agricultural material, including plant material and manure. Due to the current uncertainty regarding the potential presence of florpyrauxifen-benzyl in compost, label mitigation has been proposed to remove this exposure pathway by restricting the use of treated plant material in compost. In addition, livestock will be restricted from drinking treated water so that residues do not potentially accumulate in manure that may be used for compost. The specific label requirements are further explained in the "Mitigation and Labeling Requirements" section of the document. The registrant may elect to conduct a compost residue study in the future to determine if the restrictions could be removed.

Tank Mixing Florpyrauxifen-benzyl

The EPA has developed an interim process to evaluate mixture effects on an active ingredient basis where the U.S. Patent and Trademark Office (PTO) granted a patent basis on the applicant showing that the combined effects of the mixture are synergistic (*i.e.*, the effect of a mixture of pesticides is greater than the sum of the individual effects). To ensure that mixture effects data that may be relevant to ecological risk assessments are considered, the Agency requested that

registrants of new chemicals submit mixture toxicity data provided to the U.S. PTO. The EPA provided criteria to assist registrants in identifying relevant data for submission.
Several patent claims of synergism for specific combinations of florpyrauxifen-benzyl with other herbicides including patent claims regarding use of the two active ingredients found in the florpyrauxifen-benzyl co-formulated products (cyhalofop and penoxsulam) have been identified. The registrant has submitted data on these co-formulated products to determine if synergy exists. The studies did not show substantially increased phytotoxicity to soybeans, the most sensitive crop, and therefore did not change the overall risk profile for florpyrauxifen-benzyl.
Several other patents involving florpyrauxifen-benzyl with other ingredients have been identified. EPA is currently evaluating the nature of these patent claims and any supporting data. The EPA is continuing its work to better understand the scope of the uncertainties for these specific combinations and to develop an approach that best manages the potential risks while still maintaining the important benefits derived from tank mixing. While evaluation of these patents are still in progress, the EPA has placed a restriction on the end-use product labels that prohibits tank mixing with those active ingredients for which a patent has been approved at the time of registration. If the EPA determines that sufficient data do not exist to support true synergistic effects with a particular active ingredient, that active ingredient may be removed from the list of restricted tank mix combinations. The specific label requirements are further explained in the "Mitigation and Labeling Requirements" section of the document.

Benefits

A fundamental problem facing U.S. agriculture is the spread of herbicide-resistant weeds causing growers to experience yield and economic losses due to weeds developing resistance. This has become important as it is a significant financial, production, and pest management issue. Weed management in rice is essential for economical rice production because weeds reduce yields by competing with rice for nutrients, light, and moisture. Infestations can also interfere with harvest and reduce the quality of grain. Rice is a major field crop in the Southern United states, especially in Arkansas, Louisiana, Mississippi, Missouri, and Texas. These states produced over 75% of the total U.S. rice crop in 2012. Arkansas alone produced almost 9.7 billion pounds of rice in 2012, nearly half of the total U.S. production. The value of sales of rice in these five state was over $2 billion (in 2012) more than two-thirds of the total value of rice in the U.S. ($~3 billion). Rice production is adversely impacted by weed infestations and many resources go into weed management. In Arkansas, weed control costs from 2006 to 2012 averaged nearly $69 per acre. Barnyardgrass competes (or outcompetes) rice for nitrogen, sunlight, space, and moisture. Yield reduction of rice due to season-long weed infestation are well-known. If uncontrolled, heavy infestation of weeds impact yields by as much as 82% for red rice weed and 70% for barnyardgrass. Managing barnyardgrass, as well as other weeds, has become more difficult in recent years as several weed species have developed resistance to commonly used herbicide chemistries.

Florpyrauxifen-benzyl is expected to be a valuable tool in combating the proliferation of resistant weed populations that are causing yield and economic losses for rice farmers in the southern states of Arkansas, Florida, Louisiana, Mississippi, Missouri, South Carolina, Tennessee and Texas. It will provide a much needed control of weeds including barnyardgrass and other weeds which are significant for rice producers.

