OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: August 26, 2024

SUBJECT: Cyantraniliprole: Summary of Hazard and Science Policy Council (HASPOC) Meeting on August 15, 2024: Recommendations on the Need for a Comparative Thyroid Assay.

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FROM: Jorrell Fredericks, Executive Secretary
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Health Effects Division (HED; 7509T)

THRU: Abiy Mohammed, Co-Chair
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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

MEETING ATTENDEES:

HASPOC Members: Moana Appleyard, Adrian Britt, Sarah Dobreniecki, Joshua Godshall, Elizabeth Mendez, Emily Rogers, Ana Terman, Cassi Walls, Krystle Yozzo (Presenter, not voting), Abiy Mohammed, Brian Van Deusen, Jorrell Fredericks (non-voting), Alexandra Turley (non-voting)

Presenter: Krystle Yozzo, Ph.D.

Other Attendees: Ashlee Aldridge, Destiny Carter, Heriberto Deleon, Melantha Jackson, Elizabeth Lang, Briana Lee, Yongqi Li, Caitlin Love, Tom Moriarty, Samuel Novo, Peter Savoia, Johnny Smith, Jessie Wozniak, Charmaine Hanson, Meaghan Caruso

I. PURPOSE OF MEETING

A scoping document is currently being prepared for the registration review of cyantraniliprole. The toxicology database for cyantraniliprole is complete. However, since the thyroid is a target organ and thyroid effects were observed in the database, the need for a comparative thyroid assay (CTA) was considered. The Hazard and Science Policy Council (HASPOC) met on August 15, 2024, to determine if the CTA is necessary to support the registration review of cyantraniliprole.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

Cyantraniliprole is an insecticide currently registered on a variety of agricultural crops, as well as commercial and on-farm seed treatment uses and residential use sites including turf grass, ornamentals, and structural buildings (e.g., outdoor broadcast uses). Single maximum application rates range from 0.088-0.39 lb ai/A and retreatment intervals (RTIs) range from 5 to 14 days. Maximum annual rate of cyantraniliprole-containing products is 0.39 lb ai/A/year. End-use products are formulated as water dispersible granules, dry flowables, suspension concentrates, and suspo-emulsions. Application methods include aerial, airblast, ground equipment, and chemigation. Most occupational labels direct the user to wear baseline clothing (long-sleeved shirt, long pants, socks, shoes) and additional personal protective equipment (PPE) consisting of chemical-resistant gloves. Pre-harvest intervals (PHIs) range from 0 to 365 days and restricted entry intervals (REIs) range from 4 to 24 hours.

Humans may be exposed to cyantraniliprole in food and drinking water since it may be applied directly to growing crops, and application may result in cyantraniliprole reaching surface and ground sources of drinking water. Short- and intermediate-term occupational handler and post-application dermal and inhalation exposures to cyantraniliprole are expected. There is potential for short-term residential handler dermal and inhalation, as well as residential post-application dermal exposures to adults and children 1 to <2 years old and children's incidental oral exposure from hand-to-mouth activities while contacting previously treated surfaces. Additionally, adult's short-term dermal and children's short-term dermal and incidental oral exposures may also occur from turf residues resulting from spray drift following applications to agricultural and/or non-agricultural areas.

b. Toxicity Profile

Cyantraniliprole belongs to the anthranilic diamide class of pesticides, which control insects through unregulated activation of ryanodine receptor (RyR) channels leading to internal calcium store depletion that impairs regulation of muscle contraction. 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 (Satelle et al., 2008; Lahm et al., 2009). The toxicity database is considered complete for cyantraniliprole and no new toxicity and/or metabolism data have been received since the last risk assessment (K. Yozzo, D467446, 01-MAY-2024). Mechanistic studies on the adrenal and thyroid glands, and an in vitro thyroid peroxidase inhibition study are also available for cyantraniliprole. 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. The four metabolites were not considered mutagenic, and IN-JSE-76 showed no adverse effects at doses greater than the limit dose.

The target organs of cyantraniliprole include the liver and thyroid. With repeat dosing, liver effects, including increased liver weights and enzymes (alkaline phosphatase and alanine aminotransferase) and adverse liver histopathology (bile duct hyperplasia, focal and hepatocyte necrosis) were observed in dogs. With repeat dosing, thyroid effects, including altered thyroid hormone homeostasis and follicular epithelial cell hypertrophy/hyperplasia were observed in rats. Cyantraniliprole has low 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. 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, and there are no mutagenicity concerns.

There is no evidence of lifestage susceptibility in the developmental toxicity studies in rats and rabbits or in the two-generation reproductive toxicity study in rats. There are no neurotoxicity concerns in the acute and subchronic neurotoxicity studies. Immunotoxicity data show that cyantraniliprole is not an immunotoxicant.

III. STUDY WAIVER REQUESTS

a. Comparative Thyroid Assay (CTA)

A number of pesticides have been shown to perturb thyroid hormone homeostasis *via* reduction of circulating thyroid hormones[1]. This perturbation may be the initial, critical effect leading to adverse effects on the developing nervous system[2,3,4]. When a chemical causes thyroid effects, there is inherent uncertainty about potential impacts to the developing brain in response to changing thyroid levels. There is also a lack of empirical data on whether pregnant women or the fetus are more or less

[1] Hurley *et al*. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ. Health Perspect. 106(8): 437-445.

[2] Chan S and Kilby MD. 2000 Thyroid hormone and central nervous system development. J Endocrinol 165:1-8

[3] Fisher DA. 2000. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediat 136:274-274.

[4] Morreale de Escobar, G, Obregón, MJ, Escobar del Rey, F. 2004. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Practices & Research Clinical Endocrinology & Metabolism, Volume 18, Issue 2: 225-248.

susceptible, compared to adults, to the impact of chemicals that alter thyroid hormone homeostasis. This gap makes predictions on developmental susceptibility based on data from adult organisms difficult and very uncertain. The current 40 CFR Part 158 Toxicology Data Requirements do not include thyroid hormone measurements during these potentially sensitive lifestages. EPA has developed guidance for conducting a CTA[5] that uses a mechanistic approach to generate thyroid-specific data which can address the uncertainties associated with life stage susceptibility and allow for the establishment of PODs that would be protective of potential effects of thyroid function disruption in pregnant females on the fetus and newborn. The need for/against a CTA is based on the following considerations:

1. **Evidence for thyroid toxicity in the cyantraniliprole database:**
   Signs of thyroid toxicity, including increased thyroid organ weights, and histopathological findings, were observed following subchronic exposure at 14 mg/kg/day in the parents of the two-generation reproduction toxicity study. Similarly, thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis was observed in female rats at 27 mg/kg/day in the subchronic oral toxicity study in rats.

