Registration of the New Active Ingredient Cyantraniliprole

An Insecticide for Use on Multiple Commodities, Ornamentals, Turfgrass, and in Commercial or Residential Buildings

Approved by: _____

Steven P. Bradbury, Director
Office of Pesticide Programs

Date: 1/24/14

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Summary of the Regulatory Decision

The Agency is granting an unconditional registration under section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of the new active ingredient cyantraniliprole formulated as a technical product and fourteen end-use products. The registered uses for this new insecticide include agricultural crops (bushberry (subgroup 13-07B), citrus (group 10-10), pome fruit (group 11-10), stone fruit (group 12-12), tree nuts (group 14-12), oilseed (group 20), Brassica, Cole and leafy vegetables (group 5), bulb vegetables (group 3-07) cucurbits (group 9), fruiting vegetables (group 8-10), leafy vegetables (except Brassica) (group 4), and tuberous and corm vegetables (subgroup 1C)), ornamentals and turf (ornamental plants, shrubs, trees in and around greenhouses, nurseries, lath- and shade-houses, and interior plantscapes, landscape and recreational turfgrass (including golf courses), and sod farms), as well as structures and equipment (in and around agricultural, commercial, and residential structures (excluding food/feed handling establishments), and transportation equipment.

Product formulations include liquid, granular, and granular bait. Methods of application include broadcast sprays for aerial and ground applications, soil drench, chemigation, and seed treatment. Maximum single application rates are 0.4 lb. a.i./A for liquid, granular, or seed treatments. The maximum annual application rate is 0.4 lb. a.i./A/year for all application methods.

The Agency’s Reduced Risk Committee approved cyantraniliprole as a "reduced risk" candidate for the proposed uses. Based on the committee's evaluation of the information provided, the mammalian toxicity and ecotoxicity risk profiles for cyantraniliprole are favorable compared to registered alternatives, which include organophosphates, pyrethroids, carbamates and neonicotinoids. The novel mode of action for cyantraniliprole fits in well with resistance management strategies.

The evaluation of cyantraniliprole was conducted as a “Global Joint Review” project. EPA scientists worked in collaboration with their colleagues in the Regulatory Authorities of France, the United Kingdom, Canada, and Australia. In the course of this analysis, the agencies considered a robust database that included over 800 studies. Scientists in each partnering authority conducted primary reviews, peer reviewed evaluations conducted by their counterparts and participated in technical committee meetings to coordinate and harmonize scientific conclusions.

After review and consideration of all of the data provided by the 800+ studies, the determinations made by the multiple scientists involved in the project, and the outcome of the human health and ecological risk assessments, the Agency supports the decision of its Reduced Risk Committee; cyantraniliprole is therefore classified as a Reduced Risk Pesticide.

Cyantraniliprole is a broad spectrum insecticide, with activity on a wide variety of target pests. While it is the third compound registered in the Insecticide Resistance Action Committee (IRAC) Mode of Action Classification Group 28, ryanodine receptor modulators, it has a broader spectrum of activity than the other two compounds. It is expected to fit well in IPM programs.

I. Chemical Information

Chemical Name: cyantraniliprole, 3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide

EPA PC Code: 090098

Chemical Abstracts Service (CAS) Number: 736994-63-1

IRAC MoA Classification: Group 28 - Ryanodine receptor modulators

Mode of Action: Insecticide Resistance Action Committee (IRAC) Mode of Action Classification Group 28: ryanodine receptor modulators (RyR). The mode of action is through unregulated activation of insect RyR channels leading to internal calcium store depletion and impaired regulation of muscle contraction, causing paralysis and eventual death.

Registrants: E.I. du Pont de Nemours & Company and Syngenta Crop Protection

II. Human Health Risk

A summary of the human health effects and risk of cyantraniliprole as assessed in the Agency document entitled "Cyantraniliprole. Aggregate Human Health Risk Assessment for the Proposed New Uses of the New Active Insecticide, including Agricultural Uses on Brassica (Cole) Leafy Vegetables (Group 5), Bulb Vegetables (Group 3-07), Bushberries (Group 13-07B), Citrus Fruit (Group 10-10), Cotton, Cucurbit Vegetables (Group 9), Fruiting Vegetables (Group 8-10), Leafy Vegetables (non-Brassica) (Group 4), Oilseeds (Group 20), Pome Fruits (Group 11-10), Stone Fruits (Group 12), Tree Nuts (Group 14), Tuberous and Corm Vegetables (Subgroup 1C); Seed Treatment Uses on Canola (Rapeseed), Mustard Seed, Sunflowers, and Potatoes; and Residential, Commercial, and Agricultural Uses on Ornamentals, Turfgrass (including Sod Farms and Golf Courses), and Structural Buildings (including Indoor Crack/Crevice and Outdoor Broadcast)" is provided below.

A. Summary of Toxicological Effects

Cyantraniliprole is a second-generation ryanodine receptor (RyR) insecticide belonging to the diamide class of chemistry whose pesticidal mode of action (MOA) is through unregulated activation of insect RyR channels. This leads to internal calcium store depletion and impaired regulation of muscle contraction, causing paralysis and eventual death of the insect. Mammalian RyR are shown to be 350 to >2500 times less sensitive than those of insects. In general, cyantraniliprole administration in mammals produces both adverse and adaptive changes in the liver, thyroid gland, and adrenal cortex. With repeated dosing, consistent findings of mild to moderate increases in liver weights across multiple species (rats, mice, dogs) are observed. Dogs appear to be more sensitive than rats and mice; cyantraniliprole produces adverse liver effects (increases in alkaline phosphatase, decreases in cholesterol, and decreases in albumin) in dogs at lower dose levels than in rats. In addition, the liver effects in the dog show progressive severity with increased duration of exposure. The available data also show thyroid hormone homeostasis is altered in rats following exposure to cyantraniliprole after 28 or 90 days due to enhanced metabolism of the thyroid hormones by the liver. However, cyantraniliprole is not a direct thyroid toxicant. Cyantraniliprole is classified as "Not Likely to be Carcinogenic to Humans" based on the absence of increased tumor incidence in acceptable/guideline carcinogenicity studies in rats and mice. In addition, there are no genotoxicity,

mutagenicity, neurotoxicity, or immunotoxicity concerns. There are also no developmental or reproductive toxicity concerns. There is no evidence of an adverse effect attributable to a single dose.