New chemicals, such as florpyrauxifen-benzyl, can be helpful in pest management and resistance-management programs as an additional resource for weed control, especially where current treatments are less successful. Florpyrauxifen-benzyl is expected to be an important tool to manage weed species that have developed resistance to commonly used herbicides for weed control in rice production. For example, barnyardgrass has known resistance to alternative active ingredients, such as propanil and quincolorac, but is effectively controlled by florpyrauxifen-benzyl. Florpyrauxifen-benzyl's mechanism of action (MOA) involves a preference for a different binding site protein compared to other Group 4 herbicides. This could be a benefit in managing weeds that have developed resistance to other synthetic auxin herbicides which bind more strongly to other binding site proteins. In addition, florpyrauxifen-benzyl has a wide application window (from the 2 leaf stage up to 60 days prior to harvest), and can be applied in place of herbicides that might currently have resistant weed populations. Thus, this new active ingredient is expected to be an additional tool which could potentially be used in place of other available herbicides where resistance has developed. However, resistance management is advised to maintain efficacy since weeds can develop resistance to this active ingredient as they have to many herbicides. In addition, florpyrauxifen-benzyl will be an effective tool for spot and wide area treatments for control of problematic aquatic weeds. It will provide an additional tool to manage resistant aquatic weed species and a tool to restore aquatic habitat.

Resistance management for weeds in aquatic systems differs considerably from terrestrial herbicide resistance management. Options are limited, as there are only 14 registered aquatic herbicides in the United States. Florpyrauxifen-benzyl is expected to be an effective tool for spot and wide area treatments to quickly control problematic invasive aquatic weeds such as hydrilla, Eurasian watermilfoil, and crested floating heart. Florpyrauxifen-benzyl also provides an additional tool to manage herbicide-resistant aquatic weeds and restore aquatic habitat in ecosystems that have been compromised by invasive species. Aquatic weeds often require significant resources for control, as invasive species can interfere with use of water, increase the risk of flooding, and result in conditions that threaten public health (e.g. harmful algal blooms that produce cyanotoxins).

For invasive weed control, as an auxin herbicide (WSSA Group 4), florpyrauxifen-benzyl will provide a new effective mechanism of action (MOA) for the particularly problematic invasive weed hydrilla *(Hydrilla verticillata)*. There are multiple aquatic herbicides labeled for hydrilla

control in the United States: endothall (WSSA Group undefined), diquat (WSSA Group 22), flumioxazin (Group 14), copper products (WSSA Group not defined), fluridone (WSSA Group 12), penoxsulam (WSSA Group 2), bispyribac-sodium (WSSA Group 2), imazamox (WSSA Group 2), and topramezone (WSSA Group 28). None of these herbicides belong to WSSA Group 4. Therefore, florpyrauxifen-benzyl demonstrates an alternate MOA for the invasive aquatic weed hydrilla and could play an important role in an integrated pest management (IPM) program.

Controlling hydrilla is especially problematic because it has shown resistance to the widely used herbicides fluridone and endothall. Hydrilla reproduces efficiently, out competes native plants, reduces habitat for aquatic wildlife and fish and can obstruct water flow resulting in clogged irrigation systems and flooding. Hydrilla, particularly when very dense and expansive, is very disruptive to native environments and can threaten native species by reducing the level of dissolved oxygen, preventing sunlight penetration, and limiting nutrients for use by other native organisms. In addition to suppressing native plants, hydrilla, can also limit water flow and cause flooding, increase extinction rate of rare, threatened and endangered species, disrupt hydropower generation, provide habitat for insect-borne disease vectors, degrade water quality, reduce species diversity, change sediment chemistry, and interfere with recreational activities such as boating, fishing, and swimming. The economic impacts of controlling hydrilla (mechanical, biocontrol, and/or chemical control) can be substantial. For example, the cost of hydrilla control in Florida over a seven-year period from 2008-2015 were estimated at $66 million. Non-chemical means of control are often ineffective when used alone or prohibitively expensive. For example, mechanical control and suction control of hydrilla can cost as much as $1,000 per acre and $25,000 per acre, respectively. In addition, mechanical control methods are known to cause breakage in many invasive aquatic weeds and send viable fragments downstream where they take root and establish new populations. There is documented resistance to both fluridone and endothall in hydrilla species and florpyrauxifen-benzyl will provide a new MOA for control of this resistant species. Hydrilla has also been documented as hosting *Aetokthonos hydrillicola,* a cyanobacterium that is believed to produce a neurotoxin responsible for avian vacuolar myelinopathy (AVM). AVM is a neurological disease which impacts waterfowl in the southeastern U.S., including bald eagles. Florpyrauxifen-benzyl also provides excellent control of the troublesome watermilfoil species. Florpyrauxifen-benzyl is expected to be a helpful resource for hydrilla weed control and other troublesome weeds and provide an additional tool in resistance-management programs.

