UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**DATE:** March 7, 2013

**SUBJECT:** **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).

**PC Code:** 090098
**Decision No.:** 451670

**Petition No.:** 1F7894
**Risk Assessment Type:** Aggregate Human Health
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** D404762, D407979
**Registration Nos.:** 352-IAE, 352-IAG, 352-IAI, 352-IAL, 253-IAN, 352-ILA, 352-ILI, 352-ILO, 352-ILT, 100-RUEE, 100-RUEG, 100-RUEN, 100-RUER, 100-RUEU, 100-RURI
**Regulatory Action:** Section 3
**Case No.:** NA
**CAS No.:** 736994-63-1
**40 CFR:** to be determined (new active ingredient)

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**THROUGH:** Christine Olinger, Branch Chief
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## 1.0 Executive Summary

Cyantraniliprole is a new second-generation ryanodine receptor (RyR) insecticide currently undergoing global joint review. It is a systemic insecticide that is mobile in both the xylem and phloem of plants. Cyantraniliprole belongs to the diamide class of chemistry whose pesticidal mode of action (MOA) is through unregulated activation of insect RyR channels. This then leads to internal calcium store depletion and impaired regulation of muscle contraction, causing paralysis and eventual death of the insect.

*Proposed Use Profile*
Cyantraniliprole has been jointly developed by DuPont and Syngenta, with a proposal for one technical product and 14 U.S. end-use product (EP) registrations, including agricultural food uses (PP#1F7894). The agricultural uses include foliar, soil, and seed treatment to various crops including cotton, fruits, oilseeds, and vegetables. The residential use sites include turfgrass, ornamentals, and structural buildings (including indoor crack/crevice and outdoor broadcast).

*Exposure Profile*
Non-occupational exposures to cyantraniliprole are expected for short- and intermediate-term durations. Exposure pathways include dietary (food and drinking water), and residential exposure sources. Dietary exposures are also expected for chronic duration. Occupational exposures are expected for short- and intermediate-term durations only. The dermal route of exposure is not assessed because there is no dermal hazard. The proposed residential uses (turf, ornamentals, and indoor crack/crevice) result in inhalation exposures for adults (handlers) and post-application incidental oral exposures for children (1 to <2 years old).

*Toxicity/Hazard*
The risk assessment for cyantraniliprole is based on a well-characterized and complete toxicology database. While unregulated activation of RyR channels leads to insect death, the insect RyR are shown to be 350 to >2500 times more sensitive than those of mammals. In general, cyantraniliprole administration 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. 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. Therefore, the data support a reduction of the Food Quality Protection Act (FQPA) safety factor to 1X. There is no evidence of an adverse effect attributable to a single dose. The toxicity endpoint and points of departure (PODs) for chronic dietary and short-/intermediate-term incidental oral exposure are

based on the 1-year and 90-day dog oral toxicity studies, respectively. The toxicity endpoint and POD for inhalation exposure are based on the results of a 28-day rat inhalation toxicity study.

*Dietary Exposure (Food and Water) and Risk Estimates*

An acute dietary assessment was not conducted because there was no indication of an adverse effect attributable to a single dose. A somewhat refined chronic (food and drinking water) dietary assessment was conducted assuming average field trial residues for all proposed crops (except crop subgroup 1A) and that 100% of crops are treated (CT). Tolerance-level residues were adequate to cover residues in all livestock commodities except liver and meat byproducts for which higher anticipated residue calculations were used. The estimated drinking water concentration (EDWC) of 24.45 µg/L derived from the 1-in-10 year annual mean from surface water estimates was incorporated directly into the chronic dietary assessment. The results of the chronic dietary (food and drinking water) analysis are below the Agency's level of concern (LOC) for the general U.S. population and all population subgroups. The dietary (food and drinking water) exposure is estimated at 22% of the chronic Population Adjusted Dose (cPAD) for the general U.S. population and 50% of the cPAD for children 1-2 years old, the population subgroup with the highest estimated chronic dietary exposure to cyantraniliprole.

*Residential Exposure and Risk Estimates*

Residential exposure may occur by the dermal, oral, and inhalation routes of exposures. As previously noted, cyantraniliprole does not pose a dermal hazard; therefore, only inhalation (handler exposure for adults) and oral (post-application incidental oral for children) require assessment. The proposed uses do not result in residential handler inhalation (adults) or post-application incidental oral (children) risk estimates of concern. For the proposed residential uses (turf, ornamentals, and crack/crevice), the short-term residential handler inhalation margins of exposure (MOEs) range from 22,000 to 220,000,000. Short-term incidental oral post-application risk estimates (which are protective of intermediate-term risk estimates) for all scenarios are not of concern to HED (MOEs range from 290 to 1,000,000).

*Residential Aggregate Exposure Risk Estimates*

There is potential for short-term aggregate exposure to cyantraniliprole via the dietary and residential pathways. For adults, the oral and inhalation routes of exposure should not be aggregated since the endpoints of concern are not common. For children, the short-term aggregate risk estimate is not of concern; the MOE is 190 which is greater than the LOC of 100.

*Occupational Exposure and Risk Estimates*

Occupational handler and post-application exposure may occur by the dermal and inhalation routes of exposure only. Since there is no dermal hazard, only inhalation exposures were quantitatively assessed. The results of the occupational handler exposure and risk assessment indicate that short- and intermediate-term inhalation risk estimates are not of concern at baseline (long-sleeved shirt, long pants, shoes plus socks) without mitigation from any personal protective equipment (PPE). In general, the labels require PPE of chemical-resistant gloves. The proposed level of clothing and PPE are adequate for protection of workers. Short- and intermediate-term inhalation MOEs range from 370 to 3,900,000. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for cyantraniliprole at this time. The technical form of cyantraniliprole meets the

criteria for a 4-hour REI. However, two of the proposed EPs (EPA Reg. No. 352-ILT and EPA Reg. No. 352-ILI) have been identified as dermal sensitizers, so a 12-hour REI is required to protect agricultural workers from post-application exposures to cyantraniliprole. Aside from these two products, a 4-hour REI is adequate to protect agricultural workers from post-application exposures to cyantraniliprole.

*Environmental Justice*
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment. Dietary and non-dietary exposures were considered.

## 2.0 HED Recommendations

HED has examined the toxicology and residue chemistry databases for cyantraniliprole. Pending submission of a revised Section B (label), a revised Section F (tolerances), and submission of analytical reference standards, there are no toxicology or residue chemistry issues that would preclude granting Section 3 registration for the requested crop commodity uses of cyantraniliprole (except food/feed establishment uses), or establishment of tolerances for residues of cyantraniliprole. The specific tolerance recommendations are discussed in Section 2.2, and label modifications are discussed in Section 2.3.

## 2.1 Data Deficiencies

There are no data deficiencies to prohibit tolerance establishments or product registrations.

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

The submitted residue analytical method data are adequate. Validation data have been provided for the proposed enforcement methods. Methods for measuring cyantraniliprole include the European Union (EU) multi-residue method DFG S19 (LC/MS/MS module, Dupont-21328) and the North American Free Trade Association (NAFTA) LC/MS/MS 1187 & 1552 methods. These methods utilize two mass ion transitions so confirmatory methods are not required. EU Method DFG S19 has been independently validated with a limit of quantification (LOQ) of 0.01 ppm for parent cyantraniliprole in cereals and dry products, matrices with high water content, acidic matrices, and fatty products. NAFTA method 1187 has been independently validated with an LOQ of 0.01 ppm for parent cyantraniliprole in almonds, onions, tomato paste, and sun dried tomatoes. NAFTA method 1552 has been independently validated with an LOQ of 0.01 ppm for parent cyantraniliprole in milk, muscle, and kidney. Note that cyantraniliprole is not recovered using the FDA multi-residue methods.

### 2.2.2 Recommended Tolerances

It is recommended that tolerances be established for residues of the insecticide cyantraniliprole (3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-

pyrazole-5-carboxamide), including its metabolites and degradates, in or on the **plant commodities and livestock** specified below in Table 2.2.2.

It is recommended that **indirect or inadvertent tolerances** be established for residues of the insecticide cyantraniliprole (3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide), including its metabolites and degradates, in or on the commodities specified below in Table 2.2.2.

Compliance with the tolerance levels specified below is to be determined by measuring only cyantraniliprole in or on the commodity.

**Table 2.2.2 Tolerance Summary for Cyantraniliprole**

| Commodity | Proposed Tolerance | Recommended Tolerance | Comments *Correct Commodity Definition* |
|---|---|---|---|
| | *ppm* | *ppm* | |
| 40CFR §180 Part (a) *General:* It is recommended that tolerances be established for residues of the insecticide cyantraniliprole (3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide), including its metabolites and degradates, in or on the commodities below. Compliance with the tolerance levels specified below is to be determined by measuring only cyantraniliprole in or on the commodity. | | | |
| Almond, hulls | 30 | 8.0 | A revised Section F must be submitted to propose a tolerance at 8.0 ppm. |
| Berries and small fruits, bushberries (crop subgroup 13-07B**)** | 4 | 4.0 | *Bushberry subgroup 13-07B* |
| *Brassica* (Cole) leafy vegetables, head and stem *Brassica* (crop subgroup 5A) | 2 | 3.0 | *Brassica, head and stem, subgroup 5A*<br>A revised Section F must be submitted to propose a tolerance at 3.0 ppm. |
| *Brassica* (Cole) leafy vegetables, leafy *Brassica* greens (crop subgroup 5B) | 30 | 30 | *Brassica, leafy greens, subgroup 5B* |
| Bulb vegetables, onion, bulb (crop subgroup 3-07A) | 0.04 | 0.04 | *Onion, bulb, subgroup 3-07A* |
| Bulb vegetables, onion, green (crop subgroup 3-07B) | 8 | 8.0 | *Onion, green, subgroup 3-07B* |
| Cattle, fat | 0.01 | 0.01 | |
| Cattle, liver | 0.04 | None | Included under meat byproducts. |
| Cattle, meat | 0.01 | 0.01 | |
| Cattle, meat byproducts, except liver | 0.01 | 0.01 | *Cattle, meat byproducts* |
| Cherries | 6 | 6.0 | *Cherry subgroup 12-12A* |
| Citrus fruits (crop group 10-10) | 0.7 | 0.70 | *Fruit, citrus, group 10-10* |
| Citrus, oil | 4 | 2.4 | A revised Section F must be submitted to propose a tolerance at 2.4 ppm. |

| **Table 2.2.2 Tolerance Summary for Cyantraniliprole** | | | |
|---|---|---|---|
| Commodity | Proposed Tolerance | Recommended Tolerance | Comments *Correct Commodity Definition* |
| | *ppm* | *ppm* | |
| Citrus, raw peel | 0.9 | None | |
| Cotton, gin byproduct | 10 | 10 | *Cotton, gin byproducts* |
| Cucurbit vegetables (crop group 9) | 0.3 | 0.40 | A revised Section F must be submitted to propose a tolerance at 0.4 ppm. *Vegetable, cucurbit, group 9* |
| Fruiting vegetables (crop group 8-10) | 2 | 2.0 | *Vegetable, fruiting, group 8-10* |
| Goat, fat | 0.01 | 0.01 | |
| Goat, liver | 0.04 | None | Included under meat byproducts. |
| Goat, meat | 0.01 | 0.01 | |
| Goat, meat byproducts, except liver | 0.01 | 0.01 | *Goat, meat byproducts* |
| Hog, fat | 0.01 | None | 40CFR§180(a)(3) |
| Hog, liver | 0.04 | None | 40CFR§180(a)(3) |
| Hog, meat | 0.01 | None | 40CFR§180(a)(3) |
| Hog, meat byproducts, except liver | 0.01 | None | 40CFR§180(a)(3) |
| Horse, fat | 0.01 | 0.01 | |
| Horse, liver | 0.04 | None | Included under meat byproducts. |
| Horse, meat | 0.01 | 0.01 | |
| Horse, meat byproducts, except liver | 0.01 | 0.01 | *Horse, meat byproducts.* |
| Leafy vegetables (except *Brassica* vegetables) (crop group 4) | 15 | 20 | A revised Section F must be submitted to propose a tolerance at 20 ppm. *Vegetable, leafy, except Brassica, group 4* |
| Milk | 0.01 | 0.01 | |
| Milk fat | 0.04 | None | Covered by milk tolerance. |
| Oilseeds, except cotton byproduct (crop group 20) | 1 | 1.5 | A revised Section F must be submitted to propose a tolerance at 1.5 ppm. *Oilseed group 20* |
| Pome fruits (crop group 11-10) | 0.8 | 1.5 | A revised Section F must be submitted to propose a tolerance at 1.5 ppm. *Fruit, pome, group 11-10* |
| Potato, wet peel | 0.3 | None | |
| Root and tuber vegetables, tuberous and corm vegetables (crop subgroup 1C) | 0.15 | 0.15 | *Vegetable, tuberous and corm, subgroup 1C* |
| Sheep, fat | 0.01 | 0.01 | |
| Sheep, liver | 0.04 | None | Included under meat byproducts. |
| Sheep, meat | 0.01 | 0.01 | |

| **Table 2.2.2 Tolerance Summary for Cyantraniliprole** | | | |
|---|---|---|---|
| Commodity | Proposed Tolerance | Recommended Tolerance | Comments *Correct Commodity Definition* |
| | *ppm* | *ppm* | |
| Sheep, meat byproducts, except liver | 0.01 | 0.01 | *Sheep meat byproducts* |
| Stone fruits, except cherries (crop group 12) | 1.5 | 1.5 | *Peach subgroup 12-12B* |
| | | 0.50 | *Plum subgroup 12-12C* |
| Tree nuts, except almond hulls (crop group 14) | 0.06 | 0.04 | A revised Section F must be submitted to propose a tolerance at 0.04 ppm. *Nut, tree, group 14* |
| 40CFR §180 Part (d) *Indirect or inadvertent residues:* It is recommended that indirect or inadvertent tolerances be established for residues of the insecticide cyantraniliprole (3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide), including its metabolites and degradates, in or on the commodities below. Compliance with the tolerance levels specified below is to be determined by measuring only cyantraniliprole in or on the commodity. | | | |
| Foliage of legume vegetables (crop group 7), forage | 0.15 | None | Only one tolerance per crop group. |
| Foliage of legume vegetables (crop group 7), hay | 0.6 | 0.70 | A revised Section F must be submitted to propose a tolerance at 0.7 ppm. *Vegetable, foliage of legume, group 7* |
| Forage, fodder and straw of cereal grains (crop group 16), forage | 0.06 | None | Only one tolerance per crop group. |
| Forage, fodder and straw of cereal grains (crop group 16), hay and straw | 0.15 | 0.5 | A revised Section F must be submitted to propose a tolerance at 0.5 ppm. *Grain, cereal, forage, fodder and straw, group 16* |
| Grass forage, fodder, and hay (crop group 17), forage | 0.06 | None | Only one tolerance per crop group. |
| Grass forage, fodder, and hay (crop group 17), hay | 0.15 | 0.50 | A revised Section F must be submitted to propose a tolerance at 0.5 ppm. *Grass, forage, fodder and hay, group 17* |
| Leaves of root and tuber vegetables (human food or animal feed) (crop group 2) | 0.04 | 0.04 | *Vegetable, leaves of root and tuber, group 2* |
| Nongrass animal feeds (forage, fodder, straw, and hay) (crop group 18), forage | 0.06 | None | Only one tolerance per crop group. |
| Nongrass animal feeds (forage, fodder, straw, and hay) (crop group 18), hay | 0.15 | 0.20 | A revised Section F must be submitted to propose a tolerance at 0.2 ppm. *Animal feed, nongrass, group 18* |

| Table 2.2.2 Tolerance Summary for Cyantraniliprole | | | |
|---|---|---|---|
| Commodity | Proposed Tolerance | Recommended Tolerance | Comments *Correct Commodity Definition* |
| | *ppm* | *ppm* | |
| Peanut, hay | 0.03 | 0.01 | A revised Section F must be submitted to propose a tolerance at 0.01 ppm. *Peanut, hay* |
| Root and tuber vegetables, root vegetables (crop subgroup 1A) | 0.03 | 0.02 | A revised Section F must be submitted to propose a tolerance at 0.02 ppm. *Vegetable, root, subgroup 1A* |

### 2.2.3 Revisions to Petitioned-For Tolerances

The proposed tolerances must be modified for the following plant commodities: almond hulls, *Brassica* vegetables (crop subgroup 5A), cucurbit vegetables (crop group 9), leafy vegetables except *Brassica* (crop group 4), oilseeds (crop group 20), pome fruits (crop group 11-10), stone fruits except cherry (crop group 12-12), and tree nuts (crop group 14). The recommended primary plant commodity tolerances are derived from use of the Organization of Economic Cooperation and Development (OECD) statistical calculation procedures.

The proposed tolerances for processed commodities are not appropriate for citrus raw peel and potato wet peel. The processing studies do not show a concentration of residue in these commodities relative to the raw agricultural commodities (RAC). The proposed tolerance for citrus oil needs to be lowered from 4 ppm to 2.4 ppm, consistent with the results from application of the median processing factor to the highest average field trials (HAFT) for oranges.

The proposed tolerances for livestock commodities are acceptable, except for liver of cattle, goat, horse, and sheep; hog fat, liver, meat, and meat byproducts; and milk fat. The livestock commodity tolerances are derived from consideration of the maximum reasonably balanced livestock diets and the livestock feeding studies. A tolerance value of 0.01 ppm is appropriate for liver (of cattle, goat, horse, and sheep), which would be covered by the meat byproducts tolerance. The dietary exposures of hogs and poultry do not indicate a need for tolerances (residues are not anticipated), and there is no indication of significant concentration of cyantraniliprole in milk fat relative to milk.

With the exception of the proposed tolerance for leaves of root and tuber vegetables, all of the proposed tolerances for inadvertent residues (with a plantback interval (PBI) of 30 days) need to be revised. The revisions must reflect the recommended tolerances based on the use of the OECD statistical calculation procedures. For some crop groups, more than one tolerance was proposed for various components of the group (e.g. crop group 16 which includes forage, fodder, and straw of cereal grains); however, only one tolerance is possible per group, and the tolerance is based on the member commodity with the highest residue levels.

### 2.2.4 International Harmonization

Currently there are no Codex Maximum Residue Limits (MRLs)/tolerances for cyantraniliprole. Therefore, there are no issues with harmonization of tolerances. Canadian MRLs are being proposed concurrently with US tolerances and are harmonized for primary crop and livestock commodities except for fruiting vegetables. The US fruiting vegetables tolerance is harmonized with the European Union.

## 2.3 Recommendations

### 2.3.1 Recommendations from Residue Reviews

860.1200 Directions for Use
The use in food/feed handling establishments is not supported by the required studies of OCSPP Guideline 860.1460. Therefore, all uses related to treatment of food and feed handling/storage/ transportation are not allowed. This applies specifically to DuPont™ HGW86 SC Insect Control (EPA Reg. No. 352-IAI).

The rotational crop restrictions must be amended, as follows:

- Cereal grains (crop group 15) may not be planted immediately after use of cyantraniliprole. Cereal grains (crop group 15) must have a 30-day PBI. This is to be consistent with the 30-day PBI for crop group 16 (forage, fodder, and straw of cereal grains).
- Legume vegetables (crop group 6) may not be planted immediately after use of cyantraniliprole. Legume vegetables (crop group 6) must have a 30-day PBI. This is to be consistent with the 30 day PBI for crop group 7 (foliage of legume vegetables).
- Tuberous and corm vegetables (subgroup 1C) may not be planted immediately after use of cyantraniliprole. Subgroup 1C must have a 30-day PBI. This is to be consistent with the 30-day PBI for crop group 2 (leaves of root and tuber vegetables).

860.1650 Submittal of Analytical Reference Standards
Analytical reference standards for cyantraniliprole must be submitted to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Thuy Nguyen at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

### 2.3.2 Recommendations from Occupational Assessment

The labeled use pattern for EPA Reg. No. 352-IAG must be clarified. The proposed label states both: “For vegetable transplants in and around greenhouses,” as well as “Do not apply to greenhouse or field grown vegetables, only apply to vegetable transplants grown in enclosed structures.” Note that both use patterns have been considered in this risk assessment and neither would result in occupational risk estimates of concern.

### 2.3.3 Recommendations from Residential Assessment

There are no recommendations based on the residential exposure and risk assessment.

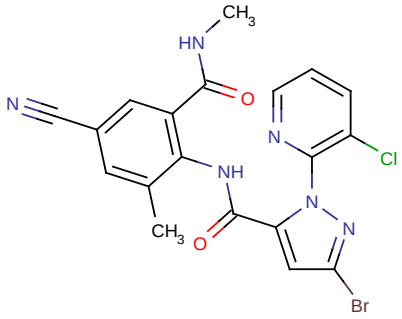
## 3.0 Introduction

Cyantraniliprole is a new second-generation RyR insecticide currently undergoing global joint review. It is a systemic insecticide that is mobile in both the xylem and phloem of plants. Cyantraniliprole belongs to the diamide class of chemistry whose pesticidal MOA is through unregulated activation of insect RyR channels. This then leads to internal calcium store depletion and impaired regulation of muscle contraction, causing paralysis and eventual death of the insect.

Cyantraniliprole has been jointly developed by DuPont and Syngenta, with a proposal for one technical product and 14 U.S. end-use product (EP) registrations, including several agricultural food-uses (PP#1F7894) and various residential use sites.

## 3.1 Chemical Identity

**Table 3.1 Test Compound Nomenclature**

| | |
|---|---|
| Chemical Structure |  |
| Empirical Formula | $C_{19}H_{14}BrClN_6O_2$ |
| Common Name | cyantraniliprole |
| Company experimental name | DPX-HGW86; SYN545377 |
| IUPAC name | 3-bromo-1-(3-chloro-2-pyridyl)-4'-cyano-2'-methyl-6'-(methylcarbamoyl)-pyrazole-5-carboxanilide |
| CAS Name | 3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide |
| CAS Registry Number | 736994-63-1 |
| End-use product/EP | 352-IAG, 18.66% SX; 352-IAI, 18.66% SC; 352-IAN, 18.66% SC; 352-IAT, 50% FS; 352-ILT, 50% FS; 352-ILD, 10.2% SE; 352-ILT, 10.26% OD. |
| Chemical Class | Anthranilic diamide |
| Known Impurities of Concern | None |

## 3.2 Physical/Chemical Characteristics

The physicochemical properties of the technical grade of cyantraniliprole are summarized in Appendix D, Table D.1. The log of the octanol/water partition coefficient is 1.9, which indicates a lack of fat solubility and, therefore, low propensity to bioaccumulate in fatty tissue or milk. The low coefficient also suggests low potential for dermal absorption. At 20°C, the Henry's Law constant was calculated to be $1.7\times10^{-13}$ Pa/m$^3$/mol ($1.7\times10^{-18}$ atm·m$^3$/mol) based on vapor pressure and water solubility. Thus, cyantraniliprole is unlikely to volatilize significantly. Cyantraniliprole is hydrolytically stable under acid and neutral conditions, and has some water solubility (0.014 g/L) which suggests persistence in ground water. However, this is counterbalanced by lack of photolytic stability, which would impact surface waters.

## 3.3 Pesticide Use Pattern

Cyantraniliprole has been jointly developed by DuPont and Syngenta, with a proposal for one technical product and 14 U.S. EP registrations, including agricultural food-uses. The agricultural uses include foliar, soil, and seed treatment to various crops including cotton, fruits, oilseeds, and vegetables. The residential uses include turfgrass, ornamentals, and structural buildings (including indoor crack/crevice and outdoor broadcast). The proposed formulations include the following: flowable suspension (FS), granular (G), oil dispersion (OD), suspension concentrate (SC), suspoemulsion (SE), and water dispersible granular (WG). A summary of all proposed EPs is summarized in Table 3.3, and a detailed use pattern is summarized in Appendix A, Table A.1.