B. Food Quality Protection Act Safety Factor (FQPA SF)

EPA has determined that reliable data show the safety of infants and children would be adequately protected. EPA believes that the appropriate Food Quality Protection Act Safety Factor (FQPA SF) for cyantraniliprole should be reduced to 1X for the following reasons:

- The toxicity database for cyantraniliprole is complete.
- There are no indications in any of the available studies that the nervous system is a target for cyantraniliprole. Effects indicative of neurotoxicity are not seen in the neurotoxicity screening battery at or above the limit dose levels in acute (2,000 mg/kg) and 90-day (1,000 mg/kg) neurotoxicity studies.
- There is no evidence of susceptibility in developmental toxicity studies in rats and rabbits. The developmental toxicity study in rats is tested up to the limit dose (1,000 mg/kg/day). In the rabbit developmental toxicity study decrease in fetal body weight is seen at a dose higher than that resulting in maternal effects. In the reproductive toxicity study, increased incidence of thyroid follicular epithelium hypertrophy/hyperplasia occurs in fetal 1 (F_1) parental animals at a dose lower than that for the parental (P) generation. A clear No-Observed Adverse Effect Level (NOAEL) (1.4 mg/kg/day) is established for F_1 parental animals, and the Point of Departures (PODs) selected for risk assessment from the dog studies (1 or 3 mg/kg/day) are protective of the effect (thyroid effect) seen in the F_1 parental animals. In addition the submitted data support the conclusion that the effects on the thyroid are secondary to effects on the liver.
- The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. The chronic dietary food exposure assessment was conservatively based on 100% crop treated (CT) assumptions, average residue levels from field trials, and conservative ground and surface drinking water modeling estimates. New 2012 Residential Standard Operating Procedures (SOPs) are used to assess post-application exposure to children including incidental oral exposure. The residential post-application assessment assumes that maximum application rates are applied and that hand-to-mouth activities occur on the day of application. All of the exposure estimates are based on conservative, health-protective assumptions and are not likely to underestimate risk.

C. Toxicological End Points and Doses Used in the Human Health Risk Assessment

1. Acute

No acute dietary toxicity endpoint was selected as an effect because no effect attributed to a single dose was identified in the mammalian toxicology database.

2. Chronic Dietary (all populations)

EPA established a chronic reference dose (cRfD) and a Chronic Population Adjusted Dose (cPAD) for cyantraniliprole of 0.01 mg/kg body wt/day, based on the NOAEL of 1 mg/kg body wt/day from a 1-year oral study in dogs and an FQPA Safety Factor of 1X. In this study, effects indicative of liver toxicity (increased liver weights and alkaline phosphatase activity), and significant decreases in albumin level were observed at the Lowest Observed Adverse Effect Level (LOAEL) of 6 mg/kg body wt/day.

3. Short- and Intermediate-Term Oral

EPA selected the NOAEL of 3 mg/kg body wt/day from the 90-day oral study in dogs, based on effects observed in the co-critical 28-day and 90-day toxicity studies in dogs. In the 90-day study, a collection of treatment-related effects indicative of liver toxicity were observed at the LOAEL = 32 mg/kg body wt/day. The effects included decreases in total protein, albumin, and cholesterol in males and females; increases in alkaline phosphatase in males and females; increases in alanine aminotransferase in females; and increases in liver weights in males and females. In the co-critical 28-day study, decreases in body weight, food consumption, food efficiency, and changes in clinical chemistry (increased ALP, decreased cholesterol, and decreased albumin) were observed at the LOAEL = 35 mg/kg body wt/day (lowest dose tested). The level of concern for assessing short- and intermediate-term occupational exposure to cyantraniliprole is a margin of exposure (MOE) that is less than 100.

4. Short-Term Dermal

No short-term dermal toxicity endpoint was selected because systemic toxicity was not seen in 28-day dermal toxicity in rats at the limit dose (1,000 mg/kg/day). There are no concerns for developmental or reproductive toxicity or neurotoxicity.

5. Short-Term Inhalation

EPA selected the NOAEL of 0.1 mg/L from the 28-day inhalation study in rats. A LOAEL was not established because the highest concentration tested (0.1 mg/L) did not demonstrate any adverse effects.

6. Cancer

EPA has classified cyantraniliprole as “Not likely to be Carcinogenic to Humans” based on data showing lack of treatment-related increase in tumor incidence in the rat and mouse carcinogenicity studies. Mutagenic concern was not reported in the mutagenicity studies.

D. Cumulative Effects

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not found cyantraniliprole to share a common mechanism of toxicity with any other substances, and cyantraniliprole does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has assumed that cyantraniliprole does not have a common mechanism of toxicity with other substances.

E. Aggregate Risk Assessment

1. Acute Dietary Risk

An acute aggregate risk assessment takes into account acute exposure estimates from dietary consumption of food and drinking water. No adverse effect resulting from a single oral exposure was identified and therefore no acute dietary endpoint was selected. Cyantraniliprole is not expected to pose an acute risk.