Florpyrauxifen-benzyl will also offer flexibility in use to meet the need for spot/partial treatment. The alternatives such as fluridone, penoxsulam, and topramezone require 2 to 4 months to provide target plant control while florpyrauxifen-benzyl provides control in several days to a few weeks.

Florpyrauxifen-benzyl is a new reduced risk pesticide based on lower risks to human health when compared to registered alternatives. The toxicity profile for florpyrauxifen-benzyl identifies no risks of concern to human health from any route of exposure and may provide a better alternative to older chemistries that require higher levels of risk mitigation practices in order to reduce exposure. For instance, several alternatives to florpyrauxifen-benzyl (diquat, endothall, triclopyr, imazapyr, and 2,4-D) have drinking water or recreational use restrictions. There are no restrictions on the use of water treated with florpyrauxifen-benzyl for recreational purposed including swimming and fishing and no drinking water restrictions. The lack of drinking water and recreational use restrictions will allow applicators more flexibility in planning their integrated weed management program.

With respect to non-target risks, florpyrauxifen-benzyl has no risk concerns for non-target wildlife and is considered "practically non-toxic" to bees, birds, reptiles, amphibians, and mammals. Overall, the EPA expects that there may be meaningful benefits for florpyrauxifen-benzyl for controlling difficult weeds in rice and aquatic systems and also helping to reduce weed resistance.

Public Comments

The proposed regulatory decision was published on June 28, 2017, remained open for 30 days, and closed on July 28, 2017. The Agency received a total of forty comments in that period. Thirty-eight of the forty comments were in support of the registration of florpyrauxifen-benzyl and agreed with the Agency's benefits assessment of florpyrauxifen-benzyl. A portion of those comments included concerns over the proposed restriction of tank mixing florpyrauxifen-benzyl products with other registered pesticides for applications to rice, and concerns over the proposed restriction of irrigating with water treated with florpyrauxifen-benzyl for aquatic plant management. The Agency's rationale for these restrictions can be found in the sections of this document "Tank Mixing Florpyrauxifen-benzyl" and "Mitigation and Labeling Requirements – Irrigating Crops," respectively. The comments opposing the registration highlighted the lack of an endangered species assessment and formal consultation under Section 7 of the Endangered Species Act and expressed concerns with EPA's assessment of the toxicity of pesticide mixtures.

The EPA acknowledges the comments Center for Biological Diversity (CBD) submitted regarding the duty to consult with the U.S. Fish and Wildlife Service (FWS) and National Marine Fisheries Service (NMFS) in regard to risk to endangered species, including the potential drift of residues, common mechanisms of toxicity, the use of Bulletins Live! and the concerns of water quality conditions and critical habitat. These considerations are encompassed in the extensive efforts and resource investments the EPA is focusing to assess impacts to listed species as part of the EPA's registration review program for currently registered pesticides. The EPA believes that, as a general matter, older chemistries present a greater degree of risk to listed

species than newest chemistries coming to market, including florpyrauxifen-benzyl, since registration standards have increased over time. Therefore, it is environmentally preferable in most circumstances for the EPA to focus resources to assess the impacts of existing pesticides sooner in the process than newer pesticides that have been held to higher standards to meet current registration requirements such as new guideline studies to assess risk to additional species and through assessment of new exposure pathways. Furthermore, florpyrauxifen-benzyl was granted reduced risk status for both of the proposed uses. The determination was based on the lack of human health risk, lower hazard to human health compared to leading market alternatives, and its efficacy against certain highly invasive weeds such as hydrilla which are not adequately suppressed and/or controlled by the alternatives. Controlling hydrilla is especially problematic because it has shown resistance to the widely used herbicides fluridone and endothall. Hydrilla reproduces efficiently, out competes native plants, reduces habitat for aquatic wildlife and fish and can obstruct water flow resulting in clogged irrigation systems and flooding. Hydrilla, particularly when very dense and expansive, is very disruptive to native environments and can threaten native species. The determination concluded that florpyrauxifen-benzyl will be an important tool for integrated pest management programs for the labeled uses. In addition, florpyrauxifen-benzyl exhibits low acute ecological risk to mammals, reptiles, amphibians, bees, and birds and shows lower acute ecological risks then many of the alternatives. As a result, the EPA does not believe the environment or the public would be best served by delaying the registration of florpyrauxifen-benzyl to complete consultation. Focusing the EPA' s, and the Services' (the FWS's and the NMFS's) limited resources on completing a consultation on the effects of florpyrauxifen-benzyl would by necessity come at the expense of putting more resources into evaluating – and consequently, regulating, where appropriate - what the EPA believes to be more toxic compounds, that, among other things, pose greater risk, to endangered species than does florpyrauxifen-benzyl.