**Table 3.3 Summary of Proposed Cyantraniliprole Products (DuPont and Syngenta Labels)**

| Trade Name | EPA Reg. File Symbol Number | % Active Ingredient | Formulation Type[a] | Target Crop/Use Site |
|---|---|---|---|---|
| **DuPont** | | | | |
| DuPont™ HGW86 fly control bait | 352-IAE | 0.5% | G (ready-to-use) | residential, commercial, and agricultural structures (including hotels, kennels, schools, food/beverage processing plants, poultry/livestock housing, horse stables, and food/feed handling establishments) |
| DuPont™ HGW86 GH & N insect control | 352-IAG | 18.66% (1.67 lb ai/gallon) | SC | ornamental plants/shrubs/trees and vegetable transplants in and around greenhouses, nurseries, interior plantscapes, lath and shadehouses (trees (including non-fruit bearing and nut trees), shrubs, evergreens, bedding plants, flowering plants, flowers, foliage plants, ground covers, vines (non-bearing), interior plantscape plants, and vegetable transplants (including fruiting, leafy, and tuberous/corm)) |
| DuPont™ HGW86 SC insect control | 352-IAI | 18.66% (1.67 lb ai/gallon) | SC | single and multi-family residential buildings, schools, institutional, commercial, agricultural and industrial facilities (including warehouses, apartments, supermarkets, restaurants, motels, hotels, hospitals, daycares, and food handling/storage/processing establishments, animal production facilities, feedlots, broiler houses, livestock barns, pet kennels) and transportation equipment such as aircraft, trains, ships, boats and buses |

| Table 3.3 Summary of Proposed Cyantraniliprole Products (DuPont and Syngenta Labels) | | | | |
|---|---|---|---|---|
| Trade Name | EPA Reg. File Symbol Number | % Active Ingredient | Formulation Type[a] | Target Crop/Use Site |
| DuPont™ HGW86 T&O insect control | 352-IAL | 18.66% (1.67 lb ai/gallon) | SC | landscape and recreational turfgrass (including golf courses), sod farms, ornamental plants and interior plantscapes |
| DuPont™ Verimark™ insect control powered by Cyazypyr™ | 352-IAN | 18.66 (1.67 lb ai/gallon) | SC | *Brassica* vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, tuberous and corm vegetables, citrus, potato seed pieces |
| DuPont™ Cyazypyr™ Technical | 352-ILA | 96.7% | white fine powder solid | all proposed uses |
| DuPont™ Dermacor® Z-103 insecticide seed treatment | 352-ILI | 50.0% (5.21 lb ai/gallon) | FS | rapeseed (canola), mustard seed |
| DuPont™ Exirel™ insect control powered by Cyazypyr™ | 352-ILO | 10.20% (0.83 lb ai/gallon) | SE | *Brassica* vegetables, bulb vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, bushberries (subgroup 13-7B), citrus fruit, pome fruit, stone fruit, tree nuts, commercial greenhouse grown (to harvest: eggplant, pepper, tomato) |
| DuPont™ Benevia™ insect control powered by Cyazypyr™ | 352-ILT | 10.26% (0.83 lb ai/gallon) | OD | bulb vegetables, cotton, oil seed crops, tuberous and corm vegetables, tree nuts |
| **Syngenta** | | | | |
| Mainspring Insecticide (MAI with thiamethoxam) | 100-RUEE | 20.0% (3.2 oz ai/lb) | WG | ornamental plants, fruit and nut trees (non-bearing), and forest seedlings grown in greenhouses, lath and shade houses, containers, field nurseries and interiorscapes, vegetable plants grown for transplant and re-sale to consumers (fruiting vegetables, cucurbit vegetables, *Brassica* vegetables) |
| A16901B Residential Insecticide | 100-RUEG | 20.0% (3.2 oz ai/lb) | WG | residential landscape plants |
| A17960A ST Insecticide | 100-RUEN | 48.8% (600 g ai/L) | FS | potato seed pieces, sunflower seeds |
| A16901B CP Insecticide (MAI with thiamethoxam) | 100-RUER | 20.0% (3.2 lb ai/oz) | WG | *Brassica* vegetables, cucurbit vegetables, fruiting vegetables, leafy vegetables, tuberous and corm vegetables |
| A16901B Turf Insecticide | 100-RUEU | 20.0% (3.2 lb ai/oz) | WG | turfgrass including golf courses, institutional, commercial and residential lawns, sod farms, sports fields, parks, municipal grounds and cemeteries |
| A17960B ST Insecticide | 100-RURI | 48.8% (600 g ai/L) | FS | potato seed pieces, sunflower seeds |

a Formulation codes: G = granular, SC = suspension concentrate, SE = suspoemulsion, WG = water dispersible granules, OD = oil dispersion, FS = flowable suspension.

## 3.4 Anticipated Exposure Pathways

Humans may be exposed to cyantraniliprole in food and drinking water, since cyantraniliprole may be applied directly to growing crops and application may result in cyantraniliprole reaching surface and ground sources of drinking water. There are also residential uses of cyantraniliprole,

so there is likely to be exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

This is the first aggregate risk assessment prepared for the proposed uses of cyantraniliprole. This risk assessment considers all of the exposure pathways based on the proposed new uses of cyantraniliprole.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and/or the CDC under the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA), and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## 4.0 Hazard Characterization and Dose-Response Assessment

Cyantraniliprole belongs to the anthranilic diamide class of pesticides. Anthranilic diamides are potent activators of RyRs; they control insects through unregulated activation of RyR channels leading to internal calcium store depletion that impairs regulation of muscle contraction. Insects exposed to anthranilic diamides exhibit general lethargy and muscle paralysis, ultimately followed by death (Cordova et al., 2006).

RyRs are present across species and their role is similar across species. However, primary sequence diversity indicates differences between the isoforms within and across species. Insects possess a single form of RyR which is distributed in muscle and neuronal tissue. Whereas mammals possess three forms of RyR: (1) RyR1 which is distributed primarily in skeletal, (2) RyR2 which is distributed primarily in cardiac muscle, and (3) RyR3 which is heterogeneously

distributed. Mammalian RyRs are substantially less sensitive to the effects of anthranilic diamides than the insect RyR, ranging from 350 to >2500 times less sensitive (Satelle et al., 2008; Lahm et al., 2009). This selectivity indicates relatively low mammalian toxicity in comparison to other pesticides that act on neuronal receptors. As seen in the cyantraniliprole toxicity studies relevant for human health, lethargy or effects on muscle control were not observed, supporting the concept that RyRs may not be the primary target in mammals. Instead, effects on the liver and thyroid are the most sensitive and are being used to derive PODs.

## 4.1 Toxicology Studies Available for Analysis

All of the required toxicity studies have been submitted to support the proposed food-use registrations for cyantraniliprole and the potential exposure scenarios associated with this action. Furthermore, subchronic toxicity studies in rats, mice, and dogs contain additional data on liver enzymes, thyroid hormones, and metabolite measurements (beyond what is typically required by Agency guidelines).

The toxicology database is acceptable for characterizing cyantraniliprole hazard. It includes the following toxicity studies: 14-day oral, 28-day oral, 90-day oral, 28-day dermal, 28- day inhalation, 2-year dietary combined chronic/carcinogenicity, 2-generation reproduction study, acute/subchronic neurotoxicity, and metabolism and pharmacokinetic in rats; 28-day oral, 90-day oral, and carcinogenicity in mice; 28-day-oral, 90-day oral, and 1-year dietary in dogs; developmental studies in rats and rabbits; mutagenicity and genotoxicity studies in bacterial & mammalian model systems; 28-day dietary immunotoxicity studies in rats and mice; and *in vivo* and *in vitro* dermal absorption factor studies on the SC, SE, and OD formulations.

Several metabolites which were not identified in the rat metabolism studies (IN-JSE-76, IN-PLT97, IN-F6L99, and IN-N5M09) were tested for mutagenic potential, and a 28-day oral toxicity study was conducted with IN-JSE-76. Mechanistic studies on the adrenal and thyroid glands, and an *in vitro* thyroid peroxidase inhibition study are also available. Summaries of all toxicology studies are presented in the Toxicology Disciplinary Chapter (DP408479, W. Phang, 11/21/2012).

## 4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

ADME was evaluated in male and female rats following single and repeated low-dose (10 mg/kg) administration, as well as a single high-dose (150 mg/kg) administration. A bile cannulation study was conducted with both single low- and single high-dose administration. All of the metabolism studies were conducted with both [Cyano-$^{14}$C]- and [pyrazo-carbonyl-$^{14}$C]-cyantraniliprole. The data do not show an appreciable difference in ADME between the two labeled compounds. Therefore, the following discussion does not reference specific radiolabels. The data also do not show a significant difference in ADME between single (at the low dose level of 10 mg/kg/day) and multiple (at 10 mg/kg/day) dosing and the results following single dosing are typical of what was seen following multiple dosing.

Cyantraniliprole is readily absorbed, and the absorption patterns are similar at low and high doses. The majority of the absorption occurs during the first 24 hours (85% of the absorbed

radioactivity), and the peak plasma concentration is reached approximately 2 hour after dosing, regardless of the sex or dose level. The values of $C_{max}$ and area-under-the-curve (AUC) demonstrate a greater internal dose in female rats than in male rats. With dose-normalized AUC, the data suggest a decrease in percent absorption at the high dose in comparison to the low dose.

Following oral dosing, the majority of the dose is initially associated with the gastrointestinal (GI) tract contents followed by uptake and distribution to all tissues. The tissue concentration data show the skin, liver, GI content, and muscle to have a higher percent of the administered dose. However, each of the four tissues had less than 0.5 % of the administered dose at 168 hours. The mean half lives in plasma are shorter in males than in females (≈ 42 hours and 129 hour in males and females, respectively). As expected, female rats contained a greater proportion of $^{14}C$ residues than male rats.

The absorbed cyantraniliprole was readily and extensively metabolized; IN-N7B69 and IN-MYX98 were initially formed due to respective hydroxylations of methylphenyl and N-methyl carbon. During the initial step, cyantraniliprole also underwent nitrogen-to-carbon ring closure to yield IN-J9Z38. Further metabolism of the hydroxylated metabolites includes N-methylation, nitrogen-to-carbon cyclization with loss of water molecule, oxidation of alcohols to carboxylic acids, amide bridge cleavage, amine hydrolysis, and O-glucuronidation. The bile was found to be very rich in metabolites, and most of the metabolites were found in both urine and feces.

Rats given a single 10 mg/kg dose eliminated a greater percentage of the dose in urine (22.0 to 34.6%) than rats dosed with 150 mg/kg (11.8 to 14.8% of the dose). For both dose levels, the majority was eliminated by 24 to 48 hours after administration with the feces as the major route of elimination. By seven days after dosing, the mean percentage for total recovery ranged from 88.3 to 96.5% of the administered dose. Furthermore, there was no appreciable tendency for bioaccumulation to occur.

### 4.3 Toxicological Effects

In general, cyantraniliprole administration 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 are observed across multiple species (rats, mice, dogs). The increases in liver weights are accompanied by hepatocellular hypertrophy along with increases in metabolic liver enzymes (cytochrome P450) and UDP-glucuronyltransferase activity. In rats, the liver effects tend to be more pronounced in females than in males, which is consistent with the pharmacokinetic data that shows a greater internal dose in female rats than in male rats. Most of the liver effects seen in the subchronic rat toxicity studies consist of increases in liver weights and hepatocellular hypertrophy. These effects are considered adaptive, whereas the liver effects in the chronic/carcinogenicity study are considered adverse based on conditions such as foci of cellular alteration and focal vacuolation. The data also show that dogs are more sensitive to liver effects than rats and mice. The adverse liver effects in rats occur at approximately 85 mg/kg with 2-year treatment while comparable effects are seen at 6 mg/kg with 1-year treatment in dogs; adverse liver effects in mice occur at even higher dose levels (769 mg/kg with 18-month treatment).

The available data also show thyroid hormone homeostasis is altered in rats following exposure to cyantraniliprole after 28 or 90 days. The findings include decreases in T4 (and in some cases, T3) and increases in TSH. Thyroid follicular cell hypertrophy (graded as minimal) is evident in both the 28-day and 90-day studies with rats. However, it does not persist with longer term dosing because it is neither present at the one year interim sacrifice nor following the two years of exposure in the 2-year chronic toxicity/carcinogenicity study in rats.

A dose-related increase in the incidence of thyroid follicular epithelial cell hypertrophy/ hyperplasia occurred in the $P_1$ and $F_1$ adult parental animals of a reproduction study. Based on the submitted mechanistic data, HED proposes an adverse outcome pathway (AOP) by which cyantraniliprole disrupts thyroid homeostasis via induction of hepatic metabolizing enzymes including UDP glucuronyltransferase (Wolf et al., 2006). However, at this time, HED has not conducted a Mode of Action Analysis using the MOA Framework. The PODs selected for risk assessment are derived from liver effects in the dog. As such, the limited mechanistic data do not inform the PODs. The submitted data do support a conclusion that the effects on the thyroid are secondary to effects on the liver. Specifically, the available data in the rats is consistent with increases in hepatic cytochrome P450 content and UDP-glucuronyltransferase activity, which lead to decreases in plasma T4 thyroid hormone level and alteration of thyroid hormone homeostasis, resulting in increases in TSH. Increased plasma TSH then stimulates the thyroid gland, which results in the thyroid follicular epithelial cell hypertrophy/hyperplasia.

Effects in the dog studies provide lower NOAELs for use in deriving PODs compared to the rat studies. In the 28-day, 90-day, and 1-year dog studies, consistent findings in clinical chemistry parameters include: increases in alkaline phosphatase, alanine aminotransferase, and gamma glutamyltransferase; and decreases in total protein, albumin, and cholesterol. The liver effects in the dog also show progressive severity with increased duration of exposure. For example, in the 28- day and 90-day dog studies, clinical chemistry parameters indicate liver toxicity; while, in the 1-year dog study, similar clinical chemistry changes are observed but are associated with hepatocellular histopathological changes. When considered in combination with altered enzyme levels, significant increases in absolute and relative liver weights are indicative of adverse liver effects. Microscopic observations in the liver include hepatocellular degeneration, inflammation of the portal regions with increased fibrous connective tissues and pigment deposition, and/or bile duct hyperplasia.

Although it is not observed in dogs, an increased incidence of adrenal cortical microvesiculation is mainly seen in males in both the 90-day rat and mouse studies, and in the 2-generation reproduction rat study. The microvesiculation in affected groups is predominantly graded as minimal with a few incidences graded as mild. These microvesiculations are not associated with changes in gross appearance, adrenal cortical cytotoxicity, hypertrophy, or atrophy. Effects on cortical cell function are not associated with the microvesiculation changes as demonstrated by studies evaluating corticosterone concentrations in serum and urine with ACTH stimulation. In addition, treatment-related neoplastic changes are not observed in the adrenal cortex of rats following chronic dietary administration of cyantraniliprole. Rats exposed to cyantraniliprole do show a slight increase in lipid storage in the adrenal cortex. However, the study report indicates that the adrenal cortex normally shows a microvesiculation appearance under light microscopes resulting from the storage of lipid to be used as precursors for steroid hormone synthesis.

Although clearly treatment-related, the slight microvesiculation of the adrenal cortex noted following exposure to cyantraniliprole is not considered toxicologically relevant.

The results of the chronic/carcinogenicity in rats and the carcinogenicity study in mice do not show compound-related increase in tumor incidence. Genotoxic potential is not found in the mutagenicity study battery.

Cyantraniliprole does not produce developmental toxicity in either rats or rabbits. In rats, there are no maternal or fetal effects up to the limit dose of 1000 mg/kg/day. In rabbits, reduced pup weight and late gestation abortions or early deliveries occur as a result of severe maternal toxicity. The 2-generation reproduction study in rats shows that cyantraniliprole has no adverse effect on any reproductive parameters. In offspring, reductions in body weight and organ weights (thymus and spleen), as well as clinical signs such as dehydration, are noted at dietary concentrations where there is evidence of maternal toxicity. A significant increase in the thyroid weights (absolute and relative) is seen in $P_1$ and $F_1$ parental animals at 14 mg/kg or above with a corresponding dose-related increase in the incidence of the thyroid follicular epithelial cell hypertrophy/hyperplasia in the $P_1$ males and females at 136 mg/kg/day or above and in F1 parental males and females at 14 mg/kg/day or above. In the $F_1$ parental males and females, the increased incidence of thyroid follicular epithelial cell hypertrophy/hyperplasia occur at lower dose level (14 mg/kg/day) relative to that of the $P_1$ parental males and females (136 mg/kg/day). However, a clear NOAEL (1.4 mg/kg/day) is demonstrated for thyroid follicular cell hypertrophy/hyperplasia in the $F_1$ parental animals, which were dosed prenatally and postnatally. Furthermore, the PODs selected for risk assessment (1 or 3 mg/kg/day) are protective of the effects seen in the $F_1$ parental animals.

Acute and subchronic neurotoxicity studies reveal no evidence of neurotoxicity. Similarly, cyantraniliprole does not adversely impact the immune system in rats and mice. The decrease in thymus and spleen weights seen in the 2-generation reproduction study weights are not observed in rat or mice. Based on the results of a 28-day dermal study in rats (as well as the dermal $LD_{50}$ study), cyantraniliprole does not demonstrate any appreciable toxicity via dermal exposure. The 28-day inhalation toxicity study in rats does not show any adverse systemic or portal of entry effect at the highest concentration tested (100 $mg/m^3$, equivalent to 18 mg/kg/day). However, an increase in the incidence of minimal laryngeal squamous metaplasia is seen at the highest tested concentration. This finding is considered to be treatment related but not adverse because the effect is graded as minimal. With longer duration of treatment and higher concentrations, the effects seen in the larynx could potentially progress and become adverse.

Cyantraniliprole has no significant acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category IV). Cyantraniliprole is not an eye or skin irritant and does not cause skin sensitization.

### 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

Based on the currently available toxicity and exposure data, the risk assessment team recommends that the FQPA Safety Factor be reduced to 1X for the following reasons: there is a complete toxicological data base, there is no evidence of neurotoxicity, the PODs based on liver

toxicity selected for risk assessment are protective of effects on the thyroid observed in the reproductive toxicity study, and there is no uncertainty in the exposure data. The details for reducing the FQPA safety factor to 1X are detailed below.

### 4.4.1 Completeness of the Toxicology Database

The toxicology database is complete for cyantraniliprole.

### 4.4.2 Evidence of Neurotoxicity

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.

### 4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

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 NOAEL (1.4 mg/kg/day) is established for $F_1$ parental animals, and the 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. As such, a comparative thyroid study is not required. The FQPA safety factor can be reduced to 1X.

### 4.4.4 Residual Uncertainty in the Exposure Database

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, and conservative ground and surface drinking water modeling estimates. New 2012 Residential 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.

## 4.5 Toxicity Endpoint and Point of Departure Selections

### 4.5.1 Dose-Response Assessment

As discussed in Section 4.3, the thyroid effects in treated animals are a consequence of a series of effects in the liver leading to disturbance in thyroid hormone homeostasis and thyroid effects.

Therefore, the liver effects are the most appropriate in selecting the toxicity endpoints and PODs for risk assessment. The liver effect seen in the 1-year dog study provides the most solid basis for a toxicity endpoint and for the POD for chronic dietary exposure risk assessment. In addition, the POD is also protective of the thyroid effects seen in all toxicity studies in rats. For dermal and inhalation exposure risks, route specific studies are considered.

A dermal POD is not chosen because systemic toxicity is not seen in the 28-day dermal toxicity study in rats up to the limit dose (1000 mg/kg/day). The short- and intermediate-term incidental oral POD is based on two co-critical studies: the 28-day and 90-day oral toxicity studies in dogs (NOAEL = 3.0 mg/kg/day). In the special 28-day study (MRID 48119942) in dog, liver effects were observed at the LOAEL of 35 mg/kg/day. As such, the liver findings in the dog are relevant for the short-term duration of 1-30 days.

The short- and intermediate-term inhalation PODs are based on the results of a 28-day inhalation toxicity study in rats (NOAEL = 10.08 mg/kg/day for occupational exposure, NOAEL = 7.2 mg/kg/day for residential exposure). To determine the inhalation PODs for residential and occupational exposure, the Agency's Reference Concentration (RfC) methodology was used to calculate human equivalent concentrations (HECs). These calculations are detailed in Appendix B, Section B.4. The HECs are based on a 28-day rat inhalation study which show no systemic or port of entry effects at the highest concentration (NOAEL = 0.1 mg/L). Because the 28-day study was conducted 6 hours per day, 5 days per week, the HECs are adjusted to represent both residential and occupational exposure scenarios. For residential exposure, the HEC is adjusted to represent continual exposure for 24 hours per day, 7 days per week. For occupational exposure, the HEC was adjusted to represent an average work week for 8 hours per day, 5 days per week. The short-term inhalation HEC of 0.21 mg/L calculated for residential exposures is then converted to a human equivalent dose NOAEL of 7.2 mg/kg/day to allow for comparison to estimated residential inhalation doses (which are in units mg/kg/day). The short- and intermediate-term inhalation HEC of 0.05 mg/L calculated for occupational exposures was also converted to a human equivalent dose NOAEL of 10.08 mg/kg/day to allow for comparison to estimated occupational inhalation doses (which are in units mg/kg/day).

Although a route specific 28-day inhalation study is used to establish the intermediate-term POD, some of the toxicity data indicate a progression in toxicity with time. The data indicate an approximate three-fold difference in the LOAEL between a 28-day oral toxicity study in rats (53 mg/kg/day) and a reproduction study in rats (14 mg/kg/day). Therefore, an uncertainty factor of 3X is selected to account for using a POD from a short-term 28-day day inhalation study to assess intermediate-term exposure (1- 6 months). Given that the 28-day inhalation study does not show any adverse effects at the highest concentration, HED acknowledges that the application of 3X is a conservative approach. However, given the progression of liver effects seen in oral studies, HED cannot rule out the potential for adverse port of entry or systemic effects given longer exposures.

The toxicity endpoints and PODs are summarized in Tables 4.5.4a and 4.5.4b, and detailed rationale for the selections is presented in Appendix B, Section B.3.

### 4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

In accordance with the requirements of the FQPA (1996), HED has considered the potential for concurrent cyantraniliprole exposure via oral, dermal, and inhalation routes. HED aggregates exposure from different routes for each population if the same toxic effects are seen for that duration of exposure by each route. The dermal route of exposure does not need to be combined with another route of exposure or included in the aggregate risk assessment because there is no identified dermal hazard. For adults, the oral and inhalation routes of exposure should not be aggregated since the endpoints of concern are not common.

### 4.5.3 Cancer Classification and Risk Assessment Recommendation

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. For cancer risk assessment, a non-linear approach is recommended and adequately accounts for all chronic toxicity.

### 4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

**Table 4.5.4a Summary of Toxicological Doses and Endpoints for Cyantraniliprole for Use in Non-Occupational/Residential Human Health Risk Assessments**[a]

| Exposure/ Scenario | Point of Departure | Uncertainty/ FQPA Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Acute Dietary (General Population, including Infants and Children and Females 13-49 years of age) | An effect attributed to a single dose was not identified in the toxicology database. | | | |
| Chronic Dietary (All Populations) | NOAEL = 1 mg/kg/day | $UF_A$ = 10x<br>$UF_H$ =10x<br>FQPA SF = 1x | cRfD = 0.01 mg/kg/day<br>cPAD = 0.01 mg/kg/day | 1-year oral study in dogs.<br>LOAEL = 6 mg/kg/day based on effects indicative of liver toxicity (increased liver weights and alkaline phosphatase activity), and significant decreases in albumin level. |

**Table 4.5.4a Summary of Toxicological Doses and Endpoints for Cyantraniliprole for Use in Non-Occupational/Residential Human Health Risk Assessments**[a]

| Exposure/ Scenario | Point of Departure | Uncertainty/ FQPA Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Incidental Oral Short-Term (1-30 days) and Intermediate -Terms (1-6 months) | NOAEL = 3 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF = 1X | LOC = 100 | 28-day and 90-day oral study in dogs.<br>28-day LOAEL = 35 mg/kg/day (lowest dose tested) based on decreases in body weight, food consumption, food efficiency, and changes in clinical chemistry (↑ALP, ↓ cholesterol and ↓ albumin).<br>90-day LOAEL = 32 mg/kg/day based on a collection of treatment-related effects indicative of liver toxicity. 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. |
| Dermal Short-Term (1-30 days) | A toxicity endpoint was not identified.<br>Systemic toxicity was not seen in 28-day dermal toxicity in rats at the limit dose (1000 mg/kg/day). There are no concerns for developmental or reproductive toxicity or neurotoxicity. | | | |
| Inhalation Short-Term (1-30 days) | NOAEL = 0.1 mg/L<br>HEC = 0.05 mg/L<br>HED = 7.2 mg/kg/day | $UF_A$ = 3X[b]<br>$UF_H$ = 10X<br>FQPA SF = 1X | LOC = 30 | 28-day inhalation toxicity study in rats.<br>A LOAEL was not established because the highest concentration tested (0.1 mg/L) did not demonstrate any adverse portal of entry or systemic effects. |
| Cancer (oral, dermal, inhalation) | Classification: "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. | | | |

a Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. HED = human equivalent dose. HEC = human equivalent concentration. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. LOC = level of concern.

b The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the pharmacokinetic (PK) differences, but not the pharmacodynamic (PD) differences. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences).