   In the two-generation reproduction toxicity study, there was an increase in the fixed thyroid lobes/parathyroid weights (absolute and relative) in the 1344 mg/kg/day P_1 and F_1 generation males (20-25%) and in the 14, 136, and 1344 mg/kg/day P_1 and F_1 generation females (25-33%). In P_1 males, thyroid follicular epithelial cell hypertrophy/hyperplasia was present in 4/30, 2/30, 3/29, 19/30, and 28/30 rats fed 0, 1.1, 11.0, 110, and 1125 mg/kg/day. In F_1 males, thyroid follicular epithelial cell hypertrophy/hyperplasia was present in 1/30, 2/30, 7/29, 18/30, and 27/30 rats fed 0, 1.1, 11.0, 110, and 1125 mg/kg/day. In P1 females, thyroid follicular epithelial cell hypertrophy/hyperplasia was present in 3/29, 5/28, 5/30, 16/29, and 25/30 rats fed 0, 1.4, 14, 136, and 1344 mg/kg/day. In F_1 females, thyroid follicular epithelial cell hypertrophy/hyperplasia was present in 1/30, 1/29, 5/28, 16/30, and 24/30 rats fed 0, 1.4, 14, 136, and 1344 mg/kg/day. Thyroid hormones were not evaluated. No effects to thyroid weights or histopathology were observed in the offspring.

   In the 90-day subchronic oral toxicity study, in males, serum T4 concentrations were decreased at dietary concentrations of 22, 168, and 1147 mg/kg/day cyantraniliprole (24, 32, and 30% decrease relative to the control, respectively). Similarly, serum T3 concentrations were decreased at dietary concentrations of 22, 168, and 1147 mg/kg/day cyantraniliprole (17%, 20%, and 22% decrease, respectively). Serum TSH concentrations were increased at dietary concentrations of 168 and 1147 mg/kg/day cyantraniliprole (41 and 55% greater than the control, respectively). The alterations in thyroid hormones were accompanied by increased total hepatic cytochrome P450 content and UDP-glucuronyltransferase activity. Absolute thyroid weights were comparable to that of the controls. Thyroid follicular cell hypertrophy was present in 0/10, 0/10, 0/10, 0/10, and 5/10 rats fed 0, 6, 22, 168, or 1147 mg/kg/day, respectively, and all were graded as minimal. In females, serum T4 concentrations were decreased at dietary concentrations of 27, 202, and 1346 mg/kg/day cyantraniliprole (58, 67, and 79% decrease relative to the control, respectively). Serum T3 concentrations were

[5] US EPA 2005. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals. Washington, DC.

decreased at dietary concentrations of 202 and 1346 mg/kg/day cyantraniliprole (31 and 29% lower than that of the control, respectively). Serum TSH concentrations were comparable between treated and the control groups. The alterations in thyroid hormones in female rats were accompanied by increased total hepatic cytochrome P450 content and UDP-glucuronyltransferase activity. Mean absolute thyroid weights were increased 17%, 8%, and 17% in the 27, 202, and 1346 mg/kg/day groups, respectively, as compared to control values. None of the increases were statistically significant. Thyroid follicular cell hypertrophy was present in 1/10, 0/10, 3/10, 4/10, and 6/10 rats fed 0, 7, 27, 202, or 1346 mg/kg/day, respectively. All were graded as minimal.

A mechanistic study (MRID 48119973) was conducted to evaluate potential mechanisms of thyroid gland changes. To explore the possible mechanisms of the thyroid effects, two groups of approximately 7 weeks old female Crl:CD®(SD) rats (15/sex/group) were fed control diet or diet containing 1903 mg/kg/day cyantraniliprole (94.5%; HGW86-230) for 29 days. Statistically significant increases in serum TSH levels (67%), as well as statistically significant decreases in T4 levels (30%) were observed. However, serum levels of T3 and reverse T3 (rT3) were unaffected. The alterations in thyroid hormones in female rats were accompanied by increased UDP-glucuronyltransferase activity (77%) and decreased hepatic microsomal 5'-deiodinase activity (23%). Additionally, mean absolute and relative thyroid weights were increased 21 and 17%, respectively, in 1903 mg/kg/day group as compared to the control values. Thyroid follicular cell hypertrophy was also present in 5/15 females from the dosed group compared to 0/15 in the control group.

Another study (MRID 48119979) was designed to evaluate the ability of cyantraniliprole to inhibit thyroid peroxidase activity *in vitro* using thyroid preparations from the Yucatan pig (microswine). Cyantraniliprole concentrations ranging from 2 to 400 μM were tested; the maximum concentration was the level where limit of solubility was present in the assay system. The result showed that for propylthiouracil (PTU), the concentration that caused a 50% reduction in enzyme activity (IC_{50}) was 7.3 μM. In contrast cyantraniliprole did not cause inhibition of thyroid peroxidase at any concentration tested; therefore, an IC_{50} value for cyantraniliprole was unable to be determined. Under the conditions of this *in vitro* study, cyantraniliprole did not inhibit thyroid peroxidase.

2. Evidence for thyroid toxicity in the toxicology database of similar pesticides:
Cyantraniliprole is in the anthranilic diamide class of chemicals. Of that class, cyclaniliprole (87%) and chlorantraniliprole (96%) were most structurally similar (>80% similarity) (CompTox Chemicals Dashboard v2.4.1). However, neither cyclaniliprole nor chlorantraniliprole showed thyroid toxicity. No single or repeated dose study performed by any route of exposure produced an adverse effect following cyclaniliprole exposure below, at, or above the limit dose (1000 mg/kg/day). Only the 18-month carcinogenicity study in mice produced adverse effects (mild eosinophilic foci) following chlorantraniliprole exposure at a dose (935 mg/kg/day) reaching the limit dose.

3. Risk assessment considerations:
Endpoints for chronic dietary, incidental oral, and inhalation exposure scenarios have been selected for cyantraniliprole. The chronic dietary exposure scenario is based on organ weight

and histopathology changes in the thyroid gland (thyroid follicular epithelial cell hypertrophy/hyperplasia) in F1 generation adult male and/or female rats at 14 mg/kg/day in the two-generation reproduction toxicity study (NOAEL = 8.3 mg/kg/day from combined chronic/carcinogenicity study). The incidental oral exposure scenario is based on thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis at 27 mg/kg/day in the subchronic oral toxicity study in rats (NOAEL = 7 mg/kg/day). The 28-day inhalation toxicity study in rats was selected to evaluate short- and intermediate term inhalation exposure scenarios. No effects were observed up to the highest dose tested, including thyroid effects (0.1 mg/L); however, this study was selected to protect for potential effects above 0.1 mg/L.