2. Chronic dietary risk

EPA has concluded that chronic exposure to cyantraniliprole from food and water will utilize 50% of the cPAD for children 1-2 years old (the population group receiving the greatest exposure) and 22% of the general U.S. population.

3. Short-term risk

Short-term aggregate exposure takes into account short-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Cyantraniliprole is proposed for uses that could result in short-term residential exposure, and the Agency has determined that it is appropriate to aggregate chronic exposure through food and water with short-term residential exposures to cyantraniliprole. Residential exposure estimates of all possible scenarios are not of concern. Short-term inhalation MOEs range from 22,000 to 220,000,000. Furthermore, these calculated risk estimates are highly conservative because the inhalation exposure POD is based on an exposure duration of 24 hours per day.

Using the exposure assumptions described in this unit for short-term exposures, EPA has concluded the combined short-term food, water, and residential exposures result in aggregate MOEs of 290 for children 1-2 years old (the population group receiving the greatest exposure) and 22,000 for adults. Because EPA's level of concern for cyantraniliprole is a MOE of 100 or below, these MOEs are not of concern.

4. Intermediate-term risk

Intermediate-term aggregate exposure takes into account intermediate-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). For adults, intermediate-term exposure is not expected for the residential exposure pathway. The intermediate-term aggregate risk would be equivalent to the chronic dietary exposure estimate. For children 1 to <2 years old, the short-term aggregate risk is protective of the intermediate-term duration.

5. Aggregate cancer risk for U.S. population

Based on the lack of evidence of carcinogenicity in two adequate rodent carcinogenicity studies, cyantraniliprole is not expected to pose a cancer risk to humans.

F. Occupational Risk Assessment

1. Handler Exposure and Risk

Occupational handler and post-application exposure may occur by the dermal and inhalation routes of exposure only. Since there is no dermal hazard from cyantraniliprole, only inhalation exposures were quantitatively assessed. Also, since no acute toxicity effects were found for cyantraniliprole, only short- and intermediate-term inhalation risk estimates were calculated.

a. Agricultural Field Uses

The results of the occupational handler exposure and risk assessment indicate that short- and intermediate-term inhalation risks do not exceed EPA's Level of Concern (LOC) (i.e. an MOE < 30 for short-term exposures and an MOE < 100 for intermediate-term exposures) at baseline mitigation (no PPE). Since the short- and intermediate-term PODs are the same, the inhalation MOEs are also the same, ranging from 1,200 to 3,900,000.

EPA has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. There are no risk estimates of concern for aerial applicators.

b. Agricultural Seed Treatment Uses

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, some occupational handler exposure is expected from the proposed seed treatment uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

Mixing/loading liquids for potato seed piece treatment,
Planting potato seed pieces,
Mixing/loading liquids for commercial seed treatment, and
Planting treated seed.

The results of the occupational handler exposure and risk assessment indicate that short-term inhalation risk estimates do not exceed EPA's LOC (i.e. an MOE < 30 for short-term exposures) at baseline, without mitigation from PPE. Short-term exposure risk estimates are protective of intermediate-term exposure risk estimates because the throughput (amount of seed treated) is greater than, or equal to, the throughput of intermediate-term exposure. The calculated inhalation risk estimates do not exceed EPA's LOC for intermediate-term exposures (i.e. an MOE < 100) at baseline, without mitigation from PPE. The inhalation MOEs range from 370 to 4,000 for primary handlers (treaters) and 2,200 to 190,000 for secondary handlers (planters).

2. Occupational Postapplication Exposure and Risk

An occupational post-application exposure and risk assessment was not conducted because a dermal hazard was not identified for cyantraniliprole.

III. Environmental Risk

A summary of the environmental fate and ecological effects and risks of cyantraniliprole as assessed in the Agency document entitled "Environmental Risk Assessment of Proposed New Global Chemical Cyantraniliprole on Bushberries, Citrus, Cotton, Oil Seeds, Pome Fruit, Stone Fruit, Tree Nuts, Vegetables (Bulb, Corm and Tuberous, Cucurbit, Fruiting, Leafy Brassica, and Leafy-Non-Brassica), and Professional Products (Fly Bait, Indoor and Outdoor Insect Control for Public Health Pests Such as Cockroaches, Ants, Flies, Termites, Nuisance Insect Pests, Turfgrass and Ornamentals, Tree Injection, and Production Greenhouse and Nursery Ornamentals)" is provided below. Additional information and points of clarification not included in the risk assessment are included in the document, dated January 24, 2014, entitled "ADDENDUM – EFED Environmental Risk Assessment of Proposed New Global Chemical Cyantraniliprole on Bushberries, Citrus, Cotton, Oil Seeds, Pome Fruit, Stone Fruit, Tree Nuts, Vegetables (Bulb, Corm and Tuberous, Cucurbit, Fruiting, Leafy Brassica, and Leafy-Non-Brassica), and Professional Products (Fly Bait, Indoor and Outdoor Insect Control for Public Health Pests Such as Cockroaches, Ants, Flies, Termites, Nuisance Insect Pests, Turfgrass and Ornamentals, Tree Injection, and Production Greenhouse and Nursery Ornamentals)." This addendum includes a revision of the chronic mammalian

endpoint, characterization of potential risk concerns to monocots, and presents a comparison of acute honey bee toxicity data for cyantraniliprole and other insecticides.