**Table 4.5.4b Summary of Toxicological Doses and Endpoints for Cyantraniliprole for Use in Occupational Human Health Risk Assessments**[a]

| Exposure/ Scenario | Point of Departure | Uncertainty/ Safety Factors | RfD, PAD, Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal Short-Term (1-30 days) and Intermediate -Terms (1-6 months) | A toxicity endpoint was not identified.<br>Systemic toxicity was not seen in 28-day dermal toxicity in rats at the limit dose (1000 mg/kg/day). There are no concerns for developmental or reproductive toxicity or neurotoxicity. | | | |
| Inhalation Short-Term (1-30 days) | NOAEL = 0.1 mg/L<br>HEC = 0.05 mg/L<br>HED = 10.08 mg/kg/day | $UF_A = 3X$[b]<br>$UF_H = 10X$ | LOC = 30 | 28-day inhalation toxicity study in rats.<br>A LOAEL was not established because the highest concentration tested (0.1 mg/L) did not demonstrate any adverse portal of entry or systemic effects. |
| Inhalation Intermediate -Term (1-6 months) | NOAEL = 0.1 mg/L<br>HEC = 0.05 mg/L<br>HED = 10.08 mg/kg/day | $UF_A = 3X$<br>$UF_H = 10X$<br>$UF_{DB} = 3X$[c] | LOC = 100 | 28-day inhalation toxicity study in rats.<br>A LOAEL was not established because the highest concentration tested (0.1 mg/L) did not demonstrate any adverse portal of entry or systemic effects. |
| Cancer (oral, dermal, inhalation) | Classification: "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. | | | |

a Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. HED = human equivalent dose. HEC = human equivalent concentration. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). $UF_{DB}$ = database uncertainty factor: use of a short-term study for intermediate-term risk assessment. FQPA SF = FQPA Safety Factor. LOC = level of concern.

b The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the pharmacokinetic (PK) differences, but not the pharmacodynamic (PD) differences. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences).

c A route specific 28-day inhalation study is used to establish the intermediate term exposure toxicity endpoint and point of departure. Some of the toxicity data on cyantraniliprole indicate that there was a progression in toxicity with time. The data indicate a ~three-fold difference in the LOAEL between a 28-day oral toxicity study in rats (53 mg/kg/day) and a reproduction study in rats (14 mg/kg/day). Therefore, an uncertainty factor of 3X was selected to account for using a POD from a short-term 28-day day inhalation study to assess intermediate-term exposure (1- 6 months).

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

The plant metabolism studies are adequate. Studies indicate that metabolism of cyantraniliprole is similar following foliar and soil application to the following crops: rice, lettuce, cotton, and tomato (respectively representing cereal, leafy vegetables, oilseeds, and fruit groups). The metabolic fate of this insecticide is complex with the formation of many low level metabolites. However, cyantraniliprole is the major component in rice, lettuce, cotton, and tomato; results in crop field trials confirm that the parent compound is the predominant residue in all crop fractions at various sampling points up to crop maturity. Numerous metabolites were detected in various crop matrices.

In plants, metabolism of cyantraniliprole appears to proceed via loss of water leading to the formation of the quinazolinone ring, oxidation of the cyano group, and hydroxylation of the N-methyl and/or tolyl methyl group. Immature and mature samples taken of four different crop groups covering a wide range of agro-climatic conditions show very similar metabolic pathways. The formation of a new metabolite soon after application would be very unlikely. The chemical names and structures of each metabolite are summarized in Appendix C, Table C.1.

The nature of the residues in livestock is adequately understood. The metabolism of cyantraniliprole in poultry and ruminants was found to be similar. The metabolism in livestock is extensive and the amount of unchanged parent present in milk, eggs, and tissues is matrix-dependent. The major components present in various tissues include a combination of the parent compound, IN-N7B69, IN-J9Z38, IN-MLA-84, and/or IN-MYX98.

In rotational crops, the parent compound is the major residue present in soybean, wheat grain, lettuce, and beet root. As in primary crops, many minor metabolites exist. In livestock feedstuffs such as wheat (forage, hay, and straw) and soybean (foliage), parent plus a few metabolites (IN-J9Z38, IN-JSE76, and/or IN-MLA84) are present as major residues.

#### 5.1.2 Summary of Environmental Degradation

Since cyantraniliprole is soluble in water (14.2 mg/L at 20ºC), it may move from the treated fields to surface water through run-off occurring shortly after application (i.e. rainfall events). Mobility and persistence of cyantraniliprole degradates may be of concern. Due to the stability and mobility of the degradates, some compounds may move from the treated field to groundwater through leaching. Batch equilibrium studies on cyantraniliprole and its degradates characterize cyantraniliprole as being moderately mobile ($K_{oc}$ = 157 to 376 mL/$g_{oc}$) in test soils. Cyantraniliprole degradates have measured $K_{oc}$ values ranging from 14 to 32,152 mL/g, indicating that some degradates are more mobile than the parent and some are less mobile than the parent.

Major routes of dissipation include alkaline-based hydrolysis, photodegradation in aqueous and moist soil environments, and aerobic and anaerobic biotransformation in terrestrial and aquatic environments. Considering abiotic degradation, hydrolytic degradation appears to be pH dependent, with degradation increasing with increasing pH. Photodegradation appears to be a major degradation pathway in aqueous and moist soil environments. The aqueous photolysis study shows a phototransformation half-life of about 7.9 hours or 0.33 days. Biodegradation is an effective dissipation pathway for cyantraniliprole, with anaerobic biotransformation occurring at a faster rate than aerobic biotransformation in terrestrial and aquatic environments. It is important to note that all aerobic soil metabolism degradation half-life values are significantly longer than that of the parent cyantraniliprole.

Based on laboratory studies, the major environmental degradates of cyantraniliprole include IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-PLT97, and IN-K5A78, IN-K5A78 and IN-PLT97. The majority of these degradates formed under both microbial-mediated and abiotic processes. Major degradates that continued to increase over time to the study termination in various fate studies include IN-J9Z38, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78 and IN-PLT97. In addition, IN-K5A77, IN-K5A79, and IN-PLT97 were also detected in the terrestrial field studies.

### 5.1.3 Comparison of Metabolic Pathways

The metabolism/degradation in plant, livestock, rat, rotational crops, and processed commodities is similar. The cyantraniliprole parent compound along with the same minor metabolites is the common theme (see Appendix C, Table C.1).

The nature of the residues in processing studies indicates that cyantraniliprole degrades under simulated conditions of pasteurization and sterilization. Further degradation of cyantraniliprole occurs under hydrolytic conditions representative of baking, brewing, or boiling at 100°C for 60 minutes in a pH 5 solution. In actual processing studies, the formation of these degradates was very minor, except for a few processed commodities (such as cooked spinach, tomato puree/paste, and apple sauce).

Rotational crop metabolism is similar to primary crop metabolism. Cyantraniliprole was the major component of the residue at all PBIs (30, 120, 365 days). Transfer of cyantraniliprole and its metabolites to animal feed items was higher than observed in the commodities for human consumption. Inadvertent tolerances for various livestock feed items were necessary and were established based on a PBI of 30 days. Residues are not anticipated in food commodities from a 30-day PBI or are covered by primary crop commodity tolerances (with the exceptions of root and tuber vegetables subgroup 1A and leaves of root and tuber vegetables group 2).

Metabolism in lactating goats and laying hens is similar. Transfer of residues to poultry commodities was low, and cyantraniliprole was generally the major component of the total radioactive residue approach (TRR) in all consumable matrices. The available feedstuffs with cyantraniliprole residues produced a relatively low dietary burden for livestock. Residues are expected in poultry and hog commodities; low levels are anticipated in ruminant commodities.

In the feeding studies, there was no indication of significant concentration of cyantraniliprole in milk fat or fat tissue.

### 5.1.4 Residues of Concern Summary and Rationale

Parent cyantraniliprole was detected as a main residue in the metabolism studies, crop field trials, and livestock feeding studies. Based on this, it is considered an appropriate marker for primary crops, rotational crops, and livestock commodities. Thus, parent cyantraniliprole is recommended as the residue of concern (ROC) for tolerance enforcement. Due to structural similarity and lack of toxicity data for the associate metabolites, hazard is expected to be similar.

*Primary Crops:* Metabolism studies show parent cyantraniliprole as a major residue in rice, lettuce, cotton, and tomato; and IN-J9Z38 as a major residue in rice and lettuce. However, in lettuce field trials, IN-J9Z38 was generally absent. The crop field trials show the presence of several metabolites at levels below the LOQ or at significantly lower amounts than parent cyantraniliprole.

*Rotational Crops:* Parent cyantraniliprole was the main residue in all the commodities for human consumption. Other metabolites were present at similar or lower levels than parent cyantraniliprole in feedstuff commodities only. Since the metabolites will not be significant contributors to the overall livestock dietary burden, inclusion of the metabolites in the residue of concern will not significantly affect the dietary risk assessment.

*Processed Commodities:* Although metabolites IN-J9Z38, IN-N5M09, and IN-F6L99 were formed under conditions of heat and/or hydrolysis, only IN-J9Z38 was generally observed at significant concentrations in a few processed commodities (e.g. cooked spinach, apple sauce). IN-N5M09 and IN-F6L99 were found at low levels in apple sauce and cooked spinach, but were absent (<LOQ) in a variety of other processed commodities. In addition to parent cyantraniliprole, metabolite IN-J9Z38 is included as a residue of concern for risk assessment.

*Livestock:* Feeding studies show that parent cyantraniliprole, IN-N7B69, IN-MLA84, IN-MYX98, and/or IN-J9Z38 are likely to be present in significant amounts in some commodities. These metabolites are assumed to have similar toxicity to parent cyantraniliprole. In addition to parent cyantraniliprole, metabolites IN-N7B69, IN-MLA84, IN-MYX98, and IN-J9Z38 are included as residues of concern for risk assessment.

*Water:* Cyantraniliprole is likely to extensively degrade in the environment through several degradation routes to form IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97. These degradates were major degradates in relevant laboratory studies, formed in the field, or both. In the absence of toxicity data and similar analogs, these degradates are considered no more toxic than the parent compound.

| Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression | | | |
|---|---|---|---|
| Matrix | | Residues included in Risk Assessment[a] | Residues included in Tolerance Expression |
| Plants | Primary Crop | Cyantraniliprole | Cyantraniliprole |
| | Rotational Crop | Cyantraniliprole | Cyantraniliprole |
| | Processed Commodities | Cyantraniliprole and IN-J9Z38 | Cyantraniliprole |
| Livestock | Ruminant | Cyantraniliprole, IN-N7B69, IN-MLA84, IN-MYX98, and/or IN-J9Z38[b] | Cyantraniliprole |
| | Poultry | | Cyantraniliprole |
| Drinking Water | | Cyantraniliprole and the degradates listed below[c] | Not Applicable |

a Cyantraniliprole is 3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide. The names and chemical structures of the metabolites can be found in Appendix C, Table C.1.

b Parent cyantraniliprole is recommended as residue of concern in all commodities along with the metabolites that are at significant amounts in the commodity under consideration.

c IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97.

## 5.2 Food Residue Profile

Quantifiable residues of cyantraniliprole from foliar application or a combination of seed treatment or at-plant applications and foliar applications were consistently found. The residue from foliar applications was primarily a surface residue, as evidenced by distribution of residue in peel and pulp.

Adequate field trial data are available to support the proposed uses on *Brassica* vegetables (Group 5), bulb vegetables (Group 3-07), bushberries (Group 13-07B), oilseeds (Group 20), citrus fruits (Group 10-10), cucurbit vegetables (Group 9), fruiting vegetables (Group 8-10), leafy vegetables (non-*Brassica)* (Group 4), pome fruits (Group 11-10), stone fruits (Group 12-12), tree nuts (Group 14), and tuberous and corm vegetables (Subgroup 1C). However, there are no data to support use in food/feed handling, storage, and transport facilities.

Processing studies have been submitted for several crops including potato, tomato, orange, apple, plum, and cottonseed. Tolerances are not needed for most processed commodities, as parent cyantraniliprole did not increase from the RAC to the processed commodity. Cyantraniliprole did concentrate in tomato dry pomace, sundried tomatoes, orange oil, apple puree, apple dry pomace (but not wet), and dried plums. Citrus oil is recognized as a processed commodity for tolerance purposes.

Storage stability data have been submitted for residues of cyantraniliprole and various metabolites in five categories of plant commodity matrices, in milk, and in eggs. The storage stability intervals cover the actual intervals of frozen storage of plant and livestock commodity samples from the crop field trials, processing studies, and livestock feeding studies. Corrections for loss during storage are not needed for any plant or livestock commodity for purposes of tolerance considerations.

Based on the livestock metabolism studies, HED concludes that storage stability data for the livestock matrices are unnecessary. This is mainly due to the fact that there was no change in the metabolic profile after 10 months of frozen storage for eggs, muscle, and fat of hens nor after 6 months of frozen storage for milk, fat, kidney and liver of goats. Furthermore, the egg, milk, and tissue samples from the livestock feeding studies were stored frozen and analyzed within 30 days of collection.

Adequate cattle and poultry feeding studies have been submitted. The data indicate that tolerances for milk and the fat, meat, and meat byproducts of cattle, goat, horse, and sheep are needed to support the proposed cyantraniliprole uses, but tolerances are not required for hog and poultry commodities.

The confined rotational crop studies are adequate. Adequate limited and extended field rotational crop studies have been submitted. The studies indicate the presence of non-quantifiable levels of parent residues in/on cereal grains, soybean seed, and legumes, and quantifiable levels in leafy vegetables, foliage of legume vegetables, and some root commodities, at a PBI of 30 days. The studies also indicate the presence of quantifiable levels of parent residues in livestock feed stuffs such as alfalfa, grass hay, and soybean hay. Inadvertent or indirect tolerances for these rotational crops are needed at a PBI of 30 days.

### 5.3 Water Residue Profile

Since cyantraniliprole is a new chemical, there is no monitoring data regarding the concentrations of the parent cyantraniliprole in surface or ground water. The drinking water residues used in the dietary risk assessment were provided by EFED (DP403747, C. Koper, 11/21/2012). This drinking water assessment was conducted on the parent cyantraniliprole and numerous degradates. The degradates included in the drinking water assessment are the following: IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97. In the absence of toxicity data and similar analogs, these degradates are considered no more toxic than the parent compound and the TRR was recommended for risk assessment purposes.

The EDWCs for use in the human health risk assessment are based on the maximum proposed application rates specified in the product labels. EDWCs for the chronic assessments were estimated using two EFED Tier I screening models. For surface water, the FIRST (FQPA Index Reservoir Screening Tool) Version1.1.1 model was used to estimate drinking water concentrations. For ground water, the SCI-GROW (Screening Concentration in Ground Water) Version 2.3 model was used to predict the maximum acute concentrations present in shallow ground water. The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/. Based on FIRST and SCI-GROW modeling, the surface and ground water EDWCs for the parent cyantraniliprole for various uses are presented in Table 5.3.

For drinking water derived from surface water, the FIRST model estimated the acute and chronic (annual average) EDWC at 43.14 µg/L and 24.45 µg/L, respectively. For drinking water derived from ground water, the SCI-GROW model estimated the ground water EDWC at 6.33 µg/L. The

EDWC chosen for chronic dietary assessment is the 1-in-10 year annual mean of 24.45 µg/L from surface water estimates.

**Table 5.3 Maximum Estimated Drinking Water Concentrations (EDWCs) Resulting from Applications of Cyantraniliprole for Various Uses**[a]

| Drinking Water Source (Model) | Label | Use | Method | Application Rate (interval between applications)[b] | PCA Adjustment Factor [c] | Peak Day (acute) Conc. | Annual Average (chronic) Conc. |
|---|---|---|---|---|---|---|---|
| | | | | | | *µg/L* | *µg/L* |
| Surface Water (FIRST) | 352-ILT 352-ILO | Various Crops | Aerial | 3 app @ 0.133 ai/acre (5 days) | 1 | 40.77 | 23.11 |
| | 352-IAN | Citrus Vegetables | Chemigation | 1 app @ 0.4 ai/acre (NA) | | 40.75 | 23.09 |
| | 352-ILI | Canola Mustard | Seed Treatment | 1 app @ 0.4 ai/acre (NA) | | 40.75 | 23.09 |
| | 352-IAE | Fly Control | Bait Broadcast | 5 app @ 0.087 ai/acre (7 days) | | **43.14** | **24.45** |
| | 100-RUEN 100-RURI | Potato | Seed Treatment | 1 app @ 0.468 ai/acre (NA) | | 23.84 | 13.51 |
| Ground Water (SCI-GROW) | 352-ILT 352-ILO | Various Crops | Aerial | 3 app @ 0.133 ai/acre (5 days) | --- | 5.40 | 5.40 |
| | 100-RUEN 100-RURI | Potato | Seed Treatment | 1 app @ 0.468 ai/acre (NA) | --- | **6.33** | **6.33** |

a Bold values denote maximum EDWCs.
b NA = Not Applicable.
c Percent Cropped Area (PCA) Adjustment Factor = 1 following updated PCA guidance document (2012).

## 5.4 Dietary Risk Assessment

### 5.4.1 Description of Residue Data Used in Dietary Assessment

A somewhat refined chronic (food and drinking water) dietary assessment was conducted assuming average field trial residues for all proposed crops (except crop subgroup 1A) and that 100% CT. Tolerance-level residues were adequate to cover residues in all livestock commodities except liver and meat byproducts for which a higher anticipated residue calculations were used. For processed commodities, input values included combined average residues of parent and the metabolite with relevant processing factors. The chronic assessment incorporated empirical processing factors if available or (Dietary Exposure Evaluation Model) DEEM Version 7.81 default processing factors as appropriate. Empirical processing factors were used for potato flakes and chips, tomatoes (paste, puree, dried, and juice), orange juice, apple juice, cottonseed oil, citrus oil, and dried plums. The processing factors for these commodities were set at 1 because the input values included combined residues of the parent and the metabolite with relevant processing factors. Crop field trial data depicting residues in/on citrus fruit peels (lemon and orange) were available and included into the assessment. The EDWC of 24.45 µg/L was incorporated directly into the dietary assessment.

### 5.4.2 Acute Dietary Risk Assessment

An acute dietary endpoint was not selected for quantitative risk assessment because acute hazard attributable to a single dose was not identified.

### 5.4.3 Chronic Dietary Risk Assessment

The results indicate that chronic dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC for the U.S. population and all population subgroups. The risk estimates are not underestimated at 22% of the cPAD for the general U.S. population and 50% of the cPAD for children (1-2 years old), the most highly exposed subgroup. Table 5.4.4 summarizes the dietary exposure and risk estimates for cyantraniliprole.

The dietary exposure and risk estimates are somewhat refined since they assume average residues for most crops and include empirical processing factors. Additional refinements may be implemented such as the incorporation of %CT data.

### 5.4.4 Summary Table

**Table 5.4.4 Summary of Dietary (Food and Drinking Water) Exposure and Risk for Cyantraniliprole**[a]

| Population Subgroup | cPAD | Chronic Dietary | |
|---|---|---|---|
| | | Dietary Exposure | cPAD |
| | *mg/kg/day* | *mg/kg/day* | *%* |
| General U.S. Population | 0.010 | 0.002223 | 22 |
| All Infants (< 1 year old) | | 0.004378 | 44 |
| **Children 1-2 years old** | | **0.005027** | **50** |
| Children 3-5 years old | | 0.003738 | 37 |
| Children 6-12 years old | | 0.002205 | 22 |
| Youth 13-19 years old | | 0.001484 | 15 |
| Adults 20-49 years old | | 0.001977 | 20 |
| Adults 50+ years old | | 0.002244 | 22 |
| Females 13-49 years old | | 0.002053 | 21 |

a The values for the highest exposed population is bolded.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential exposure may occur by the dermal, oral, and inhalation routes of exposures. However, since dermal hazard has not been identified for cyantraniliprole, the only exposures of concern are handler inhalation (for adults), and post-application incidental oral (for children). These exposures have been assessed with current policies which include updates to HED's 2012 Residential SOPs[1] along with policy changes for body weight assumptions (N. Tsaur, DP407964, 02/26/2013).

The end use products that may lead to residential exposures (handler and/or post-application exposures) include the following EPs:

1. EPA Reg. No. 352-IAE (fly bait for use in and around residential structures);

[1] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

2. EPA Reg. No. 352-IAG (foliar and systemic insect control on ornamental plants/shrubs/trees, and interior plantscapes);
3. EPA Reg. No. 352-IAI (for indoor use as a crack/crevice and for outdoor broadcast in single and multi-family residential buildings, schools, apartments, and daycares);
4. EPA Reg. No. 352-IAL (foliar and systemic insect control in landscape and recreational turfgrass, including golf courses and interior plantscapes);
5. EPA Reg. No. 100-RUEG (outdoor applications to residential landscape plants); and
6. EPA Reg. No. 100-RUEU (foliar and systemic insect control in turfgrass including golf courses, residential lawns, and recreational turfgrass).

## 6.1 Residential Handler Exposure

Of all proposed residential uses, only one WG product is intended for homeowner use: A16901B Residential (EPA Reg. No. 100-RUEG: outdoor applications to residential landscape plants). However, since the other labels include residential use sites, use by homeowners is possible, and prohibition of use by homeowners is not enforceable. Thus, residential handler exposure and risk estimates have been calculated for all possible residential exposure scenarios. Including all possible residential exposure scenarios provides a conservative and health protective assessment for the potential for homeowners to use the professionally labeled products on residential use sites. The formulations for the other labels include G and SC.

Residential handler exposure is expected to be short-term in duration. The turf and ornamental labels indicate that a maximum of two applications are allowed per season. Thus, intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners. Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[2] (Lawns/Turf; Gardens and Trees; Indoor Environments). The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[2] (Lawns/Turf; Gardens and Trees; Indoor Environments).

Handler risk estimates were assessed for all possible residential handler scenarios in which homeowners may be exposed to cyantraniliprole. Risk estimates of all possible scenarios are not of concern. Short-term inhalation MOEs range from 22,000 to 220,000,000 as summarized in Table 6.1. Furthermore, these calculated risk estimates are highly conservative because the inhalation exposure POD is based on an exposure duration of 24 hours per day.