The LOC for chronic dietary, incidental oral, and inhalation exposures is 30 (3X for interspecies extrapolation, 10X for intraspecies extrapolation, and 1X for FQPA SF [pending HASPOC]). For chronic dietary and incidental oral exposures, the UF_A (interspecies uncertainty factor) can be reduced from 10X to 3X since the effects observed at the LOAEL are based only on thyroid effects on adult animals. For inhalation exposures, the UF_A can be reduced from 10X to 3X since the RfC methodology takes into consideration the pharmacokinetic (PK) differences, but not the pharmacodynamic (PD) differences between animals and humans.

A refined chronic dietary (food and drinking water) exposure assessment was conducted assuming a combination of tolerance-level residues, average field trial residues, mean residue values from the USDA Pesticide Data Program (PDP), empirical processing factors and/or HED's default processing factors and assumed 100 percent crop treated (CT). The chronic dietary exposure estimate was 3% of the chronic population adjusted dose (cPAD) for the most highly exposed population subgroup, children 1-2 years of age (Appendix B, Table B.1).

Residential handler inhalation margins of exposure (MOEs) were not of concern and range from 46,000 to 76,000 (LOC = 30) (Appendix C, Table C.1). Residential post-application incidental oral MOEs for children 1 to <2 years old were not of concern and range from 1,200 to 670,000 (LOC = 30) (Appendix C, Table C.2.). Non-occupational spray drift hand-to-mouth incidental oral MOEs at field edge were not of concern with a range 4,500 to 19,000 (LOC = 30) (Appendix C, Table C.3.). With label-required attire and PPE, occupational handler inhalation MOEs were not of concern (LOC = 30). For mixers/loaders scenarios of all registered formulations, MOEs range from 1,100 to 4,700,000. For applicator scenarios, MOEs range from 1,500,000 to 320,000,000,000. For flagger scenarios, MOEs range from 130,000 to 170,000. For mixer/loader/applicator scenarios, MOEs range from 560 to 1,200,000. For loader/applicator scenarios, MOEs range from 230,000 to 1,100,000. See Appendix C, Table C.4 for more details. Seed treatment inhalation MOEs range from 88 to 590,000 (see Table C.5).

Based on a weight-of-evidence (WOE) approach, HASPOC recommends that a CTA not be conducted at this time for cyantraniliprole. This approach considered all of the available hazard and exposure information for cyantraniliprole including: 1) while thyroid toxicity is observed in the rat studies in the cyantraniliprole database, clear NOAELs have been established; 2) the highest current dietary exposure estimates account for 3% of the cPAD and are not of concern; 3) residential handler inhalation MOEs range from 46,000 to 76,000 and are not of concern (LOC = 30); 4) residential post-application incidental oral MOEs for children 1 to <2 years old range from 1,200 to 670,000 and are not of concern

(LOC = 30); 5) non-occupational spray drift exposure incidental oral MOEs for children 1 to <2 years old range from 4,500 to 19,000 and are not of concern (LOC = 30); 6) occupational exposure MOEs range from 560 to 320,000,000,000 and are not of concern (LOC = 30); and 7) even though 5 seed treatment inhalation MOEs are below 300 (10X LOC), there is low concern because adverse effects (including thyroid) were not observed in the inhalation study and based on the animal equivalent dose of 26.4 mg/kg/day for no observed adverse effect concentration, thyroid effects via oral exposures are protective of inhalation exposures.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available hazard and exposure data for cyantraniliprole, the HASPOC recommends that the comparative thyroid assay for cyantraniliprole not be conducted at this time. These recommendations may be revisited if the toxicological database, use patterns, or exposure patterns for cyantraniliprole change in the future.

V. APPENDIX A

Table A.1. Summary of Toxicological Doses and Endpoints for Cyantraniliprole for Use in Human Health Risk Assessments[a].

Exposure/ Scenario	POD	Uncertainty/ FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	An effect attributed to a single dose was not identified in the toxicology database.			
Chronic Dietary (All Populations)	NOAEL = 8.3 mg/kg/day	UF_A = 3X UF_H =10X FQPA SF = 1X (pending HASPOC)	cRfD = 0.28 mg/kg/day cPAD = 0.28 mg/kg/day	**Co- Critical: Combined Chronic/Carcinogenicity Study (Rats) and Two-Generation Reproduction Toxicity Study (Rats)** Parental LOAEL = 14 mg/kg/day based on organ weight and histopathology changes in the thyroid gland (thyroid follicular epithelial cell hypertrophy/hyperplasia) in F1 generation adult male and/or female rats. Parental NOAEL = 1.4 mg/kg/day
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1 to 6 months)	NOAEL = 7 mg/kg/day	UF_A = 3X UF_H = 10X FQPA SF = 1X (pending HASPOC)	LOC = 30	**90-day oral study (Rats)** LOAEL = 27 mg/kg/day based on thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis.
Dermal, Short-Term (1-30 days) and Intermediate-Term (1-6 months)	A toxicity endpoint was not identified. Systemic toxicity was not seen in 28-day dermal toxicity study in rats at the limit-dose (1000 mg/kg/day). There are no concerns for developmental, reproductive toxicity, or neurotoxicity.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEC = 0.1 mg/L HED (Residential) = 6.6 mg/kg/day HED (Occupational) = 19.9 mg/kg/day	UF_A = 3X[b] UF_H = 10X FQPA SF = 1X (pending HASPOC)	LOC = 30	**28-day inhalation toxicity study (Rats)** A LOAEC 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 incidences in the rat and mouse carcinogenicity 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. UF = uncertainty factor. UFA = extrapolation from animal to human (interspecies). UFH = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. 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 A.2. Acute Toxicity Profile – Technical Cyantraniliprole.				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral (mouse)	48119957 (94.5% a.i.)	LD_{50} > 5000 mg/kg (F)	IV
	Acute Oral (rat)	48119952 (94.5% a.i.)	LD_{50} > 5000 mg/kg (F)	IV
870.1200	Acute Dermal (rat)	48119953 (94.5% a.i.)	LD_{50} ≥ 5000 mg/kg (M & F)	IV
870.1300	Acute Inhalation (rat)	48119958 (94.5% a.i.)	LC_{50} > 5.2 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	48119955 (94.5% a.i.)	Slightly irritating; clearing by 72 hours	III
		48208421 (97.7% a.i.)	Not irritating	IV
870.2500	Primary Skin Irritation (rabbit)	48119954 (94.5% a.i.)	Not irritating	IV
870.2600	Dermal Sensitization (mouse)	48208422 (97.7% a.i.)	Not sensitizing (LLNA)	N/A
		48208423 (97.0% a.i.)	Not sensitizing (LLNA)	NA
	Dermal Sensitization (guinea pig)	48122586 (95.6% a.i.)	Not sensitizing (Buehler Method)	NA
		48119984 (94.5% a.i.)	Not sensitizing (Maximization Test)	NA