A. Environmental Fate

Cyantraniliprole is a systemic insecticide. It is soluble at neutral pH and given its low vapor pressure (3.85 x 10-17 mm Hg) and Henry's Law constants (1.70 x 10-^{18}atm*m^3/mol), is not considered volatile and is not likely prone to atmospheric transport. While cyantraniliprole is subject to both abiotic alkaline hydrolysis (half-life = 21 hrs) and photodegradation in aqueous (half-life = 8 hrs) and moist soil environments and biotic (aerobic and anaerobic biotransformation in terrestrial and aquatic environments, half-lives range from 2 days to 3 months) degradation, the chemical degrades into a total of 13 degradation products. Of these degradates, eight are major and five are minor. Based on degradate aerobic soil metabolism and mobility studies, six of the eight major degradates had longer dissipation half-life (DT_{50}) values (more persistent) and three of the eight degradates were more mobile than the parent cyantraniliprole. According to the Food and Agriculture Organization (FAO) classification system, based on organic carbon partitioning coefficients, cyantraniliprole is characterized as moderately mobile. Bioconcentration factor data (BCF value <1 in whole fish) indicate that cyantraniliprole is not likely to bioaccumulate.

Given the uncertainty of the behavior and toxicity of these degradates, their toxicity is assumed to be equivalent to the parent compound, cyantraniliprole. For the aquatic exposure modeling, a total toxic residue approach (considers the parent compound and eight major degradates including two degradates from terrestrial field studies) was utilized. For surface water, peak estimated environmental concentrations (EECs) ranged from 0.23 µg/L from cyantraniliprole use on trees using the Oregon Christmas tree scenario to 38 µg/L from cyantraniliprole use on cotton using the North Carolina cotton scenario. For pore water, peak EECs ranged from 0.22 µg/L from cyantraniliprole use on trees using the Oregon Christmas tree scenario to 37 µg/L from cyantraniliprole use on rapeseed using the North Dakota wheat scenario.

B. Ecological Risk

Ecological risk characterization integrates the results of the exposure 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 risk quotient method. For this method, risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic (RQ = Exposure/Toxicity). RQs are then compared to EPA's levels of concern (LOCs). The LOCs are criteria used by the Agency 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 ecological risk profile is described in detail below.

Risks to Aquatic Organisms

Fish

Cyantraniliprole is classified as "slightly to moderately toxic" to freshwater fish on an acute exposure basis. A conservative calculation using the peak aquatic EEC (37.97 µg ai/L) and the typical end product LC_{50} (2,400 µg ai/L) resulted in an RQ of 0.016. This is well below the acute risk to listed species LOC of 0.05. Consequently, direct acute risks to freshwater fish and aquatic-phase amphibians, for which fish serve as surrogates, from the proposed uses of cyantraniliprole are not considered likely.

Risk quotients calculated for chronic exposures to cyantraniliprole ranged from <0.001 to 0.003 and were all well below the chronic risk to listed and non-listed species LOC of 1. The risk quotient analysis indicated

that direct chronic effects to freshwater fish are not expected; none of the risk quotients exceeded the chronic risk LOC of 1.

Risk quotients could not be calculated for direct acute effects to estuarine/marine fish because the toxicity value was non-definitive. In lieu of this, the most sensitive toxicity value can be compared with the peak EEC. The most sensitive LC_{50} (>12,000 µg total ai/L), although non-definitive, is much larger than the peak aquatic EEC of 37.97 µg ai/L. There was precipitate in this toxicity test and measured concentrations were not centrifuged or filtered; therefore, the amount of dissolved cyantraniliprole is uncertain, lending uncertainty to the study's results. No mortality or sub-lethal effects were observed in any treatment group in the test. Furthermore, the LC_{50} would need to be 16 times more sensitive (759 µg ai/L) to even reach the acute risk to listed species LOC of 0.05. Thus, the likelihood of adverse effects on estuarine/marine fish from direct acute exposure from the proposed uses of cyantraniliprole is considered low.

Risk quotients could not be calculated for chronic effects to estuarine/marine fish because only non-definitive toxicity data were available. Given that the No Observed Adverse Effect Concentration (NOAEC) was a less than value (NOAEC <750 µg ai/L), it is not possible to preclude the possibility of direct chronic risks to estuarine/marine fish. Growth parameters (length and weight) were affected at the lowest concentration tested. Although the absolute value of the NOAEC (750 µg total ai/L) is one order of magnitude higher than the highest 60-day aquatic EEC of 37.42 µg ai/L, risk concerns cannot be eliminated on this alone. Risk mitigation language is included on the labels (refer to section IV. E.).

Invertebrates

Cyantraniliprole ranged in toxicity from slightly to very highly toxic to freshwater invertebrates on an acute exposure basis. Risk quotients for acute exposures to freshwater invertebrates ranged from 0.011 to 1.9. Most uses exceeded the acute risk to listed species LOC of 0.05 and some exceeded the acute risk to non-listed species LOC of 0.5.

Risk quotients for chronic exposures to freshwater invertebrates ranged from 0.035 to 5.8 with some uses exceeding the listed and non-listed species chronic risk LOC of 1.

Cyantraniliprole is moderately to highly toxic to estuarine/marine invertebrates on an acute exposure basis. Acute risk quotients for estuarine/marine invertebrates ranged from <0.001 to 0.073 showing a slight exceedance of the acute risk to listed species LOC of 0.05. Chronic risk quotients ranged from 0.001 to 0.23 (oyster) and < 0.001 to 0.12 (mysid shrimp). No scenarios exceeded the listed and non-listed species chronic risk LOC of 1. Thus, while mortality (direct) of estuarine/marine invertebrates is possible following acute exposure for eight of the proposed uses, the likelihood of (direct) adverse effects from chronic exposure is considered low.

Cyantraniliprole is highly toxic to benthic invertebrates on an acute exposure basis. Acute risk quotients for benthic invertebrates ranged from <0.001 to 0.051 but only one use exceeded the acute risk to listed species LOC of 0.05. Chronic risk quotients ranged from 0.022 to 3.7 with some uses exceeding the listed and non-listed species chronic risk LOC of 1.

To reduce the potential risk to aquatic invertebrates, risk mitigation language is included on the labels (refer to section IV.D.).