[2] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

| Table 6.1 Residential Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Application Equipment | Crop or Target | Inhalation Unit Exposure *mg/lb ai* | Maximum Application Rate[a] | Amount Handled Daily[b] | Inhalation Dose[c] *mg/kg/day* | Inhalation MOE[d] |
| **Mixer/Loader/Applicator for Granular Formulations** | | | | | | |
| Push-Type Rotary Spreader | Outdoor areas used for storage of waste around commercial establishments, commercial operations, and agricultural animal production facilities | 0.0026 | 0.0871 lb ai/A | 0.5 acres | 0.00000142 | 5,100,000 |
| Belly Grinder | | 0.039 | 0.00000200 lb ai/sq ft | 1200 sq ft | 0.00000117 | 6,200,000 |
| Spoon | | 0.087 | | 100 sq ft | 0.000000218 | 33,000,000 |
| Cup | | 0.013 | | | 0.0000000325 | 220,000,000 |
| Hand Dispersal | | 0.38 | | | 0.000000950 | 7,600,000 |
| Shaker Can | | 0.013 | | | 0.0000000325 | 220,000,000 |
| Bait Station/Trap | Indoor areas of residential, institutional, public, agricultural buildings/structures, or food/feed handling establishments (including restaurants, warehouses, supermarkets, hospitals, nursing homes, motels, hotels, schools, daycares, laboratories, computer facilities, aircraft, buses, boats/ships, trains, pet shops and zoos) | Exposure is considered negligible. | | | | |
| **Mixer/Loader/Applicator for Liquid Formulations** | | | | | | |
| Manually-Pressurized Handwand | Indoor Spot and Crack/Crevice | 1.1 | 0.00887 lb ai/gal | 0.5 gal | 0.0000610 | 120,000 |
| | Outdoor Broadcast: Gardens/Trees | 0.018 | 0.00000719 lb ai/sq ft | 1200 sq ft | 0.00000194 | 3,700,000 |
| | Outdoor Broadcast: Lawns/Turf | | 0.00418 lb ai/gal | 5 gal | 0.00000470 | 1,500,000 |
| Hose-End Sprayer | Outdoor Broadcast: Gardens/Trees | 0.0014 | 0.00000719 lb ai/sq ft | 1200 sq ft | 0.000000151 | 48,000,000 |
| | | | 0.00418 lb ai/gal | 11 gal | 0.000000804 | 9,000,000 |
| | Outdoor Broadcast: Lawns/Turf | 0.022 | 0.313 lb ai/A | 0.5 acres | 0.0000431 | 170,000 |
| Backpack | Outdoor Broadcast: Gardens/Trees | 0.14 | 0.00000719 lb ai/sq ft | 1200 sq ft | 0.0000151 | 480,000 |
| | Outdoor Broadcast: Lawns/Turf | | 0.00418 lb ai/gal | 5 gal | 0.0000365 | 200,000 |
| Sprinkler Can | Outdoor Broadcast: Gardens/Trees | 0.0014 | 0.00000719 lb ai/sq ft | 1200 sq ft | 0.000000151 | 48,000,000 |
| | | 0.0014 | 0.00418 lb ai/gal | 5 gal | 0.000000365 | 20,000,000 |
| | Outdoor Broadcast: Lawns/Turf | 0.022 | 0.00000719 lb ai/sq ft | 1000 sq ft | 0.00000198 | 3,600,000 |

| Table 6.1 Residential Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Application Equipment | Crop or Target | Inhalation Unit Exposure *mg/lb ai* | Maximum Application Rate[a] | Amount Handled Daily[b] | Inhalation Dose[c] *mg/kg/day* | Inhalation MOE[d] |
| **Mixer/Loader/Applicator for Dry Flowable Formulations** | | | | | | |
| Manually-Pressurized Handwand | Outdoor Broadcast: Gardens/Trees | 1.1 | 0.00000301 lb ai/sq ft | 1200 sq ft | 0.0000497 | 140,000 |
| | Outdoor Broadcast: Lawns/Turf | | 0.00203 lb ai/gal | 5 gal | 0.000139 | 52,000 |
| Hose-End Sprayer | Outdoor Broadcast: Gardens/Trees | 0.0014 | 0.00000301 lb ai/sq ft | 1200 sq ft | 0.0000000633 | 110,000,000 |
| | | | 0.00475 lb ai/gal | 11 gal | 0.000000914 | 7,900,000 |
| | Outdoor Broadcast: Lawns/Turf | 0.022 | 0.133 lb ai/A | 0.5 acres | 0.0000182 | 400,000 |
| Backpack | Outdoor Broadcast: Gardens/Trees | 1.1 | 0.00000301 lb ai/sq ft | 1200 sq ft | 0.0000497 | 140,000 |
| | | | 0.00475 lb ai/gal | 5 gal | 0.000327 | 22,000 |
| | Outdoor Broadcast: Lawns/Turf | | 0.00203 lb ai/gal | 5 gal | 0.000139 | 52,000 |
| Sprinkler Can | Outdoor Broadcast: Gardens/Trees | 0.0014 | 0.00000301 lb ai/sq ft | 1200 sq ft | 0.0000000633 | 110,000,000 |
| | | | 0.00475 lb ai/gal | 5 gal | 0.000000416 | 17,000,000 |
| | Outdoor Broadcast: Lawns/Turf | 0.022 | 0.00000304 lb ai/sq ft | 1000 sq ft | 0.000000836 | 8,600,000 |

a Based on maximum application rates on proposed labels:
EPA Reg. No. 352-IAE for granular application to indoor and outdoor areas,
EPA Reg. No. 352-IAI for liquid applications to indoor crack and crevices,
EPA Reg. No. 352-IAL for liquid applications to ornamentals and turf,
EPA Reg. No. 100-RUEE for dry flowable applications to ornamentals, and
EPA Reg. No. 100-RUEU for dry flowable applications to turf.

b Based on HED's 2012 Residential SOPs: Lawns/Turf; Gardens and Trees; Indoor Environments (http://www.epa.gov/pesticides/science/residential-exposure-sop.html).

c Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or lb ai/gal) × Amount Handled (A/day or gallons/day) ÷ BW (80 kg adult).

d Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Short-Term Inhalation NOAEL = 7.2 mg/kg/day. Level of concern = 30.

## 6.2 Post-Application Exposure

Although residential dermal exposure is expected following the treatment of turf or cracks/crevices, a quantitative post-application dermal risk assessment was not conducted because a dermal hazard was not identified for cyantraniliprole. Furthermore, a risk assessment for incidental oral ingestion of granules has not been conducted based on a lack of hazard via the acute dietary route of exposure; and an indoor inhalation risk assessment has not been conducted because the acute inhalation toxicity is low (Toxicity Category IV), and exposure is expected to be negligible based on the low vapor pressure of cyantraniliprole ($3.85\times10^{-17}$ mm Hg at 20ºC) and the low proposed application rate (0.391 lb ai/A). Short-term incidental oral post-application

risk estimates for all scenarios are not of concern to HED (MOEs range from 290 to 1,000,000). Furthermore, short-term incidental oral post-application risk estimates are protective of intermediate-term because the POD is the same.

The lifestage (children 1 to <2 years old) selected for each post-application scenario is based on an analysis provided as an Appendix in the 2012 Residential SOPs[3]. This lifestage is not the only lifestage that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

The end use products that may lead to residential post-application exposures include the following EPs:

1. EPA Reg. No. 352-IAE (G fly bait for use in and around residential structures);
2. EPA Reg. No. 352-IAI (SC crack and crevice use in single and multi-family residential buildings, schools, apartments, and daycares);
3. EPA Reg. No. 352-IAL (foliar and systemic insect control in landscape and recreational turfgrass, including golf courses and interior plantscapes); and
4. EPA Reg. No. 100-RUEU (foliar and systemic insect control in turfgrass including golf courses, residential lawns, and recreational turfgrass).

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[4] (Lawns/Turf; Indoor Environments). The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[5] (Lawns/Turf; Indoor Environments). Based on the SOPs, the deposited residue value for liquid application to indoor cracks/crevices was calculated to be 1.74 µg/cm$^2$.

In addition to the SOPs, the registrant has submitted chemical-specific turf transferrable residue (TTR) data (DP407965, N. Tsaur, 01/22/2013, *Cyantraniliprole. Determination of Transferable Residues of Cyantraniliprole from Turf Treated with Water-Dispersible Granule (WG) and Granule (GR) Formulations of Cyantraniliprole*). The high-end TTR value chosen to be protective of all exposure scenarios (regardless of formulation applied), is the predicted Day 0 residue from the California site of 0.0282 µg/cm$^2$. This value is based on a target application rate of 0.20 lb ai/A and must be adjusted for the proposed application rates in quantitative post-application risk estimate calculations.

Table 6.2 presents the post-application incidental oral MOE values calculated from the following application scenarios:

1. liquid application of cyantraniliprole to turf,
2. granular application to cyantraniliprole to turf, and
3. liquid application of cyantraniliprole to indoor cracks/crevices.

[3] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html
[4] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html
[5] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

Post-application risk estimates for all scenarios are not of concern to HED (MOEs range from 290 to 1,000,000). The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. However, combining these scenarios would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the hand-to-mouth post-application exposure scenario for children 1 < 2 years old should be considered a protective estimate of children's exposure to pesticides used indoors. Furthermore, incidental oral risk estimates are highly conservative because the short- and intermediate-term incidental oral POD is based on a 90-day exposure duration.

**Table 6.2 Residential Post-Application Non-Cancer Exposure and Risk Estimates for Cyantraniliprole**

| Lifestage | Post-Application Exposure Scenario | | Application Rate[a] | Dose[b] | MOEs[c] |
|---|---|---|---|---|---|
| | Use Site | Route of Exposure | | *mg/kg/day* | |
| Children 1 to <2 years old | Liquid Application to Turf | ST Hand to Mouth | 0.313 lb ai/A | 0.00604 | 500 |
| | | ST Object to Mouth | | 0.000184 | 16,000 |
| | | ST/IT Incidental Soil Ingestion | | 0.0000106 | 280,000 |
| | Granular Application to Turf | ST Hand to Mouth | 0.0871 lb ai/A | 0.000834 | 3,600 |
| | | ST Object to Mouth | | 0.0000511 | 59,000 |
| | | ST/IT Incidental Soil Ingestion | | 0.00000295 | 1,000,000 |
| | | Incidental Granular Ingestion | Acute dietary hazard not identified. | | |
| | Liquid Application to Cracks/Crevices (Carpet) | ST/IT Hand to Mouth | 0.0000355 lb ai/sq ft | 0.0103 | 290 |
| | | ST/IT Object to Mouth | | 0.00137 | 2,200 |
| | Liquid Application to Cracks/Crevices (Hard Surfaces) | ST/IT Hand to Mouth | | 0.00342 | 880 |
| | | ST/IT Object to Mouth | | 0.000910 | 3,300 |

a Based on registered or proposed label (Reg. Nos.352-IAE, 352-IAI, 352-IAL).
EPA Reg. No. 352-IAE for granular application to indoor and outdoor areas,
EPA Reg. No. 352-IAI for liquid applications to indoor crack and crevices, and
EPA Reg. No. 352-IAL for liquid applications to turf.

b Dose (mg/kg/day) equations:
*Hand-to-Mouth Dose* = hand residue loading (µg/cm$^2$) × fraction of hand mouthed (0.127) × surface area of 1 hand (150 cm$^2$) × exposure time (1.5 hrs/day) × # of replenishment intervals/hr (4 int/hr) × (1-((1-saliva extraction factor (0.5))^(Number of hand-to-mouth events per hour (13.9 events/hr) ÷ # of replenishment intervals/hr)) ÷ body weight (11 kg).
*Object-to-Mouth Dose* = object residue loading (µg/cm$^2$) × unit conversion factor (0.001 mg/µg) × object surface area mouthed / event (10 cm$^2$/event) × exposure time (1.5 hrs/day) × # replenishment intervals/hr (4 int/hr) × (1-((1- saliva extraction factor (0.50))^(# Object-to-Mouth Events/hr (8.8 events/hr) ÷ # replenishment intervals/hr)) ÷ body weight (11 kg).
*Soil Ingestion* = soil residue (µg/g) × ingestion rate (50 mg/day) × conversion factor (0.000001 g/µg) ÷ body weight (11 kg).
TTR for liquid application rate of 0.313 lb ai/A = 0.0282 µg/cm$^2$ × (0.313 lb ai/A ÷ 0.20 lb ai/A) = 0.0441 µg/cm$^2$.
TTR for granular application rate of 0.0871 lb ai/A = 0.0282 µg/cm$^2$ × (0.0871 lb ai/A ÷ 0.20 lb ai/A) = 0.0123 µg/cm$^2$.
Deposited residue for liquid application to cracks/crevices = 1.74 µg/cm$^2$.

c MOE = NOAEL ÷ Daily Dose (mg/kg/day). ST/IT Incidental Oral NOAEL = 3.0 mg/kg/day. Level of concern = 100.

## 6.3 Residential Risk Estimates for Use in Aggregate Assessment

For the purpose of the cyantraniliprole aggregate human health risk assessment, a summary of the most protective residential exposure risk estimates for all proposed residential uses are provided in Table 6.3. Based on the residential use profile, and the 2012 Revised Residential

SOPs, only short-term inhalation residential handler exposures (for adults) and short-term incidental oral post-application exposures (for children) should be included in the aggregate risk assessment. It is noted that intermediate-term incidental oral post-application exposures are possible (i.e. from indoor applications and form soil ingestion due to the persistence of cyantraniliprole); however, the short-term incidental oral exposures are protective of the possible intermediate-term incidental oral exposures because the POD for both durations is the same.

Although it is possible for residential handlers to have combined exposures from concurrent turf and ornamental applications (based on the proposed label for EPA Reg. No. 352-IAL which would result in an MOE of 90,000)[6], the suggested exposure contribution for aggregate risk estimate is based on the most protective risk estimate from dry flowable application to ornamentals only (based on the proposed label for EPA Reg. No. 100-RUEE which results in an MOE of 22,000). The most protective risk estimate for children's post-application incidental oral exposures is based on indoor liquid crack/crevice application to carpets which results in an MOE of 290.

**Table 6.3 Scenarios Recommended for Aggregate Risk Assessment of Cyantraniliprole**

| Scenario | Daily Dose[a] *mg/kg/day* | MOE[b] |
|---|---|---|
| **Adults** | | |
| Residential Handler Inhalation Exposure (Applying Dry Flowables to Ornamentals with a Backpack Sprayer) | 0.000327 | 22,000 |
| **Children (1 to <2 Years Old)** | | |
| Post-Application Incidental Oral Exposure: Hand-to-Mouth (After Liquid Application to Cracks/Crevices on Carpet) | 0.0103 | 290 |

a Daily Dose = See Table 6.1 for adult handler scenarios and Table 6.2 for post-application incidental oral scenarios. Adults based on EPA Reg. No. 100-RUEE (WG). Children based on EPA Reg. No. 352-IAI (SC).
b MOE = NOAEL/Daily Dose (mg/kg/day).
ST Inhalation NOAEL = 7.2 mg/kg/day. ST Inhalation LOC = 30.
ST/IT Incidental Oral = 3.0 mg/kg/day. ST/IT Incidental Oral LOC = 100.

## 6.4 Residential Bystander Post-Application Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for cyantraniliprole at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure ($3.85\times10^{-17}$ mm Hg at 20ºC), and the low proposed use rate (0.391 lb ai/A). However, volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[7]. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify

[6] EPA Reg. No. 352-IAL (SC) may lead to concurrent turf and ornamental exposures. A conservative health-protective calculation of these two exposures results in a daily dose of 0.0000431 mg/kg/day (liquid application to lawns/turf) + 0.0000365 mg/kg/day (liquid application to gardens/trees) = 0.0000796 mg/kg/day; thus resulting in a combined MOE of 90,000 (NOAEL of 7.2 mg/kg/day ÷ 0.0000796 mg/kg/day).
[7] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for cyantraniliprole.

### 6.5 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for cyantraniliprole. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices, and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information)[8]. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risk estimates associated with drift.

Although a quantitative residential post-application inhalation exposure assessment was not performed as a result of pesticide drift from neighboring treated agricultural fields, an inhalation exposure assessment was performed for flaggers. This exposure scenario is representative of a worse case inhalation (drift) exposure and may be considered protective of most outdoor agricultural and commercial post-application inhalation exposure scenarios.

It is noted that the 0.313 lb ai/acre application rate for turf was modeled to estimate post-application residential exposure of children. As this rate is equal to or higher than many of the agricultural application rates, this scenario is protective of any incidental inhalation exposure of farm children via spray drift from agricultural cyantraniliprole applications.

## 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g. a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

### 7.1 Acute Aggregate Risk

An acute aggregate risk assessment was not conducted since adverse effects attributable to a single dose were not identified.

[8] Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm

## 7.2 Short-Term Aggregate Risk

There is potential short-term exposure to cyantraniliprole via the dietary (which is considered background exposure) and residential (which is considered primary exposure) pathways. For adults, the oral and inhalation routes of exposure should not be aggregated since the endpoints of concern are not common. For children, the pathways lead to exposure via the dietary oral (background) and incidental oral (primary) routes. The children short-term aggregate risk estimate (dietary and residential) is not of concern (as presented in Table 7.2). The MOE is 190 which is greater than the LOC of 100.

**Table 7.2 Short-Term Aggregate Risk Calculations**

| Population | Short-Term Scenario | | | | | | |
|---|---|---|---|---|---|---|---|
| | NOAEL mg/kg/day | LOC[a] | Max Allowable Exposure[b] mg/kg/day | Average Food and Water Exposure mg/kg/day | Residential Exposure mg/kg/day[c] | Total Exposure mg/kg/day[d] | Aggregate MOE (food, water, and residential)[e] |
| Children 1-2 years old | 3.0 | 100 | 0.030 | 0.005027 | 0.0107 | 0.0157 | 190 |

a Children LOC = 100 (based on inter- and intra- species uncertainty factors, each at 10X).
b Maximum Allowable Exposure (mg/kg/day) = NOAEL ÷ LOC.
c Residential Exposure = Incidental Oral Only for children (See Table 6.3).
d Total Exposure = Average Food and Water Exposure + Residential Exposure.
e Aggregate MOE = NOAEL ÷ Total Exposure. ST Children NOAEL = 3 mg/kg/day. LOC = 100.

## 7.3 Intermediate-Term Aggregate Risk

For adults, intermediate-term exposure is not expected for the residential exposure pathway. Therefore, the intermediate-term aggregate risk would be equivalent to the chronic dietary exposure estimate. Refer to Section 5.4.3. For children, the incidental oral POD is the same for both short- and intermediate-term durations. Thus, the short-term aggregate risk estimate is protective of potential intermediate-term exposures and risks. Refer to section 7.2.

## 7.4 Chronic Aggregate Risk

There are no chronic residential exposure scenarios; therefore, the chronic aggregate risk would be equivalent to the chronic dietary (food and drinking water) risk estimate. Refer to Section 5.4.3.

## 7.5 Cancer Aggregate Risk

Cyantraniliprole is classified as "not likely to be carcinogenic to humans." Therefore, an aggregate cancer assessment was not conducted.

## 8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as

to cyantraniliprole and any other substances and cyantraniliprole does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that cyantraniliprole has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative.

## 9.0 Occupational Exposure/Risk Characterization

Occupational handler and post-application exposure may occur by the dermal and inhalation routes of exposure only. Since there is no dermal hazard, only inhalation exposures were quantitatively assessed. The results of the occupational handler exposure and risk assessment indicate that short- and intermediate-term inhalation risk estimates are not of concern (N. Tsaur, DP407964, 02/26/2013). Appendix F, Tables F.1 and F.2 summarize all assessed occupational exposure and risk estimates including those from proposed seed treatment uses.

## 9.1 Short- and Intermediate-Term Handler Risk

Agricultural Field Uses

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed agricultural uses. The quantitative exposure/risk assessment developed for occupational handlers is based on several scenarios which include mixing/loading/applying various formulations of cyantraniliprole, including liquids, dry flowables, and granules. The use sites are summarized in Section 3.0. Methods of application include aerial, airblast, chemigation, groundboom, seed treatment, and handheld equipment (refer to Appendix F for a detailed list of each scenario).

HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). The area treated or amount handled is based on HED ExpoSAC Policy No. 9.1 (refer to Appendix F for these assumptions for each scenario).

It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit

Exposure Surrogate Reference Table[9]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[10].

In general, the labels require the chemical-resistant gloves as PPE. The results of the occupational handler exposure and risk assessment indicate that short- and intermediate-term inhalation risks do not exceed HED's 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. Note that only engineering control (enclosed cockpit) data are available to assess risks to handlers operating aircrafts.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers when appropriate, agricultural aviation has changed dramatically over the past two decades. According to the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED 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. With this level of protection, there are no risk estimates of concern for applicators.

Agricultural Seed Treatment Uses

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, 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:

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

Occupational seed treatment handlers may experience short- and intermediate-term exposure to cyantraniliprole while performing seed treatment activities in commercial settings. In addition, occupational secondary handlers may experience short- and intermediate-term exposure while planting cyantraniliprole-treated seeds. No chemical-specific handler exposure data were

[9] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[10] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html

submitted in support of this use pattern. For assessing commercial seed treatment and seed planting activities, unit exposure data were taken from HED ExpoSAC Policy 14: SOPs for Seed Treatment. The amount of active ingredient handled depends on the application rate (lb ai/lb seed) and the pounds of seed treated in a day (or the pounds of seed that can be planted in a day), all of which vary depending upon the seed type. Values for the amount of seed treated and planted per day were obtained from HED ExpoSAC Policy 15.

The results of the occupational handler exposure and risk assessment indicate that short-term inhalation risk estimates do not exceed HED'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 HED'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).

## 9.2 Short- and Intermediate-Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

### 9.2.1 Dermal Post-Application Risk

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

### 9.2.2 Restricted Entry Interval

Cyantraniliprole is classified as Toxicity Category IV via the dermal route. It is not irritating to the skin and it is not a skin sensitizer. Typically, the REI specified on the proposed label is based on the acute toxicity of the active ingredient. Under 40 CFR 156.208 (c) (2) (iii), active ingredients classified as Acute III or IV for acute dermal, eye irritation and primary skin irrigation are assigned a 12-hour REI. However, REIs may be further reduced from 12 hours if certain criteria are met for both the technical material and the different end-use products in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of Worker Protection Standard (WPS) Interim Restricted Entry Intervals (REIs) for Certain Low Risk Pesticides].[11]

The criteria for reducing REIs include the following:

(1) The active ingredient is in Toxicity Category III or IV based upon data for acute dermal

[11] Available: http://www.epa.gov/PR_Notices/pr95-3.html

toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation.
(2) The active ingredient is not a dermal sensitizer.
(3) The active ingredient is not a cholinesterase inhibitor.
(4) The active ingredient is not associated with known reproductive, developmental, carcinogenic, or neurotoxic effects.
(5) EPA does not possess incident information that are "definitely" or "probably" related to the post-application exposures to the active ingredient.

With respect to the active ingredient, cyantraniliprole, these criteria have been met for the technical and all but two of the proposed EPs. Since the two products, EPA Reg. No. 352-ILT and EPA Reg. No. 352-ILI, have been identified as dermal sensitizers, a 12-hour REI is required to protect agricultural workers from post-application exposures to cyantraniliprole. Aside from these two products, the 4-hour REIs listed on all other proposed labels are adequate. Table 9.2.2 shows the acute toxicity results for each proposed label and formulation.

**Table 9.2.2 Acute Toxicity Results of All Proposed U.S. Registrations for Cyantraniliprole**

| Reg. No. | Formulation | Oral | Dermal | Inhalation | Skin Irritation | Eye Irritation | Sensitization |
|---|---|---|---|---|---|---|---|
| 352-ILA | 96.7% technical | IV | IV | IV | IV | IV | -ve |
| 352-ILT | 100 g/l OD | IV | IV | IV | IV | III | +ve |
| 352-ILO | 100 g/l SE | IV | IV | IV | III | III | +ve |
| 352-IAN | 200 g/l SC | IV | IV | IV | IV | IV | -ve |
| 352-ILI | 625 g/l FS | IV | IV | IV | IV | IV | -ve |
| 352-IAE | 0.5% RB | IV | IV | waived[a] | IV | IV | -ve |
| 352-IAI | 200 g/l SC | IV | IV | IV | IV | IV | -ve |
| 352-IAL | 200 g/l SC | IV | IV | IV | IV | IV | -ve |
| 352-IAG | 200 g/l SC | IV | IV | IV | IV | IV | -ve |
| 100-RUER | 200 +200 g/kg WG | IV | IV | IV | IV | III | -ve |
| 100-RUEE | 200 +200 g/kg WG | IV | IV | IV | IV | III | -ve |
| 100-RUEG | 200 +200 g/kg WG | IV | IV | IV | IV | III | -ve |
| 100-RUEU | 200 +200 g/kg WG | IV | IV | IV | IV | III | -ve |
| 100-RUEN | 600 g/l FS | IV | IV | IV | IV | IV | -ve |
| 100-RURI | 600 g/l FS | IV | IV | IV | IV | III | -ve |

a Waiver request granted (Technical = Tox Cat IV; Bait station, no potential for inhalation exposure, etc.)

### 9.2.3 Inhalation Post-Application Risk

Agricultural/Commercial Outdoor Uses

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for cyantraniliprole at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure ($3.85\times10^{-17}$ mm Hg at 20ºC), and

the low proposed use rate (0.391 lb ai/A). However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[12]. The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the ARTF and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for cyantraniliprole.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Greenhouse Uses

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements.[13]

Indoor Commercial Uses

Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (sites such as warehouses, food handling establishments, and hotels, etc.) and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

Seed Treatment Uses

A post-application inhalation exposure assessment is not required as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e. planters). It is expected that these exposure estimates would be protective of most post-application inhalation exposure scenarios.