Table A.3. Acute Toxicity Profile – Cyantraniliprole Metabolites.				
Guideline No.	**Study Type / Test Substance**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral (rat) - IN-JSE76-005	48119978 (93.8% a.i.)	LD_{50} > 5000 mg/kg (F)	IV
	Acute Oral (mouse) – IN-PLT97-003	48122579 (98.1% a.i.)	LD_{50} > 5000 mg/kg (F)	IV
	Acute Oral (mouse) - IN-F6L99-004	46979929 (98.6% a.i.)	LD_{50} > 2000 mg/kg (F)	III
	Acute Oral (mouse) - IN-N5M09-003	48119939 (99.9% a.i.)	LD_{50} > 5000 mg/kg (F)	IV

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
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) Acceptable/non-guideline 0, 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. Supplemental data: 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.
870.3050	28-Day feeding study (mice)	48119940 (2009) Acceptable/non-guideline 0, 300, 1,000, 3,000, and 7,000 ppm M: 0, 53, 175, 528, and 1,261 mg/kg/day F: 0, 63, 212, 664, and 1,476 mg/kg/day	NOAEL = 528/664 mg/kg /day (M/F). LOAEL = 1,261/1,476 mg/kg/day (M/F) (highest dose tested) based on increased incidence of minimal focal necrosis in the liver. Supplemental data: Cyantraniliprole does not induce hepatic b-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) Acceptable/non-guideline 0, 600, 2000, 6000, and 20,000 ppm M: 0, 53, 175, 528, and 1,776 mg/kg/day F: 0, 62, 188, 595, and 1,953 mg/kg/day	NOAEL = 53 mg/kg/day LOAEL = 175 mg/kg/day based on minimal thyroid follicular hypertrophy and significant increases in UDP-GT levels seen in males
870.3050	28-Day palatability study—dietary (dogs) *	48119942 (2007) Acceptable/non-guideline 0, 1000, 10,000, and 40,000 ppm M: 0, 35, 311, and 1,043 mg/kg/day F: 0, 35, 335, and 1,240 mg/kg/day)	As per current and standard practices, the following study is a dose-range finding study and uses only 2 animals, therefore, it is considered non-guideline. As a result, no NOAEL/LOAEL values will be set. Supplemental data: 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 A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day feeding toxicity study (mice)	48119943 (2007) Acceptable/non-guideline 48119944 (2007) supplement to 48119943 Provide information about metabolites 0, 50, 300, 1,000, and 7,000 ppm M: 0, 7, 47, 150, and 1,092 mg/kg /day. F: 0, 10, 58, 204, & 1,344 mg/kg/day.	NOAEL = 150/204 mg/kg /day (M/F). LOAEL =1,092/1,344 mg/kg /day (M/F) based on increased incidence of focal necrosis of the liver, and liver weight increase. Supplemental data: 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) [Interim sacrifice was also conducted on 5/sex/dose on 29th (♂) day and 30th day (♀)]	48119945 (2007) Acceptable/guideline 48119946 (2007) Supplement to 48119945 0, 100, 400, 3,000, and 20,000 ppm M: 0, 6, 22, 168, and 1,147 mg/kg /day F: 0, 7, 27, 202, or 1,346 mg/kg/day	NOAEL = 7 mg/kg/day. LOAEL = 27 mg/kg/day based on thyroid follicular cell hypertrophy, increased thyroid weights, and alterations in thyroid hormone homeostasis in females. Supplemental data: 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) * [T3, T4, TSH, and cytochrome P450 were also measured]	48119948 (2007) Acceptable/guideline 48119947 (2007) Supplement to 48119948 0, 30, 100, 1,000, and 10,000 ppm M: 0, 1, 3, 32, and 281 mg/kg/day F: 0, 1, 3, 34, and 294 mg/kg/day)	NOAEL = 32/34 mg/kg/day (M/F) LOAEL = 281/294 mg/kg/day based on increased body weight, increased liver weights, ALT, ALP, and liver histopathology (bile duct hyperplasia, focal and hepatocyte necrosis). 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 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 (2012) Supplement to 48663602 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 A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
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 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 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	Two-Generation reproduction study—dietary (rats)	48119967 (2011) Acceptable/guideline 0, 20, 200, 2,000, and 20,000 ppm 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 in F1 generation adult male and/or female rats. 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 0, 20, 200, 2,000, and 20,000 ppm M: 0, 0.8, 8.3, 84.8, and 906.6 mg/kg /day F: 0, 1.1, 10.5, 106.6, and 1,160.8 mg/kg/day	NOAEL = 8.3 mg/kg/day. LOAEL = 84.8 mg/kg/day based on microscopic liver pathology characterized by foci of cellular alteration (clear, eosinophilic, and basophilic) and focal vacuolation. Cyantraniliprole did not produce compound-related or dose-related increases in tumor incidence.

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b	1-Year oral study—dietary with active ingredient (dogs) * [a recovery period was also included]	48119960 (2010) Acceptable/guideline 48208427 (2010) Supplement to 48119960. 0, 40, 200, 1,000, and 5,000 ppm M: 0, 1, 6, 27, and 144 mg/kg/day F: 0, 1, 6, 27, and 133 mg/kg/day	NOAEL = 6 mg/kg/day LOAEL = 27 mg/kg/day based on increased liver weights, hepatocellular degeneration in both males and females, chronic inflammation in female dogs, and increased ALP and adverse decreases in cholesterol in females.
870.4200b	18-Month carcinogenicity study (mice)	48122578 (2011) Acceptable/guideline 0, 20, 150, 1,000, and 7,000ppm M: 0, 2, 16, 104, and 769 mg/kg/day F: 0, 2, 19, 131, and 904 mg/kg/day	NOAEL = 104/131 mg/kg/day (M/F). LOAEL = 769/904 mg/kg/day (M/F). 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. Cyantraniliprole did not produce compound-related increase in tumor incidence.
Genetic Toxicity Studies			
870.5100	Bacterial reverse mutation test (*S. typhimurium* and *E. coli)*	48122587 (2010) Acceptable/guideline	Negative. 0, 50, 150, 500, 1,500, and 5,000 mg/plate were tested (+/- S9). Precipitate was observed at 5,000 mg/plate.
		48119980 (2009) Acceptable/guideline	Negative. The dose levels tested were 0, 50, 150, 500, 1,500, and 5,000 µg/plate (+/- S9); precipitate was observed at 5,000 mg/plate.
		48208424 (2009) Acceptable/guideline	Negative. The dose levels tested were 0, 50, 150, 500, 1,500, and 5,000 µg/plate. (+/- S9). Precipitation was observed at 5,000 µg/plate.
870.5300	*In vitro* mammalian cell gene mutation test (CHO/HGPRT assay)	48122589 (2010) Acceptable/guideline	Negative. 0, 50.0, 100, 150, 250, and 500 µg/ml (+/- S9).
870.5300	*In vitro* CHO/HPRT forward mutation assay	48208443 (2011) Acceptable/guideline	Negative. 0, 10.0, 25.0, 50.0, 100, 250, 500, 750, and 1,000 µg/mL were tested. Compound precipitation was observed at concentrations in treatment medium ≥250 mg/mL.
870.5375	*In vitro* Mammalian chromosome aberration test with human lymphocytes	48208425 (2009) Acceptable/guideline	Negative. 0, 62.5, 125, 250, 500, 600, 700, 800, and 900 mg/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 mg/mL for the 20-hour non-activated treatment condition.