Aquatic Plants

Toxicity data for technical-grade cyantraniliprole was non-definitive for aquatic vascular and non-vascular plants. Thus, risk quotients were not calculated. Given the lines of evidence, it is unlikely that there will be direct adverse effects to aquatic plants based on exposure from the proposed uses of cyantraniliprole.

Risks to Terrestrial Organisms

Birds

Cyantraniliprole is classified as 'practically nontoxic' to birds on an acute oral and sub-acute dietary exposure basis. Since all of the endpoints from the acute oral and sub-acute dietary toxicity studies with birds are non-definitive (*i.e.*, they are 'greater than' values), they were not used to calculate RQs. Instead, the non-definitive toxicity values were directly compared to the EECs. The most sensitive TGAI studies were selected (in two cases, there were more sensitive results for the typical end-use product (TEP) studies, but these were also non-definitive and the lower toxicity value is probably an artifact of the largest dose of product that was given to the bird rather than the active ingredient itself). In all cases, none of the EECs were larger than the non-definitive toxicity values for the most sensitive avian species. No sub-lethal effects were observed in either the acute oral or sub-acute dietary studies for any of the species tested. Acute effects to listed and non-listed bird species are not expected.

The chronic dietary-based RQs range from <0.01 to 0.45, and are below the LOC of 1.0. Therefore, the likelihood of chronic adverse effects for listed and non-listed birds, reptiles, and terrestrial-phase amphibians from exposure to residues from the proposed cyantraniliprole uses is expected to be low.

Mammals

Cyantraniliprole is classified as 'practically nontoxic' to mammals on an acute oral exposure basis. Non-definitive toxicity values were directly compared to the EECs. In all cases, none of the EECs were larger than the non-definitive toxicity values. Furthermore, no sub-lethal effects were observed in the acute oral toxicity study. Therefore, acute effects on listed and non-listed mammalian species are not expected.

There were no LOC exceedances of the listed and non-listed species chronic risk LOC (1), except for the following uses/application types: soil injection/drench for hardwood trees (RQ of 1.3), soil drench for citrus (RQ of 1.2), and drip irrigation applications for cucurbits (RQ of 3.2). These risk quotients were conservatively calculated by estimating the concentration of cyantraniliprole in the leaf biomass of the plant, where for the screening-level risk assessment the risk quotients above were calculated assuming 100% of the animal's diet comes from the treated site (*e.g.,* citrus leaves). It is important to note that it is unlikely that these use sites make up 100% of a non-target mammalian diet; therefore the actual potential for risk is low considering the variability of non-target mammalian diets.

Terrestrial Invertebrates

Toxicity data for parasitic wasps, beetles, spiders, lacewings, predatory mites, and collembola indicated that cyantraniliprole is toxic to some terrestrial invertebrates at very low application rates (48-hr LR_{50} = 0.00008 lb ai/A – parasitic wasp), consistent with its insecticidal mode of action. Conversely, collembola, which are exposed to cyantraniliprole through direct contact with the soil, were insensitive to applications of cyantraniliprole (EC_{50} > 1,200 mg ai/kg-soil. Likewise, earthworms demonstrated a low toxic effect to cyantraniliprole (EC_{50} > 102.6 mg ai/kg-soil – based on the TEP).

While there is some uncertainty in honeybee toxicity data for cyantraniliprole, due to some non-definitive endpoints, it is highly toxic on an acute oral and contact basis; however, this compound is generally less toxic to honey bees than organophosphate, pyrethroid, neonicotinoid, and carbamate insecticides (Table 1). Refined acute oral RQs for adult honeybees using empirically-based maximum reported concentrations in nectar and pollen were determined as the ratio of cyantraniliprole consumed in pollen/nectar (i.e., dose) to the acute LD_{50} for cyantraniliprole-only TEP (0.116 µg ai/bee) and ranged from 0.017 to 0.066 and are below the LOC of 0.4. The LOC of 0.4 was established for acute risks to honeybees. If an RQ is less than LOC, the chemical being assessed does not pose a risk concern to insect pollinators on an acute exposure basis and

higher tier studies are not required. The registration packet included semi-field and field data for honeybees, which were used to confirm this conclusion. The LOC of 0.4, and framework for assessing risk to pollinators – used in the cyantraniliprole ecological risk assessment – is outlined in the Agency's White Paper for assessing potential risks to pollinators and was evaluated by the FIFRA Scientific Advisory Panel[1].

Table 1 below is a comparison of the relative honeybee acute toxicity for cyantraniliprole to organophosphates, carbamates, pyrethroids and neonicotinoids, which have similar uses to cyantraniliprole. The table below includes honeybee acute contact and acute oral toxicity ranges for organophosphates, carbamates, pyrethroids, and neonicotinoids, as well as the toxicity values for cyantraniliprole and cyantraniliprole/thiamethoxam TEP. The comparatively low toxicity of the dual a.i. product containing cyantraniliprole/thiamethoxam is largely reflective of the toxicity of thiamethoxam, although less toxic than thiamethoxam alone. This table illustrates that cyantraniliprole is typically less toxic to honeybees compared to these chemical classes.

Table 1. Comparison of relative honeybee acute toxicity*

Chemical	**Honeybee acute contact LC_{50} (µg ai/bee)**	**Honeybee acute oral LD_{50} (µg ai/bee)**
Carbamates	0.1600 to 35	0.094 to 3.01
Neonics	0.024 to <12.5	0.0037 to >10.21
Organophosphates	0.059 to 58.9	0.056 to 0.44
Pyrethroids	0.0015 to 0.52	0.172 to 0.909
Cyantraniliprole	**0.55**	**0.116**
Cyantraniliprole/thiamethoxam TEP	**0.058**	**0.0062**

*Additional comparisons to individual chemicals are included in the Addendum to the Ecological Risk Assessment.