## 10.0 References

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[12] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

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## Appendix A. Detailed Use Profile Summary

**Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels)**

| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
|---|---|---|---|---|---|---|
| ***Brassica* (Cole) Leafy Vegetables (Group 5)** | | | | | | |
| Soil at Planting (in-furrow spray, transplant water treatment, hill drench, surface band, soil shank injection) | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.00202 lb ai/gal | 1 | 0.176 lb ai/A | N/A | Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 5 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for all vegetable crops. |
| Soil (in-furrow spray at seeding or transplanting; post seeding, post transplant, hill drench; drip (trickle) chemigation; shanked into root zone) | 20.0% WG [100-RUER] A16901B CP | 0.175 lb ai/A<br>0.0175 lb ai/gal | 1 | | NA | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Make only one soil application per growing season. |
| Foliar (ground, aerial, chemigation) | 20.0% WG [100-RUER] A16901B CP | 0.0875 lb ai/A<br>0.00875 lb ai/gal | N/S | | 7 | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Use a minimum of 10 gal water per acre for ground application. |
| **Bulb Vegetables (Group 3-07)** | | | | | | |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 5 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for all vegetable crops. |
| Foliar (ground, aerial, chemigation) | 10.26% OD [352-ILT] Benevia™ | 0.133 lb ai/A<br>0.0133 lb ai/gal | N/S | 0.4 lb ai/A | 5 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for bulb vegetables. |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| **Bushberries (Group 13-07B)** | | | | | | |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 5 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for all fruit and nut crops. |
| **Citrus Fruits (Group 10-10)** | | | | | | |
| Soil drench or microsprinkler chemigation | 18.66% SC [352-IAN] Verimark™ | 0.391 lb ai/A<br>0.00449 lb ai/gal | 1 | 0.4 lb ai/A | N/A | For use on citrus nursery stock (trees less than 4 years old). Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for all fruit and nut crops. |
| **Cotton** | | | | | | |
| Foliar (ground, aerial) | 10.26% OD [352-ILT] Benevia™ | 0.133 lb ai/A<br>0.0133 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for cotton. |
| **Cucurbit Vegetables (Group 9)** | | | | | | |
| Soil at Planting (in-furrow spray, transplant water treatment, hill drench, surface band, soil shank injection) | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.00202 lb ai/gal | 1 | 0.176 lb ai/A | N/A | Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Drip chemigation | 18.66% SC [352-IAN] Verimark™ | 0.130 lb ai/A<br>0.00149 lb ai/gal | 2 (1 if at-plant app is made) | 0.260 lb ai/A | 10 | |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 1 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates; non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for all vegetable crops. |
| Soil (in-furrow spray at seeding or transplanting; post seeding, post transplant, hill drench; drip (trickle) chemigation; shanked into root zone) | 20.0% WG [100-RUER] A16901B CP | 0.175 lb ai/A<br>0.0175 lb ai/gal | 1 | 0.4 lb ai/A | NA | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Make only one soil application per growing season. |
| Foliar (ground, aerial, chemigation) | 20.0% WG [100-RUER] A16901B CP | 0.0875 lb ai/A<br>0.00875 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Use a minimum of 10 gal water per acre for ground application. |
| **Fruiting Vegetables (Group 8-10)** | | | | | | |
| Soil at Planting (in-furrow spray, transplant water treatment, hill drench, surface band, soil shank injection) | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.00202 lb ai/gal | 1 | 0.176 lb ai/A | N/A | Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Drip chemigation | 18.66% SC [352-IAN] Verimark™ | 0.130 lb ai/A<br>0.00149 lb ai/gal | 2 (1 if at-plant app is made) | 0.260 lb ai/A | 10 | |
| Foliar (ground, aerial)<br>Foliar (greenhouse) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 1 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for all vegetable crops. |
| Soil (in-furrow spray at seeding or transplanting; post seeding, post transplant, hill drench; drip (trickle) chemigation; shanked into root zone) | 20.0% WG [100-RUER] A16901B CP | 0.175 lb ai/A<br>0.0175 lb ai/gal | 1 | 0.4 lb ai/A | NA | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Make only one soil application per growing season. |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| Foliar (ground, aerial, chemigation) | 20.0% WG [100-RUER] A16901B CP | 0.0875 lb ai/A<br>0.00875 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Use a minimum of 10 gal water per acre for ground application. |
| **Leafy Vegetables (non-*Brassica*) (Group 4)** | | | | | | |
| Soil at Planting (in-furrow spray, transplant water treatment, hill drench, surface band, soil shank injection) | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.00202 lb ai/gal | 1 | 0.176 lb ai/A | N/A | Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries.<br>Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 1 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for all vegetable crops. |
| Soil (in-furrow spray at seeding or transplanting; post seeding, post transplant, hill drench; drip (trickle) chemigation; shanked into root zone) | 20.0% WG [100-RUER] A16901B CP | 0.175 lb ai/A<br>0.0175 lb ai/gal | 1 | 0.4 lb ai/A | NA | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Make only one soil application per growing season. |
| Foliar (ground, aerial, chemigation) | 20.0% WG [100-RUER] A16901B CP | 0.0875 lb ai/A<br>0.00875 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Use a minimum of 10 gal water per acre for ground application. |
| **Mustard Seed** | | | | | | |
| Seed treatment[b] | 50% FS [352-ILI] Dermacor® Z-103 | 1.0 lb ai/cwt | 1 | 0.4 lb ai/A | 7 | Apply as a water-based slurry prior to planting. May be applied with other registered seed treatment fungicides and insecticides. Use EPA-approved dye or colorant to ensure that seed pieces are dyed an unnatural color. |
| **Oilseed Crops (Group 20) (see also rapeseed)** | | | | | | |
| Foliar (ground, aerial) | 10.26% OD [352-ILT] Benevia™ | 0.133 lb ai/A<br>0.0133 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for oilseed crops. |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| **Pome Fruits (Group 11-10)** | | | | | | |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for all fruit and nut crops. |
| **Potato** | | | | | | |
| Seed piece treatment[b] | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.010 lb ai/ cwt | 1 | 0.176 lb ai/A | N/A | Apply as a water-based slurry prior to planting. May be applied with other registered seed treatment fungicides and insecticides. Use EPA-approved dye or colorant to ensure that seed pieces are dyed an unnatural color. Treat seed pieces as close to planting as possible. If planting is delayed, do not cover seed pieces as rotting can be accelerated. Best results are obtained if treated potatoes are allowed to dry during transit and planted the same day of treatment. |
| Seed piece treatment[b] | 48.8% FS [100-RUEN] A17960A ST | 0.000135 lb ai/lb seed | 1 | 0.000135 lb ai/lb seed | N/A | |
| Seed piece treatment[b] | 48.8% FS [100-RURI] A17960B ST | 0.000135 lb ai/lb seed | 1 | 0.000135 lb ai/lb seed | N/A | |
| **Rapeseed (Canola)** | | | | | | |
| Seed treatment[b] | 50% FS [352-ILI] Dermacor® Z-103 | 1.0 lb ai/cwt | 1 | 0.4 lb ai/A | N/A | Apply as a water-based slurry prior to planting. May be applied with other registered seed treatment fungicides and insecticides. Use EPA-approved dye or colorant to ensure that seed pieces are dyed an unnatural color. |
| **Stone Fruits (Group 12)** | | | | | | |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for all fruit and nut crops. |
| **Sunflower** | | | | | | |
| Seed treatment[b] | 48.8% FS [100-RUEN] A17960A ST | 0.2 mg ai/seed | 1 | 0.2 mg ai/seed | N/A | Apply as a water-based slurry prior to planting. May be applied with other registered seed treatment fungicides and insecticides. Use EPA-approved dye or colorant to ensure that seed pieces are dyed an unnatural color. |
| Seed treatment[b] | 48.8% FS [100-RURI] A17960B ST | 0.00397 lb ai/lb seed | 1 | 0.00397 lb ai/lb seed | N/A | |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| **Tree Nuts (Group 14) and Pistachio** | | | | | | |
| Foliar (ground, aerial) | 10.20% SE [352-ILO] Exirel™ | 0.133 lb ai/A<br>0.00443 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for all fruit and nut crops. |
| Foliar (ground, aerial) | 10.26% OD [352-ILT] Benevia™ | 0.133 lb ai/A<br>0.000443 lb ai/gal | N/S | 0.4 lb ai/A | 7 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 30 gallons per acre for tree nuts. |
| **Tuberous and Corm Vegetables (Subgroup 1C)** | | | | | | |
| Soil at Planting (in-furrow spray, transplant water treatment, hill drench, surface band, soil shank injection) | 18.66% SC [352-IAN] Verimark™ | 0.176 lb ai/A<br>0.010 lb ai/ cwt | 1 | 0.176 lb ai/A | N/A | Only to be applied to the soil by ground or drip chemigation application equipment. Must be applied uniformly in the root zone. Do not make aerial or airblast applications. Do not treat plants being grown for transplanting in nurseries. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. |
| Foliar (ground, aerial) Chemigation (overhead only) | 10.26% OD [352-ILT] Benevia™ | 0.133 lb ai/A<br>0.0133 lb ai/gal | N/S | 0.4 lb ai/A | 5 | Do not treat plants grown for transplanting. Do not apply to the soil or through drip irrigation systems. Use this product only in commercial and farm plantings. May be used on crops grown for seed production. Adjuvants may be used (methylated seed oils; petroleum oil concentrates: non-ionics; organosilicones/ organosilicates). Use a minimum of 10 gallons per acre for tuberous and corm vegetables. |
| Soil (in-furrow spray during planting; apply impregnated on dry granular fertilizer before or during planting; at plant emergence by direct spray to the soil near base of plant and incorporate with irrigation; at plant emergence with overhead chemigation after hilling) | 20.0% WG [100-RUER] A16901B CP | 0.125 lb ai/A<br>0.0125 lb ai/gal | 1 | 0.4 lb ai/A | NA | Use this product only in commercial and farm plantings. Do not use in greenhouses. Do not treat plants grown for transplanting. Apply within 21 days of planting or transplanting. Make only one soil application per growing season. |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| **Residential, Commercial, Agricultural Structures**<br>(Single and multi-family residential buildings, schools, institutional, commercial, agricultural and industrial facilities (including warehouses, apartments, supermarkets, restaurants, motels, hotels, hospitals, daycares, and food handling/storage/processing establishments, animal production facilities, feedlots, broiler houses, livestock barns, pet kennels) and transportation equipment such as aircraft, trains, ships, boats and buses). | | | | | | |
| Broadcast or bait station | 0.5% G [352-IAE] HGW86 Fly Control Bait | 0.0871 lb ai/A<br>0.00000200 lb ai/sq ft | As needed | Not specified | 7 | INTENDED FOR USE BY COMMERCIAL APPLICATORS ONLY.<br>Broadcast or scatter HGW86 fly control bait using suitable granular spreader equipment or directly from the container evenly to the target areas. Use in indoor areas at all the above described use sites only if HGW86 fly control bait is placed in bait stations. Use commercially available bait stations that are designed to hold granular baits. When bait stations are being used, place them where the stations are inaccessible to children or pets. |
| Outdoor: broadcast<br>Indoor: crack and crevice, including indoor areas with exposed food/feed present | 18.66% SC [352-IAI] HGW86 SC Insect Control | 0.0355 lb ai/1000 sq ft<br>0.00887 lb ai/gallon | As needed | Not specified | 7 | INTENDED FOR USE BY COMMERCIAL APPLICATORS ONLY.<br>Avoid spraying food and feed handling equipment. Do not apply to areas that are routinely washed such as cracks and crevices in tops of tables, food/feed preparation and prepared food holding surfaces. Do not apply a broadcast or general surface application to interior surfaces of residential or commercial structures. Do not apply this product to pets, edible crops, or sources of electricity. Do not make applications to structures while occupied by livestock, poultry or companion animals. Do not apply to milk rooms or feed rooms. Do not make applications to any animal feedstuffs, water, or watering equipment. Do not contaminate any animal food, feed, or water in and around livestock, poultry, or companion animal housing when making applications. |
| **Ornamentals**<br>(Ornamental plants/shrubs/trees and vegetable transplants in and around greenhouses, nurseries, interior plantscapes, lath and shadehouses (grassy, weedy, mulched, bare soil areas in and around), trees (including non-fruit bearing and nut trees), shrubs, evergreens, bedding plants, flowering plants, flowers, foliage plants, ground covers, vines (non-bearing), interior plantscape plants, vegetable transplants (including fruiting, leafy, and tuberous/corm)). | | | | | | |
| Foliar spray, soil broadcast spray, soil drench, soil injection, or chemigation | 18.66% SC [352-IAG] HGW86 GH&N Insect Control | 0.261 lb ai/A<br>0.00326 lb ai/gal | 2 | 0.418 lb ai/A | 7 | Do not apply this product with aerial application equipment. Do not apply to greenhouse or field grown vegetables, only apply to vegetable transplants grown in enclosed structures. |
| Foliar | 18.66% SC [352-IAL] HGW86 T&O Insect Control | 0.313 lb ai/A<br>0.00418 lb ai/gal | 2 | 0.418 lb ai/A | 7 | Do not apply this product through any type of irrigation system. Do not apply this product with aerial application equipment. Do not use on plants being grown for sale or other commercial use; or for commercial seed production. Do not apply this product in commercial nurseries and greenhouses. |
| Foliar, soil, chemigation, or handheld equipment | 20% WG [100-RUEE] Mainspring Insecticide | 0.131 lb ai/A<br>0.00131 lb ai/gal | 2 | 0.263 lb ai/A | 14 | Do not apply with aerial equipment. |

| Table A.1 Summary of Proposed Directions for Use of Cyantraniliprole (DuPont and Syngenta Labels) | | | | | | |
|---|---|---|---|---|---|---|
| Application Timing, Type, and Equipment | Formulation [EPA Reg. No.] Trade Name[a] | Maximum Application Rate | Max. No. of Apps per Season | Max. Seasonal Application Rate | RTI *days* | Use Directions and Limitations |
| Soil (individual fire ant mound treatment) | 20% WG [100-RUEE] Mainspring Insecticide | 0.00475 lb ai/gal | NA | NA | NA | For small mounds (<6 inch in diameter) apply 1 gal of water per mound and for larger mounds apply 2-3 gal of dilute solution per mound for optimum control. Direct the application to the center of the mound, including a 6-inch diameter circle. |
| Foliar | 20% WG [100-RUEG] A16901B Residential | 0.000781 lb ai/gal | 2 | 0.00156 lb ai/gal | 7 | Mix 1 teaspoon in 1 gallon of water.<br>Apply as a thorough cover spray.<br>1 gallon treats plants in a 400 square feet area. |
| **Turfgrass**<br>(including golf courses, institutional, commercial and residential lawns, landscape, recreational, sod farms, sports fields, parks, municipal grounds and cemeteries). | | | | | | |
| Foliar | 18.66% SC [352-IAL] HGW86 T&O Insect Control | 0.313 lb ai/A<br><br>0.00418 lb ai/gal | 2 | 0.418 lb ai/A | 7 | Do not apply this product through any type of irrigation system. Do not apply this product with aerial application equipment. Do not use on plants being grown for sale or other commercial use; or for commercial seed production. Do not apply this product in commercial nurseries and greenhouses. |
| Foliar | 20% WG [100-RUEU] A16901B Turf Insecticide | 0.133 lb ai/A<br><br>0.00203 lb ai/gal | 2 | 0.265 lb ai/A | 30 | Do not apply this product through any type of irrigation system. |

a Formulation codes: G = granular, SC = suspension concentrate, SE = suspoemulsion, WG = water dispersible granules, OD = oil dispersion, FS = flowable suspension.

b cwt = hundredweight (100 lb seed).
Seed treatment rate calculations are based on the following assumptions:
Mustard seed: 90,000 to 115,000 seeds per lb (assumed to be equivalent to rapeseed/canola).
Potato seed pieces: 5 to 11 seed pieces per lb.
Rapeseed (canola): 90,000 to 115,000 seeds per lb.
Sunflowers: 2,000 to 9,000 seeds per lb.

# Appendix B. Toxicology Profile and Executive Summaries

## B.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food and non food uses for cyantraniliprole are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

**Table B.1 Summary of Toxicology Data Requirements**

| Study | | Technical | |
|---|---|---|---|
| | | Required | Satisfied |
| 870.1100 | Acute Oral Toxicity | yes | yes |
| 870.1200 | Acute Dermal Toxicity | yes | yes |
| 870.1300 | Acute Inhalation Toxicity | yes | yes |
| 870.2400 | Primary Eye Irritation | yes | yes |
| 870.2500 | Primary Dermal Irritation | yes | yes |
| 870.2600 | Dermal Sensitization | yes | yes |
| 870.3050 | 28-Day Oral (rodent) | no | yes |
| 870.3100 | Oral Subchronic (rodent) | yes | yes |
| 870.3150 | Oral Subchronic (nonrodent) | yes | yes |
| 870.3200 | 21-Day Dermal | CR[b] | yes |
| 870.3250 | 90-Day Dermal | CR[b] | - |
| 870.3465 | 90-Day Inhalation (28-Day Inhalation) | yes | yes |
| 870.3700a | Developmental Toxicity (rodent) | yes | yes |
| 870.3700b | Developmental Toxicity (nonrodent) | yes | yes |
| 870.3800 | Reproduction | yes | yes |
| 870.4100b | Chronic Toxicity (nonrodent-dog) | no | yes |
| 870.4200b | Carcinogenicity (mouse) | yes | yes |
| 870.4300 | Chronic Toxicity/Oncogenicity (rodent-rat) | yes | yes |
| 870.5100 | Mutagenicity—Gene Mutation - bacterial | yes | yes |
| 870.5300 | Mutagenicity—Gene Mutation - mammalian | yes | yes |
| 870.5xxx | Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5xxx | Mutagenicity—Other Genotoxic Effects | yes | yes |
| 870.6100a | Acute Delayed Neurotoxicity (hen) | no | - |
| 870.6100b | 90-Day Neurotoxicity (hen) | no | - |
| 870.6200a | Acute Neurotoxicity Screening Battery (rat) | yes | yes |
| 870.6200b | 90-Day Neurotoxicity Screening Battery (rat) | yes | yes |
| 870.6300 | Develop. Neurotoxicity | CR[b] | - |
| 870.7485 | General Metabolism | yes | yes |
| 870.7600 | Dermal Penetration | CR[b] | -[a] |
| 870.7800 | Immunotoxicity | yes | yes |

a A dermal penetration study on the technical grade is not available; however, both *in-vivo* and *in-vitro* dermal penetration studies on four formulations are available. A human dermal absorption factor was calculated based on these studies.

b CR = conditionally required.

## B.2 Toxicity Profiles

| Table B.2.1 Acute Toxicity Profile – Technical Cyantraniliprole | | | | |
|---|---|---|---|---|
| Guideline No. | Study Type | MRID | Results | Toxicity Category |
| 870.1100 | Acute oral (mouse) | 48119957 | $LD_{50}$ >5000 mg/kg | IV |
| | Acute oral (rat) | 48119952 | $LD_{50}$ >5000 mg/kg | IV |
| 870.1200 | Acute dermal (rat) | 48119953 | $LD_{50}$ >5000 mg/kg | IV |
| 870.1300 | Acute inhalation—4 hour (rat) | 48119958 | $LC_{50}$ >5.2 mg/L | IV |
| 870.2400 | Acute oral (mouse) | 48119957 | $LD_{50}$ >5000 mg/kg | IV |
| 870.2500 | Skin irritation (rabbit) | 48119954 | Not irritating | NA |
| | Eye irritation (rabbit) | 48119955 | Slightly irritating; clearing by 72 hours | |
| | Eye irritation (rabbit) | 48208421 | Not irritating | |
| 870.2600 | Skin sensitization (mouse) *local lymph node assay* | 48208422 | Not sensitizing | |
| | Skin sensitization (mouse) *local lymph node assay* | 48208423 | Not sensitizing | |
| | Skin sensitization (guinea pig) *maximization test* | 48119984 | Not Sensitizing | |