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5375	*In vitro* Mammalian chromosome aberration test with human lymphocytes	48208426 (2009) Acceptable/guideline	Negative. 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.
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 mg/mL for non-activated 4-hour; 0, 62.5, 125, 250, 500, 600, 700, 800, and 900 mg/mL for activated 4-hour; and 0, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, and 1,000 mg/mL for non-activated 20-hour. Visible precipitate was observed in treatment medium at ^{3}500 mg/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 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 0, 200, 2,000, and 20,000 ppm M: 0, 11, 116, and 1,195 mg/kg/day 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 A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Metabolism Studies			
870.7485	Metabolism study—ADME (rats)	48119949 (2010) Acceptable/guideline 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. Male low dose half-lives: CN $T_{1/2}$ = 42 hrs; PC $T_{1/2}$ = 54 hrs; Female low dose half-lives: CN $T_{1/2}$ = 129 hrs; PC $T_{1/2}$ = 117 hrs; Male high dose half-lives: CN $T_{1/2}$ = 62 hrs; PC $T_{1/2}$ = 55 hrs; Females high dose half-lives: CN $T_{1/2}$ = 65 hrs; PC $T_{1/2}$ = 80 hrs. 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. 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. 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) Acceptable/non-guideline 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. 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. Metabolites found in this study were similar to those in the single dose study (MRID 48119949).

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.				
* Indicates an updated study.				
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**	
Dermal Absorption 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.		
	In vivo dermal absorption—SC formulation (rats)	48120313 (2009) Acceptable 200 g/L and 1 g/L	Maximum absorption 200 g/L = 0.34% at 498 hrs 1 g/L = 0.93% at 498 hrs	DAF 200 g/L = 0.02% 1 g/L = 0.43% 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 200 g/L & 1g/L	Maximum Dermal penetration at 24 hrs: Human skin: 200 g/L = 0.24% 1 g/L = 5.28% Rat skin: 200 g/L = 3.69% 1 g/L = 11.5%	
	In vivo dermal absorption—SE formulation (rats)	48120413 (2009) Acceptable 100 g/L and 1 g/L	Maximum absorption: 100 g/L = 1.25% at 498 hrs 1 g/L = 1.47% at 498 hrs	DAF 100 g/L = 0.25% 1 g/L = 0.83% 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 100 g/L and 1 g/L	Maximum Dermal penetration at 24 hrs: Human skin: 100 g/L = 2.7 % 1 g/L = 6.1 % Rat skin: 100 g/L =13.4 % 1 g/L = 10.7 %	
	In vivo dermal absorption—OD formulation (rats)	48120209 (2008) Acceptable 100 g/L and 1 g/L	Maximum absorption 100 g/L = 1.36% at 498 hrs 1g/L = 0.74% at 498 hrs	DAF 100 g/L = 0.06% 1 g/L = 0.03% 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 100 g/L and 1 g/L	Maximum Dermal penetration at 24 hrs: Human skin: 100 g/L = 0.25 % 1 g/L = 0.86% Rat skin: 100 g/L = 10.5% 1 g/L = 20.2 %	
	In vivo dermal absorption—cyantraniliprole/ thiamethoxam WG formulation (A16901B) formulation (rat skin)	48432511 (2011) Acceptable 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: Slurry concentrate 1/20 dilution = 0.005% Slurry concentrate 1/267 dilution = 0.07%

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.				
* Indicates an updated study.				
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 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 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 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) [assess primary humoral response to sheep red blood cells (sRBC)]	48119971 (2009) Acceptable/guideline 0, 20, 200, 2,000, and 20,000 ppm M: 0, 1.7, 17, 166, and 1,699 mg/kg/day 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. 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) [assess primary humoral response to sheep red blood cells (sRBC)]	48119972 (2009) Acceptable/guideline 0, 20, 150, 1,000, or 7,000 ppm M: 0, 3.0, 23, 154, or 1,065 mg/kg/day 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. 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) (HDT)	

Table A.4. Subchronic, Chronic, and Other Toxicity Profile for Cyantraniliprole.			
* Indicates an updated study.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Other (Non-Guideline) Studies (Mechanistic Studies)			
	Adrenal and thyroid mechanistic study (rats)	48119973 (2010) Acceptable/non-guideline For thyroid effect (female rats): 20,000 ppm (1,903 mg/kg/day) for 29 days 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 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 [thyroid preparation derived from Yucatan pig, microswine]	48119979 (2010) Acceptable/non-guideline 2, 5, 10, 20, 50, 100, 200, and 400 mM 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 mM caused a 50% reduction in enzyme activity.

Table A.6. Subchronic, Chronic, and Other Toxicity Profile for Metabolites.			
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 48208474 (2010) Supplemental study to 48119983 0, 100, 400, 3,000, and 20,000 ppm M: 0, 7, 29, 212, and 1,445 mg/kg/day F: 0, 8, 31, 232, and 1,471 mg/kg/day	NOAEL = 1,445/1,471 mg/kg/day (M/F) (highest dose tested). 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. Toxicity test: 1.5, 5.0, 15, 50, 150, 500, 1,500, and 5,000 mg/plate. Confirmatory assay, 50, 150, 500, 1,500, and 5,000 mg/plate.
870.5300	*In vitro* mammalian cell gene mutation test (CHO/HGPRT assay)	48119974 (2009) Acceptable/guideline	Negative. Test concentrations: 0, 100, 150, 500, 1,000, and 1,500 mg/mL.
870.5375	*In vitro* mammalian chromosome aberration test with human lymphocytes	48119975 (2009) Acceptable/guideline	Negative. -S9: 0, 313, 625, 1,250, and 2,500 mg/mL-4-hr exposure; -S9 156, 313, 625, 1,000, 1,500, and 2,000 mg/mL 20-hr exposure; and +S9: 156, 313, 625, 1,250, and 2,500 mg/mL-4-hr exposure.
Metabolite: IN-PLT97 Toxicity Studies			
870.5100	Bacterial reverse mutation test (*S. typhimurium* & *E. coli)*	48122580 (2009) Acceptable/guideline	Negative. 0, 50, 150, 500, 1,500, and 5,000 mg/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. 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. -S9 &+S9: 50, 100, 200, 400, 800, and 1,550 mg/mL -4 hr exposure. -S9: 25, 50, 100, 200, 500, 1000, and 1,550 mg/mL - 20-hr exposure.