It is important to understand that the development of the Interim Approaches does not by its terms suggest that existing or recently developed risk assessments using the criteria articulated in OPP's 2004 Overview document (http://www.epa.gov/espp/consultation/ecorisk-overview.pdf) are necessarily "under-protective." The Interim Approaches are intended to identify interim thresholds for interagency review as the Agencies jointly work to implement the recommendations of the National Academy of Sciences (NAS) on certain specific registration review actions. The Agencies have made no determination that these thresholds are necessary to prevent take and preclude likely jeopardy and, in any case, the Interim Approaches do not establish legally binding thresholds for consultation under the Services ' implementing regulations. As the EPA and the Services work through the initial actions that are being reviewed under the Interim Approach, the EPA will determine whether these thresholds should be modified before they are extended more broadly to additional regulatory actions. The details of the joint Interim Approaches are contained in the white paper *Interim Approaches for National-Level Pesticide Endangered Species Act Assessments Based on the Recommendations of the*

National Academy of Sciences April/2013 Report, dated November 1, 2013, available at http://www.epa.gov/espp/2013 /nas.html. With respect to the evaluation of florpyrauxifen-benzyl specifically, it is important to understand that under any internal or interagency review, the ecological risk evaluation will continue to rely on the body of information used in the current EPA ecological assessment.

For the reasons explained above, the EPA is not consulting with the Services on the issuance of the florpyrauxifen-benzyl registration. However, the EPA is currently working to prioritize its consultation activities with the Services and will evaluate the appropriate timing and scope of consultation on florpyrauxifen-benzyl in connection with those efforts. In addition, to the extent the EPA receives new information indicating that florpyrauxifen-benzyl may pose a greater risk to listed species than indicated by the existing scientific database for this pesticide, the EPA will re-evaluate the terms of registration and determine whether additional use restrictions to protect listed species are necessary.

The EPA also acknowledges the comments CBD submitted regarding the assessment of the toxicity of pesticide mixtures. The EPA has traditionally viewed tank mixes to have an additive effect, meaning the combined effect of two chemicals is predictable based on the known toxicity of both compounds; no specific interactions occur. Therefore, as long as the applicator/handler follows the most restrictive use directions for all chemical partners in the tank mix, there are no unidentified or additional risks with use of tank mixes. However, as a result of chemical companies making claims of synergism with unique combinations of chemicals for patent and licensing purposes, the topic of synergy and multiple stressors has introduced uncertainty in assessing risk with tank-mix combinations. The EPA has developed an interim process to evaluate mixture effects on an active ingredient basis where the U.S. Patent and Trademark Office (PTO) granted a patent basis on the applicant showing that the combined effects of the mixture are synergistic (*i.e.,* the effect of a mixture of pesticides is greater than the sum of the individual effects). Several patent claims of synergism for specific combinations of florpyrauxifen-benzyl with other herbicides have been identified. While evaluation of these patents are still in progress, the EPA is requiring a restriction on the end-use product labels that prohibits tank mixing with those active ingredients for which a patent has been approved at the time of registration. If the EPA determines that sufficient data do not exist to support true synergistic effects with a particular active ingredient, that active ingredient may be removed from the list of restricted tank mix combinations. Further details are outlined in the "Tank Mixing Florpyrauxifen-benzyl" section of this document.

Regulatory Rationale

In accordance with FIFRA, the EPA only registers a pesticide when it determines that it will not cause unreasonable adverse effects on humans or the environment, taking into account the

economic, social, and environmental costs and benefits of the use of the pesticide. Under FIFRA, the EPA is charged with balancing the uncertainties and risks posed by a pesticide against its benefits. The EPA must determine if the benefits in light of its use outweigh the risks in order for the EPA to register a pesticide.

The database submitted to support the assessment of human health, and environmental fate and ecological risk outlined in 40 CFR part 158 is adequate to support the risk determinations for us of florpyrauxifen-benzyl. There are no risk estimates of concern for human health. Florpyrauxifen-benzyl is not likely to result in direct risk of concern to non-target terrestrial animals, including insects, birds, reptiles, terrestrial-phase amphibians, and mammals, nor to aquatic animals including amphibians, fish, and invertebrates. As expected of an herbicide, florpyrauxifen-benzyl may pose a risk of concern to terrestrial and aquatic vascular and non-vascular plants. Label language, as outlined in the "Mitigation and Labeling Requirements" section of the document, will reduce any potential risk to non-target terrestrial and aquatic plants.