| Table B.2.2 Acute Toxicity Profile – Cyantraniliprole Metabolites | | | | |
|---|---|---|---|---|
| Test Substance | Study Type | MRID | Results | Toxicity Category |
| IN-JSE76-005 | Acute oral (rat) | 48119978 | $LD_{50}$ >5000 mg/kg | IV |
| IN-PLT97-003 | Acute oral (mouse) | 48122579 | $LD_{50}$ >5000 mg/kg | IV |
| IN-F6L99-004 | Acute oral (mouse) | 46979929 | $LD_{50}$ >2000 mg/kg | IV |
| IN-N5M09-003 | Acute oral (mouse) | 48119939 | $LD_{50}$ >5000 mg/kg | IV |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| **Subchronic Toxicity Studies** | | | |
| 870.3050 | 2-Week oral study—gavage with metabolism information (rats) | 48119938 (2010)<br>Acceptable/non-guideline<br><br>25, 300, and 1,000 mg/kg/day | NOAEL =1,000 mg/kg/day (HDT). Treatment related effects were not found at any dose levels.<br><br>Supplemental data:<br>The kinetic data indicate that the plasma $T_{1/2}$ = 3.84, 6.41, and 5.44 hours for the 25, 300, and 1,000 mg/kg/day, respectively. $T_{max}$ = 2.00, 2.33, and 1.67 hours in the 25, 300, and 1,000 mg/kg/day groups, respectively. The tissue concentration in peripheral fat was <0.1% at 24 hrs after dosing. Total cytochrome P-450 content in male or female rats was minimally elevated. In male rats, cyantraniliprole is an inducer of cytochrome P-450 isozyme CYP1A1 and CYP2B1. In female rats, cyantraniliprole is an inducer of cytochrome P-450 isozyme CYP2B1. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| 870.3050 | 28-Day feeding study (mice) | 48119940 (2009)<br>Acceptable/guideline<br><br>0, 300, 1,000, 3,000, and 7,000 ppm<br><br>M: 0, 53, 175, 528, and 1,261 mg/kg/day<br><br>F: 0, 63, 212, 664, and 1,476 mg/kg/day | NOAEL = 528/664 (M/F).<br>LOAEL = 1,261/1,476 mg/kg/day (M/F) (highest dose tested). Adverse effects were not found at any dietary concentrations.<br><br>Supplemental data:<br>Cyantraniliprole does not induce hepatic β-oxidation in male or female mice. In male mice, the total cytochrome P-450 content significantly increased at dietary concentrations of 3,000 and 7,000 ppm. In female mice, total cytochrome P-450 content significantly increased at dietary concentrations of 300, 1,000, 3,000, and 7,000 ppm. At 3,000 and 7,000 ppm, both male and female mice show adaptive liver responses such as increased liver weight and liver enzyme. |
| 870.3050 | 28-Day feeding study (rats) | 48119941 (2009)<br>Acceptable/guideline<br><br>0, 600, 2000, 6000, and 20,000 ppm<br><br>M: 0, 53, 175, 528, and 1,776 mg/kg/day<br><br>F: 0, 62, 188, 595, and 1,953 mg/kg/day | NOAEL for males cannot be established due to treated-related increase in the incidence of thyroid follicular hypertrophy at 53 mg/kg/day (LOAEL) (lowest dose tested).<br><br>For females: NOAEL = 62 mg/kg/ day. LOAEL = 188 mg/kg/day based on thyroid follicular cell hypertrophy.<br><br>Supplemental data:<br>In male rats, cyantraniliprole is a mild inducer of hepatic UDP- glucuronyltransferase activity (range from ↑39% at low dose to ↑132% at high dose) while inducing only a minimal effect on cytochrome P-450 content. In female rats, cyantraniliprole causes a slight increase in total hepatic cytochrome P-450 content while inducing a somewhat lesser effect on hepatic UDP-glucuronyltransferase activity. Cyantraniliprole does not induce hepatic β-oxidation, a measure of peroxisome proliferation, in male or female rats. |
| 870.3050 | 28-Day palatability study—dietary (dogs) | 48119942 (2007)<br>Acceptable/non-guideline<br><br>0, 1000, 10,000, and 40,000 ppm<br><br>M: 0, 35, 311, and 1,043 mg/kg/day<br><br>F: 0, 35, 335, and 1,240 mg/kg/day) | NOAEL for male and female dogs could not be determined. LOAEL = 35 mg/kg/day (lowest dose tested) based on decreases in body weight, food consumption, food efficiency, and changes in clinical chemistry (↑ALP, ↓ cholesterol and ↓ albumin).<br><br>Supplemental data:<br>Increases in hepatic cytochrome P-450 (total and 2B1, 3A2, and 4A1/2/3 isozymes) were observed in all male and female dose groups but the increase did not demonstrate a dose related response. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| 870.3100 | 90-Day feeding toxicity study (mice) | 48119943 (2007) Acceptable/ guideline<br><br>48119944 (2007) supplement to 48119943 Provide information about metabolites<br><br>0, 50, 300, 1,000, and 7,000 ppm<br><br>M: 0, 7, 47, 150, and 1,092 mg/kg /day.<br><br>F: 0, 10, 58, 204, & 1,344 mg/kg/day. | NOAEL = 150/204 (M/F)<br>LOAEL =1,092/1,344 (M/F) based on increased incidence of focal necrosis of the liver, and liver weight increase.<br><br>Supplemental data:<br>Metabolite analyses showed that IN-MLA84 was the most prevalent analyte present in male and female mice, followed by cyantraniliprole. Plasma values for all the evaluated metabolites were similar between males and females at comparable dose levels. |
| 870.3100 | 90-Day feeding study (rats)<br><br>[Interim sacrifice was also conducted on 5/sex/dose on 29th (♂) day and 30th day(♀)] | 48119945 (2007) Acceptable/ guideline<br><br>48119946 (2007) Supplement to 48119945<br><br>0, 100, 400, 3,000, and 20,000 ppm<br><br>M: 0, 6, 22, 168, and 1,147 mg/kg /day<br><br>F: 0, 7, 27, 202, or 1,346 mg/kg/day | Females: NOAEL = 7 mg/kg/day.<br>LOAEL = 27 mg/kg/day) based on thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis.<br><br>Males: NOAEL =168 mg/kg/day.<br>LOAEL= 1,147 mg/kg/day) based on thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis in male rats.<br><br>Supplemental data:<br>IN-MLA84 was the major metabolite present in the plasma of male and female rats followed by parent cyantraniliprole and IN-J9Z38. |
| 870.3150 | 90-Day oral study—dietary (dogs)<br><br>[T3, T4, TSH, and cytochrome P450 were also measured] | 48119948 (2007) Acceptable/guideline<br><br>48119947 (2007) Supplement to 48119948<br><br>0, 30, 100, 1,000, and 10,000 ppm<br><br>M: 0, 1, 3, 32, and 281 mg/kg/day<br><br>F: 0, 1, 3. 34, and 294 mg/kg/day) | NOAEL = 3 mg/kg/day.<br>LOAEL = 32 mg/kg/day based on based on a collection of treatment-related effects indicative of hepatotoxicity. The effects included decreases in total protein, albumin, and cholesterol in males and females; increases in alkaline phosphatase in males and females, and increases in alanine aminotransferase in females, and increase liver weights in males and females.<br>Supplemental data indicated the major analyte in the plasma was the parent cyantraniliprole. Thyroid hormone levels were not consistently changed. |
| 870.3200 | 28-Day dermal study (rats) | 48119970 (2009) Acceptable/guideline<br><br>0, 100, 300, and 1,000 mg/kg /day (6 hours/day) | NOAEL ≥ 1,000 mg/kg/day (highest dose tested). Systemic toxicity was not found. |
| 870.3465 | 28-Day inhalation study (rats) | 48663602 (2011) Acceptable non guideline<br><br>0, 1, 10, and 100 mg/m$^3$ | NOAEL = 100 mg/m$^3$ (0.1 mg/L). Systemic or portal of entry effects were not seen at the highest concentration. However, at 100 mg/m$^3$, an increase in the incidence of minimal laryngeal squamous metaplasia was found; it was considered to be treatment-related and non adverse. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| **Developmental and Reproductive Toxicity Studies** | | | |
| 870.3700a | Prenatal developmental study—gavage (rats) | 48119968 (2009) Acceptable/guideline<br><br>0, 20, 100, 300, and 1,000 mg/kg/day (GD 6 to 20) | Both maternal and developmental NOAELs = 1,000 mg/kg/day, the highest dosage tested. LOAELs were not established. |
| 870.3700b | Prenatal developmental study—gavage (rabbits) | 48119969 (2009) Acceptable/guideline<br><br>0, 25, 100, 250, and 500 mg/kg /day (GD 7-28) | Maternal: NOAEL = 25 mg/kg/day. LOAEL = 100 mg/kg/day based on increased mortality, increased incidences of diarrhea and reduced and/or absent of feces, decreased body weights, and reduced food consumption. Developmental: NOAEL=100 mg/kg /day. LOAEL was 250 mg/kg/day based on reductions in mean fetal body weights. |
| 870.3800 | 2-Generation reproduction study—dietary (rats) | 48119967 (2011) Acceptable/guideline<br><br>0, 20, 200, 2,000, and 20,000 ppm<br><br>0, 1.4, 14, 136, and 1,344 mg/kg/day based on premating compound intake in $P_1$ females | Parental NOAEL = 1.4 mg/kg/day. LOAEL= 14 mg/kg/day based on thyroid weight increase and corresponding dose-related increase in the incidence of thyroid follicular epithelial cell hypertrophy/ hyperplasia.<br><br>Reproductive: NOAEL = 1344 mg/kg/day (the highest dose tested) based on the lack of adverse test substance-related effects on fertility and reproductive parameters at any dose levels in the study. Offspring: NOAEL = 14 mg/kg/day. LOAEL=136 mg/kg/day based on dose-related decreases in organ weights (thymus and spleen), and pup body weight in the F2 generation pups. |
| **Chronic Toxicity Studies** | | | |
| 870.4100 | Combined chronic/ carcinogenicity study (rats) | 48122577 (2011) Acceptable/guideline<br><br>0, 20, 200, 2,000, and 20,000 ppm<br><br>M: 0, 0.8, 8.3, 84.8, and 906.6 mg/kg /day<br><br>F: 0, 1.1, 10.5, 106.6, and 1,160.8 mg/kg/day | NOAEL = 8.3 mg/kg/day<br>LOAEL = 84.8 mg/kg/day based on microscopic liver pathology characterized by foci of cellular alteration (clear, eosinophilic, and basophilic) and focal vacuolation.<br><br>Cyantraniliprole did not produce compound-related or dose-related increase in tumor incidence. |
| 870.4100b | 1-Year oral study—dietart with active ingredient (dogs)<br><br>[a recovery period was also included] | 48119960 (2010) Acceptable/guideline<br><br>48208427 (2010) Supplement to 48119960.<br><br>0, 40, 200, 1,000, and 5,000 ppm<br><br>M: 0, 1, 6, 27, and 144 mg/kg/day<br><br>F: 0, 1, 6, 27, and 133 mg/kg/day | NOAEL = 1 mg/kg/day<br>LOAEL = 6 mg/kg/day based on decreases in albumin levels, statistically significant increases in liver weight and alkaline phosphatase. At the next dose level (1,000 ppm, or 27 mg/kg bw/day) histopathological changes characterized by hepatocellular degeneration and inflammatory process with associated increases in alkaline phosphatase (ALP) and alanine aminotransferase (ALT), and decreases in total protein and albumin were found. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| 870.4200b | 18-Month carcinogenicity study (mice) | 48122578 (2011)<br>Acceptable/guideline<br><br>0, 20, 150, 1,000, and 7,000 ppm<br><br>M: 0, 2, 16, 104, and 769 mg/kg/day<br><br>F: 0, 2, 19, 131, and 904 mg/kg/day | NOAEL = 104/131 (M/F)<br>LOAEL = 769/904 (M/F)<br>Based on the finding that cyantraniliprole induced a statistically significant increase in food consumption and a decrease in food efficiency with very little changes in body weights. These changes suggest that the high dose animals were unable to adequately utilize food, and it was a compound-related effect and was considered to be adverse.<br><br>Cyantraniliprole did not produce compound-related increase in tumor incidence. |
| **Genotoxicity Toxicity Studies** | | | |
| 870.5100 | Bacterial reverse mutation test (*S. typhimurium* and *E. coli)* | 48122587 (2010)<br>Acceptable/guideline | Negative.<br>0, 50, 150, 500, 1,500, and 5,000 µg/plate were tested (+/- S9). Precipitate was observed at 5,000 µg/plate. |
| | | 48119980 (2009)<br>Acceptable/guideline | Negative.<br>The dose levels tested were 0, 50, 150, 500, 1,500, and 5,000 µg/plate (+/- S9); precipitate was observed at 5,000 µg/plate. |
| | | 48208424 (2009)<br>Acceptable/guideline | Negative.<br>The dose levels tested were 0, 50, 150, 500, 1,500, and 5,000 µg/plate. (+/- S9). Precipitation was observed at 5,000µg/ plate. |
| 870.5300 | *In vitro* mammalian cell gene mutation test (CHO/HGPRT assay) | 48122589 (2010)<br>Acceptable/guideline | Negative.<br>of 0, 50.0, 100, 150, 250, and 500 µg/ml (+/- S9). Ethyl methanesulfonate (EMS) and benzo(a)pyrene (BaP) were used as positive controls. |
| 870.5300 | *In vitro* CHO/HPRT forward mutation assay | 48208443 (2011)<br>Acceptable/guideline | Negative.<br>0, 10.0, 25.0, 50.0, 100, 250, 500, 750, and 1,000 µg/mL were tested. Ethyl methanesulfonate (EMS) and methylcholanthrene (MCA) were used as positive controls. Compound precipitation was observed at concentrations in treatment medium ≥250 µg/mL. |
| 870.5375 | *In vitro* Mammalian chromosome aberration test with human lymphocytes | 48208425 (2009)<br>Acceptable/guideline | Negative.<br>0, 62.5, 125, 250, 500, 600, 700, 800, and 900 µg/mL for the 4-hour non-activated and activated treatment conditions, and 0, 31.3, 62.5, 125, 250, 400, 500, 600, 700, and 800 µg/mL for the 20-hour non-activated treatment condition. |
| 870.5375 | *In vitro* Mammalian chromosome aberration test with human lymphocytes | 48208426 (2009)<br>Acceptable/guideline | Negative .<br>Doses ranged from 125 to 3,500 µg/mL for the non-activated and S9-activated 4-hour exposure groups, and from 15.7 to 1,500 µg/mL for the non-activated 20-hour exposure group. Compound precipitation was recorded at ≥1,000 µg/mL. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| 870.5375 | *In vitro* Mammalian chromosome aberration test with human peripheral blood lymphocytes (HPBL) | 48122588 (2010) Acceptable/guideline | Negative. 0, 62.5, 125, 250, 500, 600, 700, 800, and 1,000 µg/mL for non-activated 4-hour; 0, 62.5, 125, 250, 500, 600, 700, 800, and 900 µg/mL for activated 4-hour; and 0, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, and 1,000 µg/mL for non-activated 20-hour. Visible precipitate was observed in treatment medium at ≥500 µg/mL. |
| 870.5395 | (Other Genotoxic Effects) *In vivo* Mouse bone marrow micronucleus—gavage | 48208444 (2011) Acceptable/guideline | Negative. Doses were 0, 500, 1,000 and 2,000 mg/kg by single-dose oral gavage (10 Crl:CD1(ICR) mice/sex/dose). |
| **Neurotoxicity Studies** | | | |
| 870.6200a | Acute neurotoxicity study—gavage (rats) | 48119950 (2006) Acceptable/guideline<br><br>0, 250, 1,000, and 2,000 mg/kg | NOAEL = 2,000 mg/kg (HDT). Adverse effects were not observed at any tested dose levels. |
| 870.6200b | 90-Day neurotoxicity study—dietary (rats) | 48119966 (2009) Acceptable/guideline<br><br>0, 200, 2,000, and 20,000 ppm<br><br>M: 0, 11, 116, and 1,195 mg/kg/day<br><br>F: 0, 14, 137, and 1,404 mg/kg/day | NOAEL = 1,195/1,404 mg/kg/day (M/F) (HDT). Adverse effects were not observed at any tested dose levels. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| **Metabolism Studies** | | | |
| 870.7485 | Metabolism study—ADME (rats) | 48119949 (2010)<br>Acceptable/guideline<br><br>Single gavage dose of 10 or 150 mg/kg/day (low- and high-dose, respectively) of either [CN-$^{14}$C]-cyantraniliprole or [PC-$^{14}$C]-cyantraniliprole | Cyantraniliprole was absorbed readily either at low (10 mg/kg/day) or high (150 mg/kg/day) dose with oral dosing (62-80% of the administered dose was absorbed). The majority of the absorption occurred during the first 48 hours, and the peak plasma concentration was reached at approximately 2 hour after dosing irrespective of the position of label, sex of the test animal, and dose level.<br>Male low dose half-lives: CN $T_{1/2}$ = 42 hrs; PC $T_{1/2}$ = 54 hrs;<br>Female low dose half-lives: CN $T_{1/2}$ = 129 hrs; PC $T_{1/2}$ = 117 hrs;<br>Male high dose half-lives: CN $T_{1/2}$ = 62 hrs; PC $T_{1/2}$ = 55 hrs;<br>Females high dose half-lives: CN $T_{1/2}$ = 65 hrs; PC $T_{1/2}$ = 80 hrs.<br>The distribution data showed that the majority of the dose was initially associated with the GI tract contents and subsequently showed uptake and distribution to all tissues. Female rats retained a greater proportion of $^{14}$C residues than male rats.<br>Cyantraniliprole was readily hydroxylated to form IN-N7B69 and IN-MYX98. IN-N7B69 was further metabolized to a glucuronide. Cyantraniliprole also underwent ring closure to generate IN-J9Z38. The metabolites which were found to be greater than 5% of the administered dose were bis-hydroxy-cyantraniliprole, IN-N7B69, IN-MYX98, INDBC80, and the parent compound.<br>There was very little difference in elimination between rats administered [CN-$^{14}$C]-cyantraniliprole or [PC-$^{14}$C]-cyantraniliprole. Majority of the administered dose was eliminated during the first 24 to 48 hour after administration. The major route of elimination was via feces (approximately 80% of the administered dose). The data show no bioaccumulation). |
| 870.7485 | Disposition during and after multiple dosing—kinetics and metabolism study (male and female rats) | 48119951 (2009)<br>Acceptable/non-guideline<br><br>A mixture of [CN-$^{14}$C]-cyantraniliprole and [PC-$^{14}$C]-cyantraniliprole at a 1:1 mg ratio: 10 mg/kg /day multiple doses by gavage | The data on the tissue concentrations and the tissue percent recovery showed that tissue concentration fell rapidly following the end of dosing. The tissue concentration half-lives ranged from 2.6 days in fat to approximately 6 days in whole blood. Very little tissue accumulation was found.<br>The total percent of the administered dose eliminated via urine was 29% in males and 20% in females and that eliminated via feces was approximately 60% in males and females.<br>Metabolites found in this study were similar to those in the single dose study (MRID 48119949). |
| **Dermal Absorption Toxicity Studies** | | | |
| 870.7600 | Dermal penetration | No dermal penetration study on technical grade is available, but several *in vivo* and *in vitro* dermal penetration studies on three formulations are available. | |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | | |
|---|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results | |
| | *In vivo* dermal absorption—SC formulation (rats) | 48120313 (2009) Acceptable<br><br>200 g/L and 1 g/L | Maximum absorption<br>200 g/L = 0.34% at 498 hrs<br>1 g/L = 0.93% at 498 hrs | DAF<br>200 g/L = 0.02%<br>1 g/L = 0.43%<br><br>Nearly all the applied dose was readily removed from the skin surface with gentle skin washing. |
| | *In vitro* dermal penetration study—SC formulation (rat and human skin) | 48120314 (2009) Acceptable<br><br>200 g/L & 1g/L | Maximum Dermal penetration at 24 hrs:<br><br>Human skin:<br>200 g/L = 0.24%<br>1 g/L = 5.28%<br><br>Rat skin:<br>200 g/L = 3.69%<br>1 g/L = 11.5% | |
| | *In vivo* dermal absorption—SE formulation (rats) | 48120413 (2009) Acceptable<br><br>100 g/L and 1 g/L | Maximum absorption:<br>100 g/L = 1.25% at 498 hrs<br>1 g/L = 1.47% at 498 hrs | DAF<br>100 g/L = 0.25%<br>1 g/L = 0.83%<br><br>Nearly all the applied dose was readily removed from the skin surface with gentle skin washing. |
| | *In vitro* dermal penetration study—SE formulation (rat and human skin) | 48120412 (2009) Acceptable<br><br>100 g/L and 1 g/L | Maximum Dermal penetration at 24 hrs:<br><br>Human skin:<br>100 g/L = 2.7 %<br>1 g/L = 6.1 %<br><br>Rat skin:<br>100 g/L =13.4 %<br>1 g/L = 10.7 % | |
| | *In vivo* dermal absorption—OD formulation (rats) | 48120209 (2008) Acceptable<br><br>100 g/L and 1 g/L | Maximum absorption<br>100 g/L = 1.36% at 498 hrs<br>1g/L = 0.74% at 498 hrs | DAF<br>100 g/L = 0.06%<br>1 g/L = 0.03%<br><br>Nearly all the applied dose was readily removed from the skin surface with gentle skin washing. |
| | *In vitro* dermal penetration study—OD formulation (rat and human skin) | 48120210 (2008) Acceptable<br><br>100 g/L and 1 g/L | Maximum Dermal penetration at 24 hrs:<br><br>Human skin:<br>100 g/L = 0.25 %<br>1 g/L = 0.86%<br><br>Rat skin:<br>100 g/L = 10.5%<br>1 g/L = 20.2 % | |
| | *In vivo* dermal absorption—cyantraniliprole/ thiamethoxam WG formulation (A16901B) formulation (rat skin) | 48432611 (2011) Acceptable<br><br>Slurry concentrate, 1/20 and 1/267 dilution, correspond to 10.0, 1.0, and 0.75 mg/rat respectively | At 24 hours after dosing: 0.08%, 0.92%, and 1.23% of the applied dose were absorbed with slurry concentrate, 1/20 dilution and 1/267 dilution, respectively. | DAF for WG formulation:<br><br>Slurry concentrate 1/20 dilution = 0.005%<br><br>Slurry concentrate 1/267 dilution = 0.07% |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | | |
|---|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results | |
| | *In vitro* dermal penetration study—cyantraniliprole/ thiamethoxam WG formulation (A16901B) formulation (rat skin) | 48432513 (2011) Acceptable<br><br>Slurry concentrate, 1/20 dilution and 1/267 dilution | At 24 hours after dosing, the total absorbable dose were 0.133%, 2.57%, and 15.78% of the applied dose for slurry concentrate, 1/20 dilution and 1/267 dilution, respectively. | Nearly all the applied dose was readily removed from the skin surface with gentle skin washing. |
| | *In vivo* dermal absorption—cyantraniliprole/ thiamethoxam WG formulation (A16901B) formulation (human skin) | 48432512 (2011) Acceptable<br><br>Slurry concentrate, 1/20 dilution and 1/267 dilution | At 24 hours after dosing, the total absorbable dose were 0.008%, 0.128% and 0.92% of the applied dose for slurry concentrate, 1/20 dilution and 1/267 dilution, respectively. | |
| | *In vitro* dermal penetration study—cyantraniliprole/ thiamethoxam WG formulation (A16901B) formulation (human skin) | 48432412 (2011) Acceptable<br><br>Slurry concentrate, 1/534 dilution and 1/1,600 dilution | The total absorbable dose expressed as percent of the applied dose over 24 hours was 0.010, 1.597, and 0.561% for concentrate slurry, 1/534 w/w dilution, and 1/167 w/w dilution, respectively. Irrespective of the applied dose, greater than 97% of the applied dose remained on the skin surface after a 24 hour exposure period and was readily removed by gentle skin washing. Very low proportions of the dose were associated with the *stratum corneum* and the remaining epidermal membrane. | |
| **Immunotoxicity Toxicity Studies** | | | | |
| 870.7800 | 28-Day immunotoxicity study—dietary (rats)<br><br>[assess primary humoral response to sheep red blood cells (sRBC)] | 48119971 (2009) Acceptable/guideline<br><br>0, 20, 200, 2,000, and 20,000 ppm<br><br>M: 0, 1.7 , 17, 166, and 1,699 mg/kg/day<br><br>F: 0, 1.8 , 18, 172, and 1,703 mg/kg/day | Systemic toxicity NOAEL = 1,699/1,703 mg/kg/day (M/F) (highest dose tested). A LOAEL was not established.<br><br>The SRBC-specific IgM ELISA results did not indicate any treatment-related immunosuppressive effects. Therefore, the immunotoxicity NOAEL = 1,699/1,703 mg/kg/day (M/F). | |
| 870.7800 | 28-Day immunotoxicity study—dietary (mice)<br><br>[assess primary humoral response to sheep red blood cells (sRBC)] | 48119972 (2009) Acceptable/guideline<br><br>0, 20, 150, 1,000, or 7,000 ppm<br><br>M: 0, 3.0, 23, 154, or 1,065 mg/kg/day<br><br>F: 0, 4.1, 32, 224, or 1,386 mg/kg/day | The systemic toxicity NOAEL = 1,065/1,386 mg/kg/day (M/F) (highest dose tested). The LOAEL was not established.<br><br>The SRBC-specific IgM ELISA results did not indicate any treatment-related immunosuppressive effects. There were no statistical differences in quantity of SRBC-specific IgM in any treatment group when compared with the vehicle controls. Evaluation of individual animal data did not show any trend or distribution that would demonstrate significant suppression of SRBC-specific antibody response. Therefore, the immunotoxicity NOAEL = 1,065/1,386 mg/kg/day (M/F) (highest dose tested). | |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| **Metabolite: IN-JSE76 Toxicity Studies** | | | |
| 870.3050 | 28-Day feeding study with IN-JSE76 (up to 20,000ppm) | 48119983 (2010) Acceptable/guideline<br><br>48208474 (2010) Supplemental study to 48119983<br><br>0, 100, 400, 3,000, and 20,000ppm<br><br>M: 0, 7, 29, 212, and 1,445 mg/kg/day<br><br>F: 0, 8, 31, 232, and 1,471 mg/kg/day | NOAEL = 1,445/1,471 mg/kg /day (M/F) (highest dose tested).<br><br>A LOAEL was not established because toxicity was not seen at any tested dose level. |
| 870.5100 | Bacterial reverse mutation test (*S. typhimurium* & *E. coli)* | 48119976 (2009) Acceptable/guideline | Negative.<br>Toxicity test: 1.5, 5.0, 15, 50, 150, 500, 1,500, and 5,000 μg/plate.<br>Confirmatory assay, 50, 150, 500, 1,500, and 5,000 μg/plate. |
| 870.5300 | *In vitro* mammalian cell gene mutation test (CHO/HGPRT assay) | 48119974 (2009) Acceptable/guideline | Negative.<br>Test concentrations: 0, 100, 150, 500, 1,000, and 1,500 μg/mL. |
| 870.5375 | *In vitro* mammalian chromosome aberration test with human lymphocytes | 48119975 (2009) Acceptable/guideline | Negative.<br>-S9: 0, 313, 625,1,250, and 2,500 μg/mL-4-hr exposure;<br>-S9 156, 313, 625, 1,000, 1,500, and 2,000 μg/mL 20-hr exposure; and<br>+S9: 156, 313, 625, 1,250, and 2,500 μg/mL-4-hr exposure. |
| **Metabolite: IN-PLT97 Toxicity Studies** | | | |
| 870.5100 | Bacterial reverse mutation test (*S. typhimurium* & *E. coli)* | 48122580 (2009) Acceptable/guideline | Negative.<br>0, 50, 150, 500, 1,500, and 5,000 μg/plate were tested in the confirmatory test. The test substance was administered as a workable suspension in DMSO. |
| 870.5300 | *In vitro* mammalian cell gene mutation test (CHO/HGPRT assay) | 48122582 (2010) Acceptable/guideline | Negative.<br>Test concentrations: 10, 25, 50, 100, and 150 μg/ml. Exposure time = 5 hours. Precipitation occurred at ≥ 150 μg/ml. |
| 870.5375 | *In vitro* mammalian chromosome aberration test with human lymphocytes | 48122581 (2011) Acceptable/guideline | Negative.<br>-S9 &+S9: 50, 100, 200, 400, 800, and 1,550 μg/mL -4 hr exposure.<br>-S9: 25, 50, 100, 200, 500, 1000, and 1,550 μg/mL - 20-hr exposure. |

| Table B.2.3 Subchronic, Chronic, and Other Toxicity Profile | | | |
|---|---|---|---|
| Guideline No. | Study Type | MRID No. (year)/ Classification /Doses | Results |
| **Metabolite: IN-F6L99 Toxicity Studies** | | | |
| 870.5100 | Bacterial reverse mutation test (*S. typhimurium* & *E. coli)* | 46979931 (2006) Acceptable/guideline | Negative. Initial toxicity (Trial I): 33.3, 66.7, 100, 333, 667, 1,000, 3,333, and 5,000 μg/plate. Confirmatory test (Trail II): 333, 667, 1,000, 3,333, and 50,00 μg/plate . |
| **Metabolite: IN-N5M09 Toxicity Studies** | | | |
| 870.5100 | Bacterial reverse mutation test (*S. typhimurium* & *E. coli)* | 48119982 (2009) Acceptable/guideline | Negative. Toxicity test (Trial I):1.5, 5.0, 15, 50, 150, 500 1,500, and 5,000 μg/plate. Confirmatory assay(Trial II): 50, 150, 500, 1,500, and 5,000 μg/plate. |
| **Other (Non-Guideline) Studies (Mechanistic Studies)** | | | |
| | Adrenal and thyroid mechanistic study (rats) | 48119973 (2010) Acceptable/non-guideline<br><br>For thyroid effect (female rats): 20,000 ppm (1,903 mg/kg/day) for 29 days<br><br>For adrenal effect (male rats): 20,000 ppm (1,230 mg/kg/day) for 93 days | In 20,000 ppm females, increased liver and thyroid weights and minimal thyroid follicular cell hypertrophy were seen. These effects were associated with increased hepatic UDP-glucuronyltransferase (UDPGT) activity and reduced serum $T_4$ and increased TSH levels. |
| | 90-Day adrenal mechanistic study—feeding (male mice) | 48119985 (2010) Acceptable/non-guideline<br><br>7,000 ppm (1,120 mg/kg/day) for 93 days | Cyantraniliprole at 1,120 mg/kg/day did not adversely affect the following parameters: survival, clinical signs of toxicity, body weight, food consumption, or food efficiency. No gross or microscopic pathology effects were attributed to test substance exposure. No adverse effects on adrenal cortical structure or function were found. Basal urinary corticosterone was comparable between the control and treated groups. The electron microscopy results showed that cyantraniliprole did not affect adrenal cortical cell structure. The finding of the microvesiculation of the adrenal cortex in male mice at ≥ 50 ppm in the 90-day study (MRID 48119943) was not duplicated in this study where male mice were fed dietary concentration of 7,000 ppm (1,120 mg/kg/day) of cyantraniliprole for 93 days. |
| | *In vitro* thyroid peroxidase inhibition<br><br>[thyroid preparation derived from Yucatan pig, microswine] | 48119979 (2010) Acceptable/non-guideline<br><br>2, 5, 10, 20, 50, 100, 200, and 400 μM<br><br>Positive control: Propylthiouracil (PTU) | Cyantraniliprole did not cause inhibition of thyroid peroxidase at any concentration tested; therefore, an $IC_{50}$ value for cyantraniliprole was unable to be determined. The positive control, PTU at 7.2 μM caused a 50% reduction in enzyme activity. |

## B.3 Hazard Identification and Endpoint Selection

### B.3.1 Acute Reference Dose (aRfD) - General Population

Not established. An endpoint attributable to a single dose was not seen in the database (including the pre-natal toxicity studies in rats and rabbits).