The semi-field studies indicated transient effects on behavior, foraging activity and mortality. Observations of brood health and colony strength (up to 28 days) suggested no significant lethal or sub-lethal adverse effects on larvae or colony strength from cyantraniliprole applications. The field studies provide *in situ* information about the effects of cyantraniliprole applications to brood development and longer-term colony health. If the larvae in a hive are undergoing adverse toxicological effects to a significant degree, a decrease in hive population or other colony-level effects will be seen over time – especially during the overwintering period; which was not observed in the cyantraniliprole studies.

Non-target Terrestrial and Semi-Aquatic Plants

Based on the risk quotient analysis, the LOC for risk to listed terrestrial plants was not exceeded for monocots or dicots. There is some uncertainty regarding the analysis for monocots because seedling emergence data were available for only one monocot species. However, available data indicate that onion was the most sensitive monocot using a vegetative vigor study, where it is approximately 2X more sensitive than the available monocot (corn) species data. Therefore it would be reasonable to expect the seedling emergence endpoint for onion to be lower than the monocot and dicot observed endpoints. Taking into account this uncertainty, the analysis suggests risks are not of concern for non-listed monocot or dicot plant species, nor for listed animal species that do not possess an obligate relationship with a particular monocot. Risk was identified for listed monocot species within a short distance of the treated field and for listed animal species with an obligate relationship with a particular monocot plant. Further, the registration package includes uses on monocots (specifically bulb vegetables, onion); therefore it is unlikely that the potential impact on onions is significant. Additionally, exceedance of the Agency's LOC is lowered

[1]Regulations.gov docket for the FIFRA SAP: http://www.regulations.gov/#!docketBrowser;rpp=25;po=0;dct=SR;D=EPA-HQ-OPP-2012-0543; and the Agency's White paper: http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0543-0004

significantly as distance increases from the treated field; therefore the implemented buffers on the labels are intended to mitigate this potential risk.

IV. Regulatory Decision

The Agency is unconditionally granting the registration of the new active ingredient, cyantraniliprole, formulated as a technical product and fourteen end use products, under section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act for the following uses (a complete list of all registered products is included in the attachment):

Agricultural crops
bushberry (crop subgroup 13-07B); fruit, citrus (crop group 10-10); fruit, pome (crop group 11-10); fruit, stone (crop group 12-12); nut, tree (crop group 14-12); oilseed (crop group 20); vegetable, Brassica (Cole) leafy (crop group 5); vegetable, bulb (crop group 3-07); vegetable, cucurbit (crop group 9); vegetable, fruiting (crop group 8-10); vegetable, leafy (except Brassica) (crop group 4); and vegetable, tuberous and corm (crop subgroup 1C).

Ornamentals and turf
ornamental plants, shrubs, trees in and around greenhouses, nurseries, lath- and shade-houses, and interior plantscapes; landscape and recreational turfgrass (including golf courses); sod farms.

Structures and equipment
in and around agricultural, commercial, and residential structures (excluding food/feed handling establishments); and transportation equipment.

For the food uses, Canadian Maximum Residue Levels (MRLs) and U.S. tolerances are harmonized for primary crop commodities and livestock commodities. A few items are not harmonized: a) Canada will establish import tolerances for grapes and olives; the US does not have this request. b) Canada does not establish MRLs for livestock only commodities whereas the US does. c) Canada is setting MRLs for poultry commodities at the level of quantification (LOQ) of the analytical method (0.01 ppm) in accord with Canadian policy for situations of no residues anticipated in the livestock commodities where there are feed items with residues. The US is not establishing tolerances for poultry commodities as no significant accumulation in poultry tissues or eggs is expected, i.e., category 40CFR §180.6(a)(3).

U.S. and Canadian tolerances are not entirely harmonized with European Union (EU) MRLs. This is due both to differences in regional use patterns and climate as well as how the maximum levels are calculated. Examples of different maximum levels include: citrus (0.70 ppm US/CA vs. 0.9 ppm EU); leafy vegetables (20 ppm US/CA vs. 15 ppm EU); pome fruit (1.5 ppm US/CA vs. 0.8 ppm EU); plums (0.5 ppm US/CA vs. 1.5 ppm EU); tree nuts (0.04 ppm US/CA vs. 0.03 ppm EU). Fruiting vegetables (including peppers) are harmonized at 2 ppm except tomatoes (2 ppm US/CA vs. 1.5 ppm EU) and eggplant (2 ppm US/CA vs. 0.4 ppm EU).

Codex maximum residue levels (MRLs) for cyantraniliprole were proposed in September, 2013 but have not been adopted to date.

A. Public Comments

Notice of Receipt

On April 26, 2012, EPA published a Notice of Receipt in the Federal Register of an application for registration of cyantraniliprole and announced a public comment period of 30 days. Only two comments were received, one from the San Francisco Bay Regional Water Quality Control Board and the other from the California Stormwater Quality Association. The comments were similar in that they requested that EPA consider adverse impacts to aquatic systems from urban use sites.

EPA addressed these comments during the risk assessment process by employing the Total Toxic Residue approach (i.e. including parent chemical and all potential degradates) in its evaluation of cyantraniliprole and its degradates in aquatic systems. The Total Toxic Residue approach essentially extends the duration of the predicted EECs to account for the time it would take for both the parent and degradates of concern to dissipate in the environment. It assumes that the degradates have equivalent fate and ecotoxicity properties as the parent which is a conservative assumption.

Notice of Filing
On May 23, 2012, EPA published a Notice of Filing in the Federal Register; no comments were received.