It should be noted that florpyrauxifen-benzyl was granted Reduced Risk status for both the rice and aquatic uses based on reduced risk to human health when compared to registered alternatives. The Office of Pesticide Program's Conventional Reduced Risk Pesticide Program expedites the review and regulatory decision-making process of conventional pesticides that pose less risk to human health and the environment than existing conventional alternatives. In addition, florpyrauxifen-benzyl demonstrates an alternate mode of action to control hydrilla, and should play an important role in integrated pest management (IPM). Introduction of an alternate mode of action should also help to prolong the effectiveness of existing reduced risk chemistries when introduced into resistance management strategies with these chemicals.

Florpyrauxifen-benzyl is expected to be a valuable tool in combating the proliferation of resistant weed populations that are causing yield and economic losses for rice producers. It will provide a much needed control of weeds including barnyardgrass and other weeds which are significant for producers. In addition, florpyrauxifen-benzyl will be an effective tool for spot and wide area treatments for control of problematic aquatic weeds. It will provide an additional tool to manage resistant aquatic weed species and a tool to restore aquatic habitat. Florpyrauxifen-benzyl will improve control of economically detrimental aquatic weed species, control of resistant species, and increase flexibility in integrated weed management plans as well as reduce the economic impact of controlling invasive hydrilla and protecting native species.

After weighing the risks against the benefits of the registered use, the EPA finds that, when the mitigation measures are implemented, the potential risks that may remain are minimal, while the benefits are potentially significant. Therefore, the EPA concludes that the benefits outweigh the risks and registering these uses will not generally cause unreasonable adverse effects on human health or the environment. Therefore, the EPA proposes to grant the registration of

florpyrauxifen-benzyl for use on rice in Arkansas, Florida, Louisiana, Mississippi, Missouri, South Carolina, Tennessee and Texas and for aquatic uses intended for management of freshwater aquatic vegetation in slow-moving/quiescent waters with little or no continuous outflow in ponds, lakes, reservoirs, freshwater marshes, wetlands, bayous, drainage ditches, and non-irrigation canals, including shoreline and riparian areas in or adjacent to these sites, as well as for management of invasive freshwater aquatic vegetation in slow-moving/quiescent areas of rivers (coves, oxbows, or similar sites). The available data and scientific assessments as well as the overall considerations for benefits for weed management in rice and the specified aquatic uses support a registration under FIFRA Section 3(c)(5).

Mitigation and Labeling Requirements

For Occupational Handlers

The required personal protective equipment (PPE) is a long sleeved shirt and long pants, socks, shoes, protective eyewear, and waterproof gloves. The restricted entry interval (REI) is 12 hours.

Potential for Contamination of Compost

With the current uncertainty that exists regarding the potential for adverse effects to non-target plants exposed to compost containing residues of florpyrauxifen-benzyl, the following label restrictions will be included until additional information is provided to address this uncertainty:

- Do not compost any plant material from treated area.
- To minimize potential exposure in compost, do not allow livestock to drink treated water.

The inclusion of this language on the label is intended to prevent potential contamination of compost by restricting the use of plant material treated with florpyrauxifen-benzyl or manure with florpyrauxifen-benzyl residues to be used as compost inputs.

Irrigating crops

No data have been provided to account for potential residues on irrigated crops resulting from the use of water from treated irrigation ditches and channels. With the current uncertainty that exists regarding the potential for adverse effects to non-target plants exposed to residues from treated irrigation water, the EPA proposed the following label restriction until additional information is provided to address this uncertainty:

- Do not use treated water for any form of irrigation.

Potential for exposure to non-target plants downstream for the aquatic use:
In order to minimize the risk of exposure to non-target plants downstream, the aquatic use sites will be limited to:

- Slow moving/quiescent waters with little or no continuous outflow.
- Only invasive weeds may be treated in moving water which is limited to slow-moving/quiescent areas of rivers (coves, oxbows, or similar sites).

Potential for exposure to marine/estuarine invertebrates downstream for the aquatic use:
In order to minimize the risk of exposure to marine/estuarine invertebrates downstream, the aquatic use label will include the following restriction:

- Do not apply to salt/brackish water.