### B.3.2 Chronic Reference Dose (cRfD)

Study Selected
One-Year Oral Toxicity Study in Dogs

MRID No.
48119960

Dose and Endpoint for Establishing cRfD
NOAEL = 1 mg/kg/day. LOAEL = 6 mg/kg/day based on effects indicative of liver toxicity (increased liver weights and alkaline phosphatase activity, and significant decreases in albumin levels).

Uncertainty Factor (UF)
100X (10X intraspecies, 10X interspecies, 1X FQPA).

Comments about Study/Endpoint/Uncertainty Factor
The one-year dog study is appropriate for both the duration and population of concern. The dogs appear to be more sensitive to the liver effects than rats. The results of the one-year dog study provide the most sensitive LOAEL (6 mg/kg/day) for liver effects. The POD is also protective of the thyroid effects seen in all toxicity studies in rats, including the 2-generation reproduction study (LOAEL = 14 mg/kg/day).

$$\text{cRfD} = \frac{1 \text{ mg/kg/day}}{100} = 0.01 \text{ mg/kg/day}$$

$$\text{cPAD} = \frac{0.01 \text{ mg/kg/day}}{1} = 0.01 \text{ mg/kg/day}$$

### B.3.3 Incidental Oral Exposure (Short- and Intermediate-Term)

Selected Study
90-Day Oral Toxicity Study in Dogs

MRID No.
48119947, 48119948

Dose and Endpoint for Risk Assessment
NOAEL = 3 mg/kg/day. LOAEL = 32 mg/kg/day based on a collection of treatment-related effects indicative of liver toxicity. The effects include 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 increased liver weights in males and females.

Uncertainty Factor (UF)
100X (10X intraspecies, 10X interspecies, 1X FQPA).

Comments about Study/Endpoint/Margins of Exposure
This study is appropriate for the duration of exposure. While the population of concern is for children engaged in hand-to-mouth behavior, the POD (NOAEL of 3 mg/kg/day) selected from the 90-day study is protective of the effects seen in the 2-generation reproduction study in rats.

### B.3.4 Dermal Exposure (Short-, Intermediate- and Long-Term)

Systemic toxicity was not seen in the 28-day dermal toxicity in rats up to the limit dose (1000 mg/kg/day). The target organs of toxicity were looked at in this study. In addition, there are no concerns for developmental, reproductive, or neurotoxicity. The lack of effects in the dermal study is consistent with the low dermal absorption factor of 1%.

### B.3.5 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study
28-Day Inhalation Toxicity Study - Rats

MRID No.
48663602

Dose and Endpoint for Risk Assessment
NOAEL =0.1 mg/L. A LOAEL was not established since the highest concentration (0.1 mg/L) tested did not demonstrate any adverse effects.

Uncertainty Factor (UF)
Short-term = 30X (10X intraspecies, 3X interspecies, 1X FQPA for residential only).
Intermediate-term = 100X (10X intraspecies, 3X interspecies, 3X database uncertainty).

The UF is reduced from the default 100X because the RfC methodology was used to calculate inhalation risk. The RfC methodology accounts for the pharmacokinetic (PK) differences between rats and humans, **but does not account for the pharmacodynamic (PD) differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X. For intermediate-term exposures, the occupational and residential LOC for MOE = 100. An additional 3X UF was added to the intermediate-term exposure scenarios. This was based on a number of factors:

- The database indicates a progression in the severity of toxicity with time;
- The chemical has a low vapor pressure, and;
- The 28-day inhalation study is protective of critical effects.

Although a 10X UF is typically applied for extrapolating for durations of exposure, a 3X UF is sufficient for cyantraniliprole. This conclusion is supported by the observation that the LOAEL for the multigeneration reproduction toxicity study in rats (a long-term study) is ≈3X lower than the LOAEL for the 28-day oral toxicity study in rats (14 versus 53 mg/kg/day, based on thyroid toxicity). In addition, the lack of toxicity in the acute inhalation toxicity study at a dose 50X higher than the 28-day inhalation study supports that a 3X UF for duration of exposure extrapolation is sufficiently protective.

Comments about Study/Endpoint/Margins of Exposure

The route-specific 28-day inhalation toxicity study is appropriate to use for this assessment. Although this 28-day inhalation toxicity study in rats could be tested[14] at higher concentrations and adverse effects were not identified in the study, it is appropriate for risk assessment. This conclusion is based on a weight of evidence (WOE) approach that takes into consideration the overall toxicity profile for this chemical. Liver and thyroid toxicity are the critical effects identified in the cyantraniliprole database, with thyroid toxicity being most likely the result of liver enzyme activation. Although the inhalation study did not measure thyroid hormones, it does provide histopathology data on the thyroid; clinical chemistry observations for liver enzymes; liver histopathology; and liver weights (all of the endpoints of concern). Since the thyroid effect is secondary to liver effect and the liver is not affected in this study, the inhalation study provides a conservative NOAEL. While the POD selected for the inhalation risk assessment may be artificially low (i.e. resulting in an overestimation of risk) due to dose selection, the inhalation study is selected because it is route-specific and protective of the effects seen throughout the database.

## B.4 Human Equivalent Concentrations (HEC) and Human Equivalent Dose Calculations

The HEC and human equivalent dose calculations were based on the results of a 28-day rat inhalation study in rats (MRID 48697401). In this study, cyantraniliprole was administered (as an aerosol) to Crl:CD(SD) rats (10/sex/dose) for 6 hours/day, 5 days/week, for 4-weeks. The test animals were exposed nose-only to target concentrations of 0 (air control), 1, 10, or 100 mg/m³ of cyantraniliprole (equivalent to 0.001, 0.01, and 0.1 mg/L, respectively). Adverse effects were not seen at any concentration tested, although laryngeal metaplasia was considered treatment related but not adverse at 0.1 mg/L. The NOAEL was 0.1 mg/L.

RDDR for Cyantraniliprole

Calculations used to estimate the inhalation risk to humans from aerosols are dependent not on the regional gas dose ratio (RGDR) as for gases, but on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter [mass median aerodynamic diameter (MMAD)] and the geometric standard deviation ($\sigma_g$), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the affected region (r) or target tissue.

[14] An acute inhalation toxicity study tested concentrations 50-fold higher than the highest concentration in the 28-day inhalation study.

$RDDR_r = (RDD_r/\text{Normalizing Factor})_{A\,/}\ (RDD_r/\text{Normalizing Factor})_H$

As with calculations for gases, the affected regions and potential target tissues are the three respiratory regions (extrathoracic, tracheobronchial, and pulmonary). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and $\sigma_g$ defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry." The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the PK differences, **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

Regional Deposited Dose Ratio (RDDR)
MMAD = 3.00
Sigma g = 2.30

| SPECIES | Body Weight (g) | Minute Ventilation (VE, ml) | deposited fraction |
|---|---|---|---|
| rat | 236 | 171.5 | 0.587 |
| human | 70000 | 13800.0 | 0.759 |
| RATIO | | | 0.734 |

$RDDR = (VE/SA)_{animal} \div (VE/SA)_{human} \times \text{deposited fraction}_{animal} \div \text{deposited fraction}_{human}$
$= (171.5/236)_{animal} \div (13800/70000)_{human} \times 0.587 \div 0.759$
$= 2.8$

Example for HEC calculations for short-term occupational exposure:
Assume workers will be in the greenhouse for 8 hrs/day and 5 days/week:

$HEC = NOAEL_{study} \times (\text{daily duration of exposure}_{animal} \div \text{daily duration of exposure}_{human}) \times (\text{days/week of exposure}_{animal} \div \text{days/week of exposure}_{human}) \times RDDR$

$HEC = 0.1\ mg/L \times (6 \div 8) \times (5 \div 5) \times 2.8 = 0.21\ mg/L$

**Table B.4. HEC Array for Non-Occupational and Occupational Risk Assessment**

| Relevant Study | LOAEL (mg/L) | NOAEL (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | inter | intra | UF |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Short-& Intermediate-Term Occupational Exposure | | | | | | | | | | | |
| Inhalation – Rat (MRID 48697401 ) 28-day | Not Obs. | 0.1 | 6 | 8 | 5 | 5 | 2.8 | 0.21 | 3 | 10 | NA |
| Short-& Intermediate-Term Non-Occupational (Residential) Exposure | | | | | | | | | | | |
| Inhalation – Rat (MRID 48697401 ) 28-day | Not Obs. | 0.1 | 6 | 24 | 5 | 7 | 2.8 | 0.05 | 3 | 10 | NA |

| **Table B.4. HEC Array for Non-Occupational and Occupational Risk Assessment** | |
|---|---|
| Long Term Exposure: Not Appropriate | |
| Key: | *Dh*: Anticipated daily human exposure (hrs/day) |
| *LOAEL*: Lowest observed adverse effect level | *Wh*: Anticipated weekly human exposure (days/week) |
| *Da*: Daily animal exposure (hrs/day) | *HC:* Human Concentration |
| *Wa*: Weekly animal exposure (days/week) | *HEC*: Human Equivalent Concentration |
| *RRDR*: Regional Deposited Dose Ratio | *intra*: intraspecies variation uncertainty factor |
| *inter*: interspecies extrapolation uncertainty factor | *UF*: Other uncertainty factor(s) |

Summary of Human Equivalent Concentrations

| Occupational Short-Term | | | | | | |
|---|---|---|---|---|---|---|
| Study | NOAEL (m/L) systemic | RDDR | Daily Duration (6 hrs rat/8 hrs human) | Weekly (days/week) Duration (rat 5 days/human 5 days) | HEC (mg/L) | UF |
| 28-day rat | 0.1 | 2.8 | 0.75 | 1 | 0.21 | 30 |
| Non-Occupational Short-Term | | | | | | |
| Study | NOAEL (m/L) systemic | RDDR | Daily Duration (6 hrs rat/24 hrs human) | Weekly (days/week) Duration (rat 5 days/human 7 days) | HEC (mg/L) | UF |
| 28-day rat | 0.1 | 2.8 | 0.25 | 0.714 | 0.05 | 30 |

Human Equivalent Doses

The HEC is in mg/L but exposure data are in mg/kg/day. Therefore, conversion of the human mg/L value to human mg/kg/day was conducted as follows:

Inhalation to Oral Equation:
dose (systemic HEC value) mg/L × A × CF (L/hr/kg) × D (hours) × AF = mg/kg;

**Occupational:** (0.21 mg/L) × 1 × 6 × 8 × 1 = 10.08 mg/kg/day

**Residential:** (0.05 mg/L) × 1 × 6 × 24 × 1 = 7.2 mg/kg/day

Where:

A absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route. A default A of 1 was used.

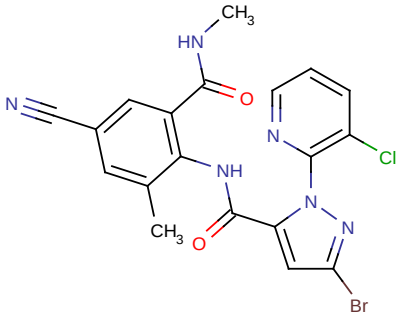
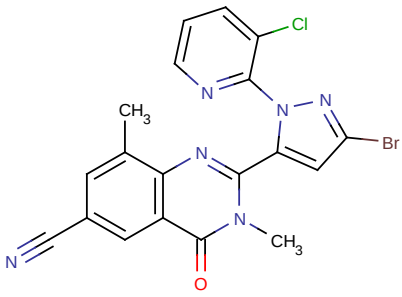
CF Conversion Factor: A L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (A human conversion factor of 6 for ages 10-30 yrs was used for both occupational and non-occupational calculations).

D Duration: Duration of daily animal or human exposure (hours). The default assumption for occupational is 8 hrs while non-occupational could potentially be 24 hrs.

AF Activity Factor: The default human activity factor is 1.

## Appendix C. Metabolism Summary Table

**Table C.1 Tabular Summary of Metabolites and Degradates**

| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
|---|---|---|---|
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| Cyantraniliprole<br>DPX-HGW86<br>SYN545377<br><br>CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6 [(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide<br><br>  | Rice | Foliage: 57.4 (0.232) [CN]<br>48.7 (0.205) [PC]<br>Grain: 62.7 (0.007) [CN]<br>46.2 (0.014) [PC]<br>Straw: 44.9 (0.125) [CN]<br>42.1 (0.125) [PC] | |
| | Lettuce | Leaves: 37.1 (0.004) [CN]<br>69.0 (0.039) [PC] | |
| | Cotton | Gin byproducts:<br>25.6 (0.025) [CN]<br>46.8 (0.011) [PC] | |
| | Tomato | Leaves: 43.4 (0.562) [CN/PC] | |
| | Rotational Crops | | |
| | Ruminant | Milk: 39.5 (0.030) [CN]<br>49.6 (0.070) [PC]<br>Liver: 17.1 (0.073) [CN]<br>27.3 (0.136) [PC]<br>Kidney: 12.7 (0.017) [CN]<br>18.9 (0.0.040) [PC]<br>Muscle: 30.3 (0.009) [CN]<br>15.3 (0.006) [PC]<br>Fat: 30.8 (0.016) [CN]<br>45.4 (0.054) [PC] | |
| | Poultry | Egg white: 32.5 (0.084) [CN]<br>41.7 (0.085) [PC]<br>Egg yolk: 10.3 (0.009) [CN]<br>9.3 (0.008) [PC] | |
| | Rat | | |
| | Water | | |
| IN-J9Z38<br><br>CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile<br><br>  | Rice | Foliage: 16.2 (0.066) [CN]<br>22.1 (0.093) [PC]<br>Grain: 10.2 (0.001) [CN]<br>Straw: 18.4 (0.051) [CN]<br>14.3 (0.042) [PC] | |
| | Lettuce | Leaves: 10.0 (0.005) [PC] | |
| | Cotton | | Gin byproducts |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | Egg white: 29.2 (0.075) [CN]<br>17.1 (0.034) [PC]<br>Egg yolk: 13.1 (0.011) [PC] | Liver |
| | Rat | | |
| | Water | | |
| IN-JCZ38 | Rice | | Foliage, grain, straw |

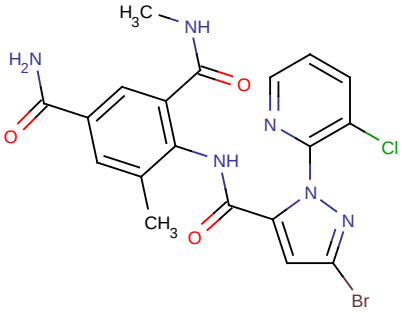
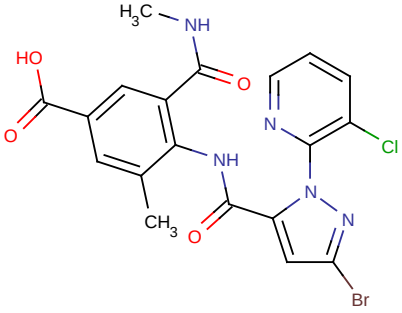
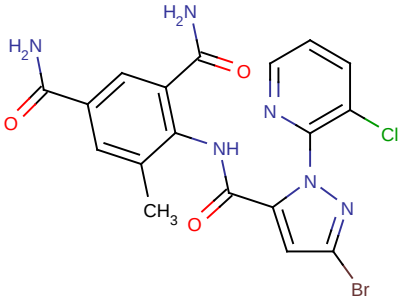
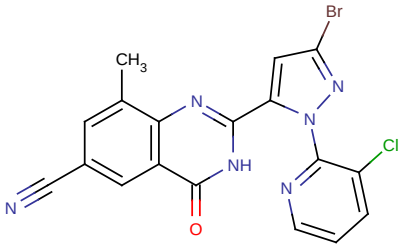
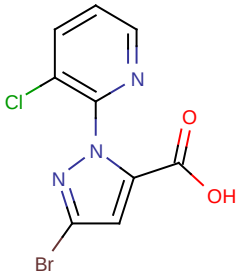
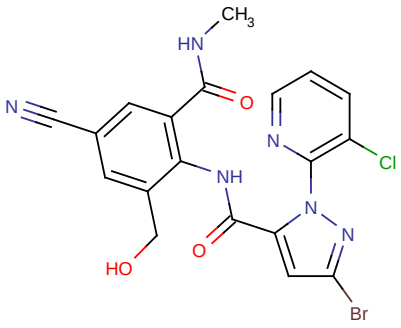
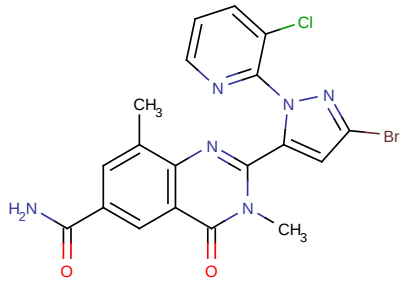
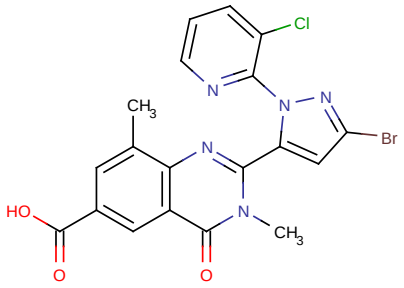
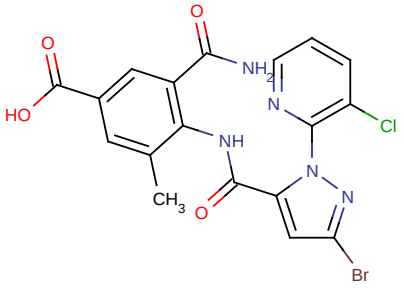
| Table C.1 Tabular Summary of Metabolites and Degradates | | | |
|---|---|---|---|
| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| CAS Name: 4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-N'3',5-dimethyl-1,3-benzenedicarboxamide  | Cotton | | Gin byproducts |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | | Milk, liver |
| | Poultry | | |
| | Rat | | |
| | Water | | |
| IN-JSE76<br><br>CAS Name: 3-(Methylaminocarbonyl)-4-[[[3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methylbenzoic acid  | Rice | | Foliage, grain, straw |
| | Cotton | | Gin byproducts |
| | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | Egg yolk |
| | Rat | | |
| | Water | | |
| IN-K7H19<br><br>CAS Name: 4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methyl-1,3-benzenedicarboxamide  | Rice | | Straw |
| | Cotton | | Gin byproducts |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | | Milk, liver, kidney, muscle, fat |
| | Poultry | | |
| | Rat | | |
| | Water | | |
| IN-MLA84<br><br>CAS Name: 2-[3-Bromo-1-(3-chloro-2- | Rice | | Foliage, straw |
| | Lettuce | | Leaves (+ IN-NXX70) |

**Table C.1 Tabular Summary of Metabolites and Degradates**

| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
|---|---|---|---|
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarbonitrile  | Cotton | | Gin byproducts |
| | Tomato | | Leaves (+ IN-NXX70) |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | Egg white: 18.7 (0.049) [CN]<br>18.2 (0.037) [PC]<br>Egg yolk: 11.6 (0.011) [CN]<br>16.8 (0.015) [PC] | Liver |
| | Rat | | |
| | Water | | |
| IN-DBC80<br><br>CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxylic acid  | Rice | | Foliage, grain, straw |
| | Cotton | | |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | |
| | Rat | | |
| | Water | | |
| IN-N7B69<br><br>CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-(hydroxymethyl)-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carbonitrile  | Rice | | Foliage, grain |
| | Cotton | | Gin byproducts |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | Milk: 11.8 (0.008) [CN] | |
| | Poultry | | Liver |
| | Rat | | |
| | Water | | |
| IN-K5A77<br><br>CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8- | Rice | | Foliage, straw |
| | Cotton | | |

| Table C.1 Tabular Summary of Metabolites and Degradates | | | |
|---|---|---|---|
| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| dimethyl-4-oxo-6-quinazolinecarboxamide  | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | |
| | Rat | | |
| | Water | | |
| IN-K5A78<br><br>CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarboxylic acid  | Rice | | Foliage, grain, straw |
| | Cotton | | |
| | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | Liver |
| | Rat | | |
| | Water | | |
| IN-K5A79<br><br>CAS Name: 3-(Aminocarbonyl)-4-[[[3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-methylbenzoic acid  | Rice | | |
| | Cotton | | |
| | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | Egg white, yolk, liver |
| | Rat | | |
| | Water | | |
| IN-HGW87 | Rice | | |

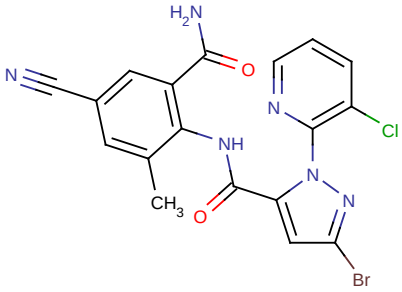
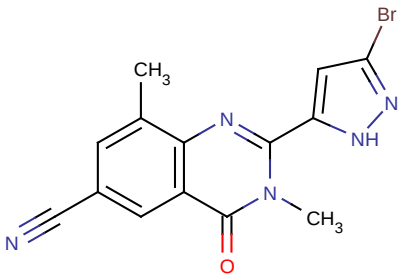
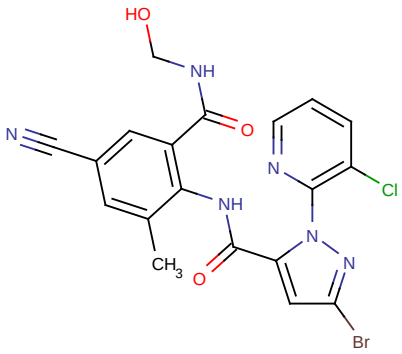
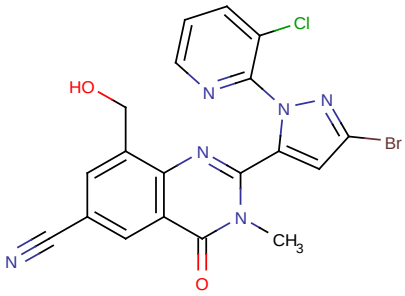
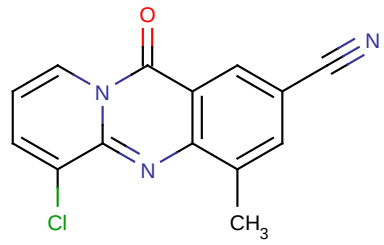
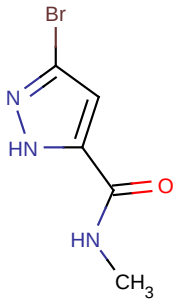
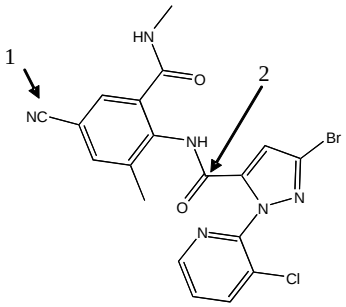
| Table C.1 Tabular Summary of Metabolites and Degradates | | | |
|---|---|---|---|
| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| CAS Name: N-[2-(Aminocarbonyl)-4-cyano-6-methylphenyl]-3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide  | Lettuce | | Leaves |
| | Cotton | | |
| | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | Egg yolk: 12.0 (0.011) [CN] | Egg white |
| | Rat | | |
| | Water | | |
| IN-QKV54<br><br>CAS Name: 2-[3-Bromo-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile  | Rice | | |
| | Lettuce | | Leaves |
| | Cotton | | Gin byproducts |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | | |
| | Poultry | | |
| | Rat | | |
| | Water | | |
| IN-MYX98 | Rice | | |

**Table C.1 Tabular Summary of Metabolites and Degradates**

| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
|---|---|---|---|
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-[[(hydroxymethyl) amino]carbonyl]-6-[(methylphenyl]-1*H*-pyrazole-5-carboxamide  | Cotton | | |
| | Tomato | | Leaves |
| | Rotational Crops | | |
| | Ruminant | Milk: 15.1 (0.011) [CN]<br>18.3 (0.026) [PC] | Liver, kidney |
| | Poultry | | Egg white, yolk, liver |
| | Rat | | |
| | Water | | |
| IN-NBC94<br><br>CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3-methyl-4-oxo-8-hydroxymethyl-6-quinazolinecarbonitrile  | Rice | | |
| | Cotton | | |
| | Tomato | | |
| | Rotational Crops | | |
| | Ruminant | | Fat |
| | Poultry | | Egg white, yolk, liver |
| | Rat | | |
| | Water | | |
| IN-N5M09  | Processing Conditions | | |

| Table C.1 Tabular Summary of Metabolites and Degradates | | | |
|---|---|---|---|
| Chemical Name (other names in parenthesis) and Structure | Matrix | Percent TRR (*ppm*) | |
| | | Matrices - Major Residue (>10%TRR) | Matrices - Minor Residue (<10%TRR) |
| IN-F6L99  | Processing Conditions | | |

a Cyantraniliprole is labeled with carbon-14 either in the cyano group [CN] or in the carbonyl next to the pyrazole ring [PC]. The label positions are depicted below.