Table A.6. Subchronic, Chronic, and Other Toxicity Profile for Metabolites.			
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 mg/plate. Confirmatory test (Trail II): 333, 667, 1,000, 3,333, and 50,00 mg/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 mg/plate. Confirmatory assay (Trial II): 50, 150, 500, 1,500, and 5,000 mg/plate.

VI. APPENDIX B

Table B.1. Summary of Chronic Dietary (Food and Drinking) Water Exposure and Risk for Cyantraniliprole.		
Population Subgroup	**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% cPAD***
General U.S. Population	0.004194	1.5
All Infants (<1 year old)	0.007587	2.7
Children 1-2 years old*	**0.008526**	**3**
Children 3-5 years old	0.006677	2.4
Children 6-12 years old	0.004146	1.5
Youth 13-19 years old	0.003094	1.1
Adults 20-49 years old	0.003971	1.4
Adults 50-99 years old	0.003971	1.4
Females 13-49 years old	0.003948	1.4

* The population subgroup with the highest risk estimates is **bolded**.

VII. APPENDIX C

Table C.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Scenario	Formulation	Application Equipment/ Method	Comment/ Note	Application Rate	Units	Area Treated or Amount Handled Daily	Inhalation Unit Exposure (mg/lb ai)	Adult			
								Exposure	Absorbed Dose	MOE (LOC = 30)	
								Inhalation Exposure (mg/day)	Inhalation Absorbed Dose (mg/kg/day)	Inhalation MOE	Inhalation MOE (Rounded)
Gardens / Trees	Water-dispersible Granule / Dry Flowable	Manually-pressurized handwand	Surrogate data: wettable powders with manually-pressurized handwand	5.25E-06	lb ai/ft^2	1200 ft^2	1.1	0.00693	0.0000866	76,190	76,000
Gardens / Trees	Water-dispersible Granule / Dry Flowable	Manually-pressurized handwand	Surrogate data: wettable powders with manually-pressurized handwand	0.0021	lb ai/gal	5 gal	1.1	0.01155	0.0001444	45,714	46,000
Gardens / Trees	Water-dispersible Granule / Dry Flowable	Backpack	Surrogate data: wettable powders with manually-pressurized handwand	5.25E-06	lb ai/ft^2	1200 ft^2	1.1	0.00693	0.0000866	76,190	76,000

Table C.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Scenario	Formulation	Application Equipment/ Method	Comment/ Note	Application Rate	Units	Area Treated or Amount Handled Daily	Inhalation Unit Exposure (mg/lb ai)	Adult			
								Exposure	Absorbed Dose	MOE (LOC = 30)	
								Inhalation Exposure (mg/day)	Inhalation Absorbed Dose (mg/kg/day)	Inhalation MOE	Inhalation MOE (Rounded)
Gardens / Trees	Water-dispersible Granule / Dry Flowable	Backpack	Surrogate data: wettable powders with manually-pressurized handwand	0.0021	lb ai/gal	5 gal	1.1	0.01155	0.0001444	45,714	46,000

[1] Based on maximum application rates from EPA Reg. No. 100-1423.
[2] Based on HED's 2012 Residential SOPs: Gardens and Trees (http://www.epa.gov/pesticides/science/residential-expsoure-sop.html).
[3] Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/ft^2 or lb ai/gal) × Amount Handled (ft^2/day or gal/day) ÷ BW (80 kg adult).
[4] Inhalation MOE = Inhalation HED (6.6 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table C.2 Residential Post-Application Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Lifestage	Post-Application Exposure Scenario		Application Rate[1]	Dose[2] (mg/kg/day)	Incidental Oral MOE (rounded) (LOC = 30)
	Use Site	Route of Exposure			
Children 1 to <2 years old	Liquid Application to Turf	Hand-to-Mouth	0.31 lb ai/A	0.00599	1,200
		Object-to-Mouth		0.00018	38,000
		Incidental Soil Ingestion		0.000010	670,000

[1] Based on maximum application rates from EPA Reg. No. 100-1551.
[2] Incidental Oral Dose = Exposure (mg/day) ÷ BW (11 kg for children 1 to <2).
[3] Incidental Oral MOE = Incidental Oral POD (7 mg/kg/day) ÷ Incidental Oral Dose (mg/kg/day).

Table C.3. Non-Occupational Spray Drift Hand-to-Mouth Exposure and Risk Estimates for Children 1 to <2 years old from Cyantraniliprole.				
Crop/Rate Group	**Spray Type/Nozzle Configuration**	**Application Rate (lb ai/A)**	**Estimated or Adjusted TTR_t (µg/cm²)**	**At Edge HtM MOE (LOC = 30)**
Orchard/Vineyard - Soil-directed				-
Groundboom	***High Boom Very fine to Fine***	0.39	0.05499	**5,000**
	Low Boom Very fine to Fine			11,000
	High Boom Fine to Medium/Coarse			19,000
	Low Boom Fine to Medium/Coarse			28,000
Sod				
Aerial	***Fine to Medium***	0.31	0.04371	**4,500**
	Medium to Coarse			5,500
	Coarse to Very Coarse			6,400
	Very Fine to Fine			3,100
	AT401, M, 10 mph, 37% SD			5,000
	WASP, M, 10 mph, 37% SD			5,400
	AT401, C, 10 mph, 25% SD			5,900
	WASP, C, 10 mph, 25% SD			6,800
	AT401, VC, 10 mph, 20% SD			6,700
	WASP, VC, 10 mph, 20% SD			8,500
Groundboom	***High Boom Very fine to Fine***			**6,300**
	Low Boom Very fine to Fine			14,000
	High Boom Fine to Medium/Coarse			24,000
	Low Boom Fine to Medium/Coarse			35,000
Field crop, typical				
Aerial	***Fine to Medium***	0.18	0.02538	**7,800**
	Medium to Coarse			9,500
	Coarse to Very Coarse			11,000
	Very Fine to Fine			5,400
	AT401, M, 10 mph, 37% SD			8,600
	WASP, M, 10 mph, 37% SD			9,200
	AT401, C, 10 mph, 25% SD			10,000
	WASP, C, 10 mph, 25% SD			12,000
	AT401, VC, 10 mph, 20% SD			12,000
	WASP, VC, 10 mph, 20% SD			15,000
Groundboom	***High Boom Very fine to Fine***			**11,000**
	Low Boom Very fine to Fine			24,000
	High Boom Fine to Medium/Coarse			41,000