Proposed Registration Decision
On June 6, 2013 EPA posted a Proposed Registration of Cyantraniliprole to the public docket (EPA-HQ-OPP-2011-0668). Twenty three public comments were received. A detailed review of the public comments can be found in Cyantraniliprole - Response to Public Comments on EPA's "Proposed Registration of the New Active Ingredient Cyantraniliprole: An Insecticide for Use on Multiple Commodities, Ornamentals, Turfgrass, and in Commercial or Residential Buildings" posted to the docket.

B. Regulatory Rationale

Cyantraniliprole is a broad spectrum insecticide, with activity on a wide variety of target pests. While it is the third compound registered in the Insecticide Resistance Action Committee (IRAC) Mode of Action Classification Group 28; ryanodine receptor modulators, it has a broader spectrum of activity than the other two compounds. It is expected to fit well in IPM programs.

As an efficacious insecticide, cyantraniliprole is expected to have invertebrate biological activity and therefore it may pose a risk to pollinators, as is the base for insecticides in general. Cyantraniliprole was granted classification as a Reduced Risk pesticide. This means that compared to existing conventional pesticides such as the organophosphates, carbamates and pyrethroids, it presents characteristics that include lower impact on human health, lower toxicity to non-target organisms, low potential for groundwater contamination, and compatibility with IPM practices. Based on the committee's evaluation of the information provided, the mammalian toxicity and ecotoxicity risk profiles for cyantraniliprole are favorable compared to registered alternatives, which include organophosphates, pyrethroids and abamectin. The novel mode of action for cyantraniliprole fits in well with resistance management strategies. After review and consideration of all of the data provided by the 800+ studies, the determinations made by the multiple scientists and international partners involved in the project, and the outcome of the human health and ecological risk assessments, the Agency supports the decision to register cyantraniliprole as a reduced risk compound.

In light of this determination, the Agency considered the potential risks posed by cyantraniliprole. The risks were found not to be unreasonable when weighed against the benefits it provides. Cyantraniliprole controls lepidoptera, whiteflies, leafminers, psyllids, leaf-feeding beetles, fruit flies, and sawflies. Cyantraniliprole is effective at controlling the establishment and population growth of aphids, weevils and thrips. In a comparative qualitative analysis of efficacy, cyantraniliprole is considered to be more efficacious than current registrations of more toxic compounds for control of citrus psylla, citrus leafminer, citrus aphid, beet

armyworm, cotton bollworm, Silverleaf whitefly, cotton thrips, oriental fruit moth, and obliquebanded leafroller.

Cyantraniliprole is expected to be an essential tool to citrus growers and blueberry growers. The citrus industry is under serious threat from citrus greening disease (HLB). Once a tree becomes infected, there is no cure and it will die. The only way to protect citrus trees from HLB is through prevention by control of the Asian Citrus Psyllid and there are very few effective alternatives; cyantraniliprole is one of the least toxic alternatives that would be available for citrus growers. Florida and California growers need cyantraniliprole to provide an additional mode of action to combat this psyllid. Deaths of trees resulting in serious losses to the citrus industry will also affect beekeepers that rely on citrus for honey production and as a resource for their bees.

The Agency is also aware of the threat to numerous crops from the invasive fruit fly, the spotted wing Drosophila (SWD). This pest has already seriously injured the US blueberry crop. On July 29, 2013, the Washington Post wrote an article about the concern that Maine's wild blueberry growers have for the threat posed by SWD. There is a zero tolerance standard for SWD in blueberries, a load of harvested blueberries will be rejected no matter the level of infestation. Extension agents in blueberry growing states have recommended carbaryl, diazinon, malathion, methomyl, phosmet, bifenthrin, esfenvalerate and other conventional chemicals, however pre-harvest intervals for these compounds are long and SWD infestations occur when fruit is ripe therefore growers are in need of tools with short PHIs. Michigan and New Jersey State Lead Agencies have made crisis declarations under FIFRA Section 18 Emergency Exemption provisions on behalf of blueberry growers for the use of malathion to combat SWD. Registration of cyantraniliprole will provide the growers with an effective tool that has a short PHI and a more favorable toxicological profile compared to currently registered alternatives.

Cyantraniliprole is expected to be an alternative to a number of insecticide classes (organophosphates, carbamates, pyrethroids and some neonicotinoids). Compared to these alternatives cyantraniliprole generally presented a more favorable environmental fate profile including its low volatility, low accumulation and leaching potential in addition to microbial-mediated and abiotic dissipation pathways. Additionally, it is generally less toxic towards mammals, birds and fish than the leading alternatives, and also honey bees (see Section III.B., Table 1). In critical pest situations, cyantraniliprole may also replace multiple or repeated applications of these other compounds, which expose non-target organisms many times and present greater risks to a wider range of non-target species. Registration of cyantraniliprole should therefore serve to reduce overall risks to such species, including listed species, when users substitute this product for the majority of the available registered alternatives.

C. Data Requirements

No additional studies required, the cyantraniliprole database is complete for the proposed uses.

D. Labeling Requirements

As noted in section III. B., aquatic invertebrates may be affected by cyantraniliprole. To mitigate the potential risk, cyantraniliprole labels will state:

> "Do not make ground applications within 25' or aerial applications within 50' of lakes, rivers, reservoirs, permanent streams, marshes, natural ponds, estuaries or coastal areas. Do not cultivate within 25' of these aquatic areas to allow growth of a vegetative filter strip."

Additionally, an extensive "Spray Drift Management" section is included on the labels, which provides applicators with information intended to decrease drift potential. The information addresses droplet size, boom length, application height, wind speed and other weather conditions.