1. [CN-$^{14}$C]-cyantraniliprole
2. [PC-$^{14}$C]-cyantraniliprole

## Appendix D. Physical/Chemical Properties

| Table D.1 Physicochemical Properties of the Technical Grade of Cyantraniliprole | | |
|---|---|---|
| Parameter | Value | Reference |
| Molecular Weight | 473.72 g/mol | MRID 48208438 |
| Physical state | White fine powder solid | |
| Melting point | 224 ºC | |
| Density | 1.4965 g/cm$^3$ at 20 ºC | |
| pH | pH 4: Stable<br>pH 7: Stable | |
| Water solubility (20°C) | 14.24 mg/L | |
| Solvent solubility (g/L at 20°C) | Acetone 6.54<br>Ethyl acetate 1.96<br>Dichloromethane 5.05<br>Toluene 0.576<br>n-Octanol 0.79<br>Methanol 4.73<br>o-Xylene 0.29<br>Acetonitrile 2.45 | |
| Vapor pressure (20°C) | 5.13 x $10^{-15}$ Pa<br>3.85×$10^{-17}$ mm Hg | |
| Henry's Law Constant (20 °C) | at pH7 = 1.7 x $10^{-18}$ atmosphere.m$^3$/mole | |
| Dissociation constant, pKa (20°C) | 8.80 $\pm$ 1.38 | |
| Octanol/water partition coefficient, log $K_{OW}$ (20°C) | Log Kow = 1.94 $\pm$ 0.11 | |
| Hydrolysis and photolysis | pH 9: Hydrolyzed very rapidly with a half-life of <1 day. One major metabolite was observed: IN-J9Z38. Photolysis: 0.233 days at 40º latitude in the summer to 4.12 days at 60º latitude in the winter. | |

## Appendix E. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; ExpoSAC Policy 14 and 15.1 (SOPs for Seed Treatment); and the Residential SOPs (Lawns/Turf; Gardens and Trees; Indoor Environments), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[15].

[15] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html

## Appendix F. Occupational Exposure/Risk Summary Tables

**Table F.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole**

| Exposure Scenario | Crop or Target[a] | Baseline Inhalation Unit Exposure[b] | Maximum Application Rate[c] | Area Treated or Amount Handled Daily[d] | Baseline Inhalation | |
|---|---|---|---|---|---|---|
| | | | | | Dose[e] | MOE[f] |
| | | *µg/lb ai* | *lb ai/A* | *Acres* | *mg/kg/day* | *ST LOC = 30 IT LOC = 100* |
| **Mixer/Loader** | | | | | | |
| Mixing/Loading Dry Flowables for Aerial Application | Sod Farms | 8.96 | 0.133 | 350 | 0.00520 | 1,900 |
| | Typical Field Crops | | 0.175 | | 0.00686 | 1,500 |
| Mixing/Loading Dry Flowables for Airblast Application | Nursery Plants | | 0.131 | 20 | 0.000294 | 34,000 |
| Mixing/Loading Dry Flowables for Chemigation Application Only | Typical Field Crops | | 0.175 | 350 | 0.00686 | 1,500 |
| | Greenhouse Plants | | 0.131 | 60 | 0.000883 | 11,000 |
| | Nursery Plants | | | | | |
| Mixing/Loading Dry Flowables for Groundboom Application | Golf Courses (tees and greens only) | | 0.133 | 5 | 0.0000743 | 140,000 |
| | Golf Courses (fairways, tees, and greens) | | 0.133 | 40 | 0.000594 | 17,000 |
| | Field-Grown Ornamentals | | 0.131 | 40 | 0.000588 | 17,000 |
| | Nursery Plants | | 0.131 | 60 | 0.000883 | 11,000 |
| | Greenhouse Plants | | | | | |
| | Sod Farms | | 0.133 | 80 | 0.00119 | 8,500 |
| | Typical Field Crops | | 0.175 | 80 | 0.00156 | 6,500 |
| Mixing/Loading Liquids for Aerial Application | Orchard Crops | 0.219 | 0.133 | 350 | 0.000128 | 79,000 |
| | Sod Farms | | 0.313 | 350 | 0.000300 | 34,000 |
| | Typical Field Crops | | 0.133 | 350 | 0.000128 | 79,000 |
| | High-Acreage Field Crops | | 0.133 | 1200 | 0.000436 | 23,000 |
| Mixing/Loading Liquids for Airblast Application | Nursery Plants | | 0.261 | 20 | 0.0000143 | 700,000 |
| | Orchard Crops | | 0.133 | 40 | 0.0000145 | 700,000 |
| Mixing/Loading Liquids for Chemigation | Orchard Crops | | 0.391 | 350 | 0.000375 | 27,000 |
| | Sod Farms | | 0.313 | 350 | 0.000300 | 34,000 |
| | Typical Field Crops | | 0.133 | 350 | 0.000128 | 79,000 |
| | High-Acreage Field Crops | | 0.133 | 350 | 0.000128 | 79,000 |
| | Greenhouse Plants | | 0.261 | 60 | 0.0000429 | 230,000 |
| | Nursery Plants | | 0.391 | 60 | 0.0000643 | 160,000 |
| Mixing/Loading Liquids for Groundboom Application | Golf Courses (tees and greens only) | | 0.313 | 5 | 0.00000429 | 2,300,000 |
| | Golf Courses (fairways, tees, and greens) | | 0.313 | 40 | 0.0000343 | 290,000 |
| | Field-Grown Ornamentals | | 0.261 | 40 | 0.0000286 | 350,000 |
| | Nursery Plants | | 0.391 | 60 | 0.0000643 | 160,000 |
| | Greenhouse Plants | | 0.261 | 60 | 0.0000429 | 230,000 |
| | Sod Farms | | 0.313 | 80 | 0.0000686 | 150,000 |
| | Typical Field Crops | | 0.133 | 80 | 0.0000291 | 350,000 |
| | High-Acreage Field Crops | | 0.133 | 200 | 0.0000728 | 140,000 |
| **Applicator** | | | | | | |

| Table F.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target[a] | Baseline Inhalation Unit Exposure[b] | Maximum Application Rate[c] | Area Treated or Amount Handled Daily[d] | Baseline Inhalation | |
| | | | | | Dose[e] | MOE[f] |
| | | *µg/lb ai* | *lb ai/A* | *Acres* | *mg/kg/day* | *ST LOC = 30 IT LOC = 100* |
| Applying Sprays for Aerial Application | Orchard Crops | 0.068 | 0.133 | 350 | 0.0000395 | 260,000 |
| | Sod Farms | | 0.133 | 350 | 0.0000394 | 260,000 |
| | Typical Field Crops | | 0.175 | 350 | 0.0000521 | 190,000 |
| | High-Acreage Field Crops | | 0.133 | 1200 | 0.000135 | 75,000 |
| Applying Sprays for Airblast Application | Nursery Plants | 4.71 | 0.131 | 20 | 0.000155 | 65,000 |
| | Orchard Crops | | 0.133 | 40 | 0.000313 | 32,000 |
| Applying Sprays for Groundboom Application | Golf Courses (tees and greens only) | 0.34 | 0.133 | 5 | 0.00000281 | 3,600,000 |
| | Golf Courses (fairways, tees, and greens) | | 0.133 | 40 | 0.0000225 | 450,000 |
| | Field-Grown Ornamentals | | 0.131 | 40 | 0.0000224 | 450,000 |
| | Nursery Plants | | 0.131 | 60 | 0.0000335 | 300,000 |
| | Greenhouse Plants | | | | | |
| | Sod Farms | | 0.133 | 80 | 0.0000450 | 220,000 |
| | Typical Field Crops | | 0.175 | 80 | 0.0000595 | 170,000 |
| | High-Acreage Field Crops | | 0.133 | 200 | 0.000113 | 89,000 |
| Applying Granules via Hand Dispersal | Poultry/Livestock Houses/Horse Barns/Feedlots | 470 | 0.0871 | 1 | 0.000511 | 20,000 |
| **Flagger** | | | | | | |
| Flagging for Aerial Applications | Orchard Crops | 0.35 | 0.133 | 350 | 0.000204 | 49,000 |
| | Sod Farms | | 0.133 | 350 | 0.000203 | 50,000 |
| | Typical Field Crops | | 0.175 | 350 | 0.000268 | 38,000 |
| | High-Acreage Field Crops | | 0.133 | 350 | 0.000204 | 49,000 |
| **Mixer/Loader/Applicator** | | | | | | |
| M/L/A Dry Flowables for Backpack Sprayers | Greenhouse Plants (Foliar) | 140 | 0.00131 lb ai/gal | 40 gallons | 0.0000919 | 110,000 |
| | Nursery Plants (Foliar) | | | | | |
| | Nursery Plants (Ground/Soil) | 2.58 | 0.00475 lb ai/gal | | 0.00000613 | 1,600,000 |
| | Landscaping (trees/shrubs/bushes) | 140 | 0.00131 lb ai/gal | | 0.0000919 | 110,000 |
| | Landscaping (plants/flowers) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | 2.58 | 0.00203 lb ai/gal | | 0.00000261 | 3,900,000 |
| M/L/A Dry Flowables for Manually-Pressurized Handwand Sprayers | Greenhouse Plants (Foliar) | 30 | 0.00131 lb ai/gal | 40 gallons | 0.0000198 | 510,000 |
| | Nursery Plants (Foliar) | | | | | |
| | Landscaping (trees/shrubs/bushes) | | | | | |
| | Landscaping (plants/flowers) | | | | | |
| | Interior Landscaping | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | 30 | 0.00203 lb ai/gal | | 0.0000304 | 330,000 |
| M/L/A Dry Flowables for Mechanically- | Greenhouse Plants (Foliar) | 120 | 0.00131 lb ai/gal | 1000 gallons | 0.00198 | 5,100 |

| Table F.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target[a] | Baseline Inhalation Unit Exposure[b] | Maximum Application Rate[c] | Area Treated or Amount Handled Daily[d] | Baseline Inhalation | |
| | | | | | Dose[e] | MOE[f] |
| | | *µg/lb ai* | *lb ai/A* | *Acres* | *mg/kg/day* | *ST LOC = 30 IT LOC = 100* |
| Pressurized Handgun Sprayers | Greenhouse Plants (Ground/Soil) | | 0.00475 lb ai/gal | | 0.00713 | 1,400 |
| | Nursery Plants (Foliar) | 3.9 | 0.00131 lb ai/gal | | 0.0000640 | 160,000 |
| | Nursery Plants (Ground/Soil) | | 0.00475 lb ai/gal | | 0.000231 | 44,000 |
| | Landscaping (trees/shrubs/bushes) | | 0.00131 lb ai/gal | | 0.0000640 | 160,000 |
| | Typical Field Crops (Foliar) | 3.9 | 0.00875 lb ai/gal | | 0.000426 | 24,000 |
| | Typical Field Crops (Ground/Soil) | 3.9 | 0.0175 lb ai/gal | | 0.000854 | 12,000 |
| | Golf Courses (tees and greens only) | 42 | 0.133 | 5 acres | 0.000348 | 29,000 |
| | Golf Courses (fairways, tees, and greens) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | | | | | |
| M/L/A Liquids for Backpack Sprayers | Orchard (Ground/Soil) | 2.58 | 0.00443 lb ai/gal | 40 gallons | 0.00000571 | 1,800,000 |
| | Greenhouse Plants (Foliar) | 140 | 0.00326 lb ai/gal | | 0.000229 | 44,000 |
| | Nursery Plants (Foliar) | | | | | |
| | Nursery Plants (Ground/Soil) | 2.58 | | | 0.00000421 | 2,400,000 |
| | Landscaping (trees/shrubs/bushes) | 140 | 0.00418 lb ai/gal | | 0.000293 | 34,000 |
| | Landscaping (plants/flowers) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | 2.58 | | | 0.00000539 | 1,900,000 |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | 30 | 0.00887 lb ai/gal | | 0.000133 | 76,000 |
| | Poultry/Livestock Houses/Horse Barns/Feed Lots | | | | | |
| | Foundations/Perimeters | 2.58 | | | 0.0000115 | 880,000 |
| M/L/A Liquids for Manually-Pressurized Handwand Sprayers | Greenhouse Plants (Foliar) | 30 | 0.00326 lb ai/gal | 40 gallons | 0.0000489 | 210,000 |
| | Nursery Plants (Foliar) | | | | | |
| | Landscaping (trees/shrubs/bushes) | | 0.00418 lb ai/gal | | 0.0000626 | 160,000 |
| | Landscaping (plants/flowers) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | 30 | 0.00418 lb ai/gal | | 0.0000626 | 160,000 |
| | Interior Landscaping | | | | | |

| Table F.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target[a] | Baseline Inhalation Unit Exposure[b] | Maximum Application Rate[c] | Area Treated or Amount Handled Daily[d] | Baseline Inhalation | |
| | | | | | Dose[e] | MOE[f] |
| | | *µg/lb ai* | *lb ai/A* | *Acres* | *mg/kg/day* | *ST LOC = 30 IT LOC = 100* |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | 30 | 0.00887 lb ai/gal | | 0.000133 | 76,000 |
| | Poultry/Livestock Houses/Horse Barns/Feedlots | | | | | |
| | Foundations/Perimeters | | | | | |
| | Structural Areas (bridges, shipyards, home decks, foundations) | | | | | |
| | Warehouses | 1100 | | | 0.00448 | 2,100 |
| | Residential Living Spaces (homes, apartments) | | | | | |
| | Childcare Center/Schools/Institutions | | | | | |
| M/L/A Liquids for Mechanically-Pressurized Handgun Sprayers | Orchard Crops (Foliar) | 3.9 | 0.00443 lb ai/gal | 1000 gallons | 0.000216 | 47,000 |
| | Orchard Crops (Ground/Soil) | 3.9 | 0.00449 lb ai/gal | | 0.000219 | 46,000 |
| | Greenhouse Plants (Foliar) | 120 | 0.00326 lb ai/gal | | 0.00489 | 2,100 |
| | Greenhouse Plants (Ground/Soil) | | | | | |
| | Nursery Plants (Foliar) | 3.9 | | | 0.000159 | 63,000 |
| | Nursery Plants (Ground/Soil) | | | | | |
| | Landscaping (trees/shrubs/bushes) | 3.9 | 0.00418 lb ai/gal | | 0.0000626 | 160,000 |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | 3.9 | 0.00887 lb ai/gal | | 0.000433 | 23,000 |
| | Warehouses | 79 | | | 0.00876 | 1,200 |
| | Poultry/Livestock Houses/Horse Barns/Feedlots | | | | | |
| | Structural (bridges, shipyards, home decks, foundations, etc) | | | | | |
| | Typical Field Crops (Foliar) | 3.9 | 0.00202 lb ai/gal | | 0.0000985 | 100,000 |
| | Typical Field Crops (Ground/Soil) | | | | | |
| | Golf Courses (tees and greens only) | 1.9 | 0.313 | 5 acres | 0.0000371 | 270,000 |
| | Golf Courses (fairways, tees, and greens) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | | | | | |
| **Loader/Applicator** | | | | | | |
| L/A Granules for Belly Grinders | Orchard Crops | 62 | 0.0871 | 1 acre | 0.0000675 | 150,000 |
| | Greenhouse Plants | | | | | |
| | Nursery Plants | | | | | |

| Table F.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target[a] | Baseline Inhalation Unit Exposure[b] | Maximum Application Rate[c] | Area Treated or Amount Handled Daily[d] | Baseline Inhalation | |
| | | | | | Dose[e] | MOE[f] |
| | | *µg/lb ai* | *lb ai/A* | *Acres* | *mg/kg/day* | *ST LOC = 30 IT LOC = 100* |
| | Landscaping (trees/shrubs/bushes) | | | | | |
| | Landscaping (plants/flowers) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | | | | | |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | | | | | |
| | Poultry/Livestock Houses/Horse Barns/Feedlots | | | | | |
| | Foundations/Perimeters | | | | | |
| L/A Granules for Rotary Spreaders | Orchard Crops | 10 | 0.0871 | 5 acres | 0.0000545 | 180,000 |
| | Greenhouse Plants | | | | | |
| | Nursery Plants | | | | | |
| | Golf Courses (tees and greens only) | | | | | |
| | Golf Courses (fairways, tees, and greens) | | | | | |
| | Landscaping (turf, lawns, athletic fields, parks, etc) | | | | | |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | | | | | |
| | Poultry/Livestock Houses/Horse Barns/Feed Lots | 10 | 0.0871 | 1 acre | 0.0000109 | 920,000 |
| L/A Granules for Backpack Sprayers | Nursery Plants | 23.8 | 0.0871 | 1 acre | 0.0000259 | 390,000 |
| | Industrial/Commercial Areas (tires, rail yards, junk yards, etc) | | | | | |
| L/A Granules for Cups | Poultry/Livestock Houses/Horse Barns/Feed Lots | 12.5 | 0.0871 | 1 acre | 0.0000136 | 740,000 |
| L/A Granules for Spoons | Poultry/Livestock Houses/Horse Barns/Feed Lots | 121 | 0.0871 | 1 acre | 0.000131 | 77,000 |
| Hand Dispersal of Granules | Poultry/Livestock Houses/Horse Barns/Feed Lots | 470 | 0.0871 | 1 acre | 0.000511 | 20,000 |

a "Typical Field Crops" include *Brassica* (Cole) leafy vegetables (Group 5), bulb vegetables (Group 3-07), bushberries (Group 13-07B), citrus fruits (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), potatoes, stone fruits (Group 12), sunflowers, tree nuts (Group 14), tuberous and corm vegetables (Subgroup 1C).
"High-Acreage Field Crops" includes cotton.
"Nursery Plants" include ornamentals, vegetables, trees, container stock.
"Greenhouse Plants" include ornamentals, roses, cut flowers, container stock, vegetables grown for re-sale to consumers.

b Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2012); Level of mitigation = Baseline.

c Based on the maximum application rates on the proposed labels (Reg. Nos. 352-IAE, 352-IAG, 352-IAI, 352-IAL, 253-IAN, 352-ILA, 352-ILI, 352-ILO, 352-ILT, 100-RUEE, 100-RUEG, 100-RUEN, 100-RUER, 100-RUEU, and 100-RURI).
d Exposure Science Advisory Council Policy #9.1.
e Inhalation Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg adult).
f Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

**Table F.2 Summary of Short-Term Handler Exposures and Risks for Cyantraniliprole (Seed Treatment Only)[a]**

| Seed Type | Max Application Rate[b] | Inhalation UE[c] | Amount of Seed Treated or Planted Per Day[d] | Inhalation Dose[e] | Inhalation MOE[f] |
|---|---|---|---|---|---|
| | *lb ai/lb seed* | *mg/lb* | *lb seed/day* | *mg/kg/day* | *ST LOC = 30* |
| **Loader/Applicator** | | | | | |
| Potato Seed Pieces | 0.000135 | 0.0064* | 800,000 | 0.00864002 | 1,200 |
| Rapeseed/Canola | 0.0100 | 0.00034 | 125,000 | 0.00531939 | 1,900 |
| Mustard Seed | 0.0100 | | 125,000 | 0.00531939 | 1,900 |
| Sunflowers | 0.00397 | | 339,500 | 0.00572580 | 1,800 |
| **Sewer** | | | | | |
| Rapeseed/Canola | 0.0100 | 0.00023 | 125,000 | 0.00359841 | 2,800 |
| Mustard Seed | 0.0100 | | 125,000 | 0.00359841 | 2,800 |
| Sunflowers | 0.00397 | | 339,500 | 0.00387333 | 2,600 |
| **Bagger** | | | | | |
| Rapeseed/Canola | 0.0100 | 0.00016 | 125,000 | 0.00250324 | 4,000 |
| Mustard Seed | 0.0100 | | 125,000 | 0.00250324 | 4,000 |
| Sunflowers | 0.00397 | | 339,500 | 0.00269449 | 3,700 |
| **Multiple Activities** | | | | | |
| Rapeseed/Canola | 0.0100 | 0.0016 | 125,000 | 0.02503242 | 400 |
| Mustard Seed | 0.0100 | | 125,000 | 0.02503242 | 400 |
| Sunflowers | 0.00397 | | 339,500 | 0.02694492 | 370 |
| **Planter** | | | | | |
| Potato Seed Pieces | 0.000135 | 0.0034 | 800,000 | 0.0045900 | 2,200 |
| Rapeseed/Canola | 0.0100 | | 400 | 0.0001702 | 59,000 |
| Mustard Seed | 0.0100 | | 560 | 0.0002383 | 42,000 |
| Sunflowers | 0.00397 | | 320 | 0.0000540 | 190,000 |

a Seed treatment rate calculations are based on the following assumptions:
Mustard seed: 90,000 to 115,000 seeds per lb; 7 lbs of seed planted per day, 80 acres planted per day.
Potato seed pieces: 5 to 11 seed pieces per lb; 800,000 seed pieces planted per day.
Rapeseed (canola): 90,000 to 115,000 seeds per lb; 5 lbs of seed planted per day, 80 acres planted per day.
Sunflowers: 2,000 to 9,000 seeds per lb; 4 lbs of seed planted per day, 80 acres planted per day.
b Application Rates based on proposed label uses for cyantraniliprole (EPA Reg. Nos. 352-IAN, 100-RUEN, and 100-RURI).
c Unit Exposures from HED Exposure Science Advisory Council Policy 14: Standard Operating Procedures for Seed Treatment (baseline inhalation = no respirator).
* The inhalation unit exposure for potato seed pieces comes from D378750.
d HED default for lb seed treated/planted per day from HED Exposure Science Advisory Council Interim Policy 15.1 and the BEAD memo "Acres Planted Per Day and Seeding Rates of Crops Grown in the United States" (J. Becker, March 2011).
e Daily Inhalation Dose (mg/kg/day) = daily inhalation unit exposure (mg/lb ai) × application rate (lb ai/lb seed) × amount planted (lb seed/day) ÷ body weight (80 kg adult).
f Inhalation MOE = NOAEL (10.08 mg/kg/day for short-term exposure) ÷ Inhalation Dose (mg/kg/day). Short-term level of concern = 30.