Table C.3. Non-Occupational Spray Drift Hand-to-Mouth Exposure and Risk Estimates for Children 1 to <2 years old from Cyantraniliprole.				
Crop/Rate Group	**Spray Type/Nozzle Configuration**	**Application Rate (lb ai/A)**	**Estimated or Adjusted TTR_t (µg/cm²)**	**At Edge HtM MOE (LOC = 30)**
	Low Boom Fine to Medium/Coarse			61,000
Field crop, high acreage				
Aerial	***Fine to Medium***	0.18	0.02538	**7,800**
	Medium to Coarse			9,500
	Coarse to Very Coarse			11,000
	Very Fine to Fine			5,400
	AT401, M, 10 mph, 37% SD			8,600
	WASP, M, 10 mph, 37% SD			9,200
	AT401, C, 10 mph, 25% SD			10,000
	WASP, C, 10 mph, 25% SD			12,000
	AT401, VC, 10 mph, 20% SD			12,000
	WASP, VC, 10 mph, 20% SD			15,000
Groundboom	***High Boom Very fine to Fine***			**11,000**
	Low Boom Very fine to Fine			24,000
	High Boom Fine to Medium/Coarse			41,000
	Low Boom Fine to Medium/Coarse			61,000
Orchard/Vineyard - Foliar				
Aerial	***Fine to Medium***	0.13	0.01833	**11,000**
	Medium to Coarse			13,000
	Coarse to Very Coarse			15,000
	Very Fine to Fine			7,500
	AT401, M, 10 mph, 37% SD			12,000
	WASP, M, 10 mph, 37% SD			13,000
	AT401, C, 10 mph, 25% SD			14,000
	WASP, C, 10 mph, 25% SD			16,000
	AT401, VC, 10 mph, 20% SD			16,000
	WASP, VC, 10 mph, 20% SD			20,000
Groundboom	***High Boom Very fine to Fine***			**15,000**
	Low Boom Very fine to Fine			33,000
	High Boom Fine to Medium/Coarse			57,000
	Low Boom Fine to Medium/Coarse			84,000
Airblast	***Sparse***			**19,000**
	Normal			930,000
	Dense			66,000