While a potential chronic risk to mammals was identified for three specific application/use scenarios (soil injection/drench for hardwood trees, soil drench for citrus, and drip irrigation applications for cucurbits), it was based on a screening-level risk assessment that assumes that 100% of the animal's diet has been treated with cyantraniliprole from these three specific application sites. Thus, the potential risk is based on conservative assumptions where it is unlikely that these sites make up 100% of a non-target mammalian diet; therefore the actual potential for risk is low considering the variability of non-target mammalian diets. Additionally, cyantraniliprole is expected to be an alternative to compounds in the organophosphate and carbamate chemical classes, which adversely affect mammals.

Since cyantraniliprole is an insecticide, and as with other insecticides (see Table 1) it was not unexpected that the data indicate that it is highly toxic on an acute oral and contact basis to honeybees and other insect pollinators. However, it is ranked lower compared to neonicotinoids, carbamates and pyrethroids. In order to reduce exposure to these organisms, and to alert applicators, cyantraniliprole labels must include pollinator protective labeling, as follows:

1. A "Pollinator Protection Box" that contains information regarding routes of exposure, a web site resource for Best Management Practices, and contacts for reporting beekills.
2. Use of a "Bee Icon" to call attention to the protective text
3. Prohibition of applications to crops during bloom, except under certain specific conditions
4. Restrictions for ornamentals that prohibit application during bloom.

ATTACHMENT A

Complete List of Registered Products:

EPA Registration #	product name	formulation	use sites (with crop group #)
352-856	DuPont Cyazypyr Technical	96.7% technical	- Agricultural crops bushberry (subgroup 13-07B); fruit, citrus (group 10-10); fruit, pome (group 11-10); fruit, stone (group 12-12); nut, tree (group 14-12); oilseed (group 20); vegetable, Brassica (Cole) leafy (group 5); vegetable, bulb (group 3-07); vegetable, cucurbit (group 9); vegetable, fruiting (group 8-10); vegetable, leafy (except Brassica), (group 4) vegetable, tuberous and corm (subgroup 1C) - industrial, public, & residential: turf, ornamentals - commercial production: ornamentals, sod farms - in & around residential, public, commercial, agricultural structures; transportation vehicles (excluding food/feed handling establishments): indoors - spot or crack & crevice only outdoors - spot; crack & crevice; band - in & around residential, commercial, agricultural structures: scatterbait and bait stations
352-857	DuPont Benevia Insect Control	10.26% OD 0.83 lb ai/gal	- nut, tree 14-12 - oilseed 20 (includes cotton) - vegetable, bulb 3-07 - vegetable, tuberous & corm 1C
352-858	DuPont Lumiderm Insecticide Seed Treatment	50% FS 5.21 lb ai/gal	- rapeseed (canola) - mustard seed

EPA Registration #	product name	formulation	use sites (with crop group #)
352-859	DuPont Exirel Insect Control	10.20% SE 0.83 lb ai/gal	- bushberry 13-07B - fruit, citrus 10-10 - fruit, pome 11-10 - fruit, stone 12-12 - nut, tree 14-12 - vegetable Brassica (Cole) leafy 5 - vegetable, bulb 3-07 - vegetable, cucurbit 9 - vegetable, fruiting 8-10 including eggplant, pepper, tomato in commercial greenhouses - vegetable, leafy except Brassica 4
352-860	DuPont Verimark Insect Control	18.66% SC 1.67 lb ai/gal	- fruit, citrus 10-10 - vegetable Brassica (Cole) leafy 5 - vegetable, cucurbit 9 - vegetable, fruiting 8-10 - vegetable, leafy except Brassica 4 - vegetable, tuberous & corm 1C
352-862	HGW86 Fly Control Bait	0.5% RB	- in & around residential, commercial, agricultural structures: scatterbait and bait stations
352-863	HGW86 GH & N Insect Control	18.66% SC 1.67 lb ai/gal	- ornamentals and "grassy, weedy, mulched, or bare soil areas" in & around greenhouses, nurseries, shadehouses, lathhouses - ornamentals in interior plantscapes
352-865	HGW86 T & O Insect Control	18.66% SC 1.67 lb ai/gal	- outdoor turfgrass & ornamentals (residential & public incl. golf courses) - interior plantscapes - sod farms
352-868	HGW86 SC Insect Control	18.66% SC 1.67 lb ai/gal	- in & around residential, public, commercial, agricultural structures; transportation vehicles (excluding food/feed handling establishments): indoors - spot or crack & crevice only' outdoors - spot; crack & crevice; band
100-1418	Fortenza Red Insecticide [seed treatment]	48.8% FS 600 g/l	- potato - sunflower

EPA Registration #	product name	formulation	use sites (with crop group #)
100-1420	Fortenza Insecticide [seed treatment]	48.8% FS 600 g/l	- potato - sunflower
100-1421	Minecto Duo Insecticide	20% + 20% WG	vegetable Brassica (Cole) leafy 5 vegetable, cucurbit 9 vegetable, fruiting 8-10 vegetable, leafy except Brassica 4 vegetable, tuberous & corm 1C
100-1422	A16901B Ornamental Insecticide	20% + 20% WG	- ornamentals, non-bearing fruit and nut trees, and forest seedlings in commercial greenhouse, nurseries, and interiorscapes - certain crop plants grown for sale as transplants to consumers (only): .vegetable, Brassica leafy 5 .vegetable, cucurbit 9 .vegetable, fruiting 8-10
100-1423	A16901B Residential Insecticide	20% + 20% WG	- outdoor residential ornamentals
100-1424	Spinner Insecticide	20% + 20% WG	- turfgrass (residential & public including golf courses) - sod farms - ornamentals, non-bearing fruit and nut trees, and forest seedlings in commercial greenhouse, nurseries, and interiorscapes - certain crop plants grown for sale as transplants to consumers (only): .vegetable, Brassica leafy 5 .vegetable, cucurbit 9 .vegetable, fruiting 8-10