Potential for exposure to non-target plants downstream from release of patty water:
In order to minimize the risk of exposure to non-target plants downstream from release of patty water for the rice use, the following restrictions are proposed:

- Do not apply to ratoon rice.
- Do not apply within 60 days of rice harvest.

Tank-mixing Restrictions

- DO NOT TANK MIX ANY PESTICIDE PRODUCT WITH THIS PRODUCT without first referring to the following website for the specific product: www.3206kmix.com; www.3301tankmix.com; www.3480tankmix.com; or www.3565tankmix.com. This website contains a list of active ingredients that are currently prohibited from use in tank mixture with this product. Only use products in tank mixture with this product that: 1) are registered for the intended use site, application method and timing; 2) are not prohibited for tank mixing by the label of the tank mix product; and 3) do not contain one of the prohibited active ingredients listed on www.3206kmix.com; www.3301tankmix.com; www.3480tankmix.com; or www.3565tankmix.com website.
- Applicators and other handlers (mixers) must access the website within one week prior to application in order to comply with the most up-to-date information on tank mix partners.
- Do not exceed specified application rates for respective products or maximum allowable application rates for any active ingredient in the tank mix.
- Read carefully and follow all applicable use directions, precautions, and limitations on the respective product labels. It is the pesticide user's responsibility to ensure that all products in the mixtures are registered for the intended use. Users must follow the most

restrictive directions for use and precautionary statements of each product in the tank mixture.
- Always perform a (jar) test to ensure the compatibility of products to be used in tank mixture.

Potential for Off-site Transport via Spray Drift

In order to minimize the risks of spray drift, language is included on the label that is intended to reduce off-site transport, thereby reducing the potential for exposure to non-target plants. This includes minimum droplet size restrictions of coarse or coarser droplet category per S-572 ASABE standard, application pressures less than 30 psi, maximum wind speed restriction of 10 mph with a minimum wind speed of 2 mph, maximum boom heights of 36 inches for ground application and 10 feet for aerial application, and extensive Spray Drift Management language. Additional labeling is required to reduce risk to non-target plants through drift as follows:

Susceptible Plants

- Do not apply under circumstances where spray drift may occur to food, forage, or other plantings. Spray drift may damage or render crops unfit for sale, use or consumption. Small amounts of spray drift that may not be visible may injure susceptible broadleaf plants.
- Before making an application, please refer to your state's sensitive crop registry (if available) to identify any commercial specialty or certified organic crops that may be located nearby.
- Do not apply when wind is blowing toward adjacent cotton, carrots, soybeans, corn, grain sorghum, wheat, grapes, tobacco, vegetable crops, flowers, ornamental shrubs or trees, or other desirable broadleaf plants.

International Harmonization

Maximum Residue Limits (MRLs) have not been established by Codex for florpyrauxifen-benzyl for the commodities affected by this action. However, tolerances are being established on rice, freshwater fish and shellfish for international trade purposes.

Regulatory Decision

The database submitted to support the assessments of human health risk and environmental fate and ecological risk is adequate to support use of florpyrauxifen-benzyl on rice and use in aquatic vegetation management. Considering the assessed risk to human health and the environment, the EPA concludes that florpyrauxifen-benzyl meets the regulatory standard under FIFRA. The EPA is concluding that, in consideration of the approaches and mitigation described above, the risks are not unreasonable when considered in conjunction with the benefits of a new chemical and

new mode of action for control of hydrilla in freshwater aquatic weed control management. Therefore, the EPA granting an unconditional registration of florpyrauxifen-benzyl under Section 3(c)(5).

The EPA is registering the following five products:

Rinskor™ Technical

- 94.6% florpyrauxifen-benzyl
- Only for formulation into an herbicide for use on rice and freshwater aquatic use sites

GF-3301

- 26.5% florpyrauxifen-benzyl
- Only for use on rice in AR, FL, LA, MS, MO, SC, TN, and TX and for freshwater aquatic use sites

GF-3206

- 2.7% florpyrauxifen-benzyl
- Only for use on rice in in AR, FL, LA, MS, MO, SC, TN, and TX

GF-3565

- 1.3% florpyrauxifen-benzyl
- 2.1% penoxsulam
- Only for use on rice in in AR, FL, LA, MS, MO, SC, TN, and TX

GF-3480

- 2.13% florpyrauxifen-benzyl
- 10.64% cyhalofop-butyl
- Only for use on rice in in AR, FL, LA, MS, MO, SC, TN, and TX