Table C.3. Non-Occupational Spray Drift Hand-to-Mouth Exposure and Risk Estimates for Children 1 to <2 years old from Cyantraniliprole.				
Crop/Rate Group	Spray Type/Nozzle Configuration	Application Rate (lb ai/A)	Estimated or Adjusted TTR_t (µg/cm^2)	At Edge
				HtM MOE (LOC = 30)
	Vineyard			350,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.									
Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Mixer/Loader									
Dry Flowable, Aerial, Broadcast	Orchard/Vineyard	8.96	No-R	0.13	lb ai/acre	350	acres	0.0051	3,900
Dry Flowable, Aerial, Broadcast	Field crop, typical	8.96	No-R	0.18	lb ai/acre	350	acres	0.00705	2,800
Dry Flowable, Aerial, Broadcast	Field crop, high-acreage	8.96	No-R	0.13	lb ai/acre	1200	acres	0.0175	1,100
Dry Flowable, Airblast, Broadcast	Orchard/Vineyard	8.96	No-R	0.13	lb ai/acre	40	acres	0.000583	34,000
Dry Flowable, Chemigation, Broadcast	Orchard/Vineyard	8.96	No-R	0.13	lb ai/acre	350	acres	0.0051	3,900
Dry Flowable, Chemigation, Broadcast	Field crop, typical	8.96	No-R	0.18	lb ai/acre	350	acres	0.00705	2,800
Dry Flowable, Chemigation, Broadcast	Field crop, high-acreage	8.96	No-R	0.13	lb ai/acre	350	acres	0.0051	3,900
Dry Flowable, Chemigation, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	8.96	No-R	0.13	lb ai/acre	60	acres	0.000874	23,000
Dry Flowable, Chemigation, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	8.96	No-R	0.13	lb ai/acre	60	acres	0.000874	23,000
Dry Flowable, Groundboom, Broadcast	Golf course (tees and greens only)	8.96	No-R	0.13	lb ai/acre	5	acres	0.0000728	270,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Dry Flowable, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	8.96	No-R	0.13	lb ai/acre	5	acres	0.0000728	270,000
Dry Flowable, Groundboom, Broadcast	Golf course (fairways, tees, greens)	8.96	No-R	0.13	lb ai/acre	40	acres	0.000583	34,000
Dry Flowable, Groundboom, Broadcast	Field-grown ornamental crops	8.96	No-R	0.13	lb ai/acre	40	acres	0.000583	34,000
Dry Flowable, Groundboom, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	8.96	No-R	0.13	lb ai/acre	60	acres	0.000874	23,000
Dry Flowable, Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	8.96	No-R	0.13	lb ai/acre	60	acres	0.000874	23,000
Dry Flowable, Groundboom, Broadcast	Sod	8.96	No-R	0.26	lb ai/acre	80	acres	0.00233	8,500
Dry Flowable, Groundboom, Broadcast	Orchard/Vineyard	8.96	No-R	0.13	lb ai/acre	40	acres	0.000583	34,000
Dry Flowable, Groundboom, Broadcast	Field crop, typical	8.96	No-R	0.18	lb ai/acre	80	acres	0.00161	12,000
Dry Flowable, Groundboom, Broadcast	Field crop, high-acreage	8.96	No-R	0.13	lb ai/acre	200	acres	0.00291	6,800
Liquid, Aerial, Broadcast	Orchard/Vineyard	0.219	No-R	0.13	lb ai/acre	350	acres	0.000125	160,000
Liquid, Aerial, Broadcast	Field crop, typical	0.219	No-R	0.13	lb ai/acre	350	acres	0.000125	160,000
Liquid, Aerial, Broadcast	Field crop, high-acreage	0.219	No-R	0.13	lb ai/acre	1200	acres	0.000428	46,000
Liquid, Airblast, Broadcast	Orchard/Vineyard	0.219	No-R	0.13	lb ai/acre	40	acres	0.0000143	1,400,000
Liquid, Chemigation, Broadcast	Orchard/Vineyard	0.219	No-R	0.39	lb ai/acre	350	acres	0.000374	53,000
Liquid, Chemigation, Broadcast	Field crop, typical	0.219	No-R	0.18	lb ai/acre	350	acres	0.000173	120,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Liquid, Chemigation, Broadcast	Field crop, high-acreage	0.219	No-R	0.13	lb ai/acre	350	acres	0.000125	160,000
Liquid, Groundboom, Broadcast	Golf course (tees and greens only)	0.219	No-R	0.31	lb ai/acre	5	acres	0.00000424	4,700,000
Liquid, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.219	No-R	0.31	lb ai/acre	5	acres	0.00000424	4,700,000
Liquid, Groundboom, Broadcast	Golf course (fairways, tees, greens)	0.219	No-R	0.31	lb ai/acre	40	acres	0.000034	590,000
Liquid, Groundboom, Broadcast	Sod	0.219	No-R	0.31	lb ai/acre	80	acres	0.0000679	290,000
Liquid, Groundboom, Broadcast	Orchard/Vineyard	0.219	No-R	0.39	lb ai/acre	40	acres	0.0000428	460,000
Liquid, Groundboom, Broadcast	Field crop, typical	0.219	No-R	0.18	lb ai/acre	80	acres	0.0000394	510,000
Liquid, Groundboom, Broadcast	Field crop, high-acreage	0.219	No-R	0.18	lb ai/acre	200	acres	0.0000985	200,000
Applicator									
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	0.0049	EC/No-R	0.13	lb ai/acre	350	acres	0.00000279	7,100,000
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	0.0049	EC/No-R	0.18	lb ai/acre	350	acres	0.00000386	5,200,000
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	0.0049	EC/No-R	0.18	lb ai/acre	1200	acres	0.0000133	1,500,000
Spray (all starting formulations), Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	0.068	EC/No-R	0.13	lb ai/acre	20	acres	0.00000221	9,000,000
Spray (all starting	Orchard/Vineyard	0.068	EC/No-R	0.13	lb ai/acre	40	acres	0.00000443	4,500,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.									
Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
formulations), Airblast, Broadcast									
Flagger									
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	0.202	No-R	0.13	lb ai/acre	350	acres	0.000115	170,000
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	0.202	No-R	0.18	lb ai/acre	350	acres	0.000159	130,000
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	0.202	No-R	0.13	lb ai/acre	350	acres	0.000115	170,000
Mixer/Loader/Applicator									
Dry Flowable, Backpack, Ground/soil-directed	Orchard/Vineyard	2.58	No-R	0.039	lb ai/gallon solution	40	gallons solution	0.0000503	400,000
Dry Flowable, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	140	No-R	0.013	lb ai/gallon solution	7	gallons solution	0.000159	130,000
Dry Flowable, Backpack, Broadcast (foliar)	Christmas Tree farm	69.1	No-R	0.013	lb ai/gallon solution	40	gallons solution	0.000449	44,000
Dry Flowable, Backpack, Ground/soil-directed	Christmas Tree farm	2.58	No-R	0.013	lb ai/gallon solution	40	gallons solution	0.0000168	1,200,000
Dry Flowable, Backpack, Ground/soil-directed	Conifer plantation	2.58	No-R	0.013	lb ai/gallon solution	40	gallons solution	0.0000168	1,200,000
Liquid, Backpack, Ground/soil-directed	Orchard/Vineyard	2.58	No-R	0.039	lb ai/gallon solution	40	gallons solution	0.0000503	400,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Liquid, Backpack, Ground/soil-directed	Christmas Tree farm	2.58	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.0000271	730,000
Liquid, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	140	No-R	0.021	lb ai/gallon solution	7	gallons solution	0.000258	77,000
Liquid, Backpack, Broadcast (foliar)	Christmas Tree farm	69.1	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000725	27,000
Liquid, Backpack, Ground/soil-directed	Conifer plantation	2.58	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.0000271	730,000
Liquid, Backpack, Broadcast (foliar)	Nursery (ornamentals, vegetables, trees, container stock)	69.1	No-R	0.021	lb ai/gallon solution	15	gallons solution	0.000273	73,000
Liquid, Backpack, Broadcast (foliar)	Landscaping, trees/shrubs/bushes	69.1	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000725	27,000
Liquid, Backpack, Broadcast	Conifer plantation	69.1	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000725	27,000
Liquid, Backpack, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	2.58	No-R	0.031	lb ai/gallon solution	40	gallons solution	0.00004	500,000
Liquid, Manually-pressurized Handwand, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	23.6	No-R	0.021	lb ai/gallon solution	7	gallons solution	0.0000434	460,000
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Christmas Tree farm	23.6	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000248	80,000
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Nursery (ornamentals,	23.6	No-R	0.021	lb ai/gallon solution	15	gallons solution	0.0000929	210,000

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
	vegetables, trees, container stock)								
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Landscaping, trees/shrubs/bushes	23.6	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000248	80,000
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Landscaping, plants/flowers	23.6	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000248	80,000
Liquid, Manually-pressurized Handwand, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	23.6	No-R	0.031	lb ai/gallon solution	40	gallons solution	0.000366	54,000
Liquid, Manually-pressurized Handwand, C&C	Warehouse	1044	No-R	0.0087	lb ai/gallon solution	40	gallons solution	0.00454	4,400
Liquid, Manually-pressurized Handwand, Broadcast	Exterior Building Components (e.g., foundations, perimeters, door/window frames, etc.)	23.6	No-R	0.0087	lb ai/gallon solution	40	gallons solution	0.000103	190,000
Liquid, Manually-pressurized Handwand, Broadcast (foliar)	Interior landscaping	23.6	No-R	0.021	lb ai/gallon solution	40	gallons solution	0.000248	80,000
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Orchard/Vineyard	8.68	No-R	0.013	lb ai/gallon solution	1000	gallons solution	0.00141	14,000
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Orchard/Vineyard	8.68	No-R	0.039	lb ai/gallon solution	1000	gallons solution	0.00424	4,700
Liquid, Mechanically-pressurized Handgun, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	448	No-R	0.021	lb ai/gallon solution	175	gallons solution	0.0206	970

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	448	No-R	0.021	lb ai/gallon solution	175	gallons solution	0.0206	970
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	1.9	No-R	0.31	lb ai/acre	5	acres	0.0000369	540,000
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	1.9	No-R	0.31	lb ai/acre	5	acres	0.0000369	540,000
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Christmas Tree farm	8.68	No-R	0.021	lb ai/gallon solution	1000	gallons solution	0.00228	8,700
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Nursery (ornamentals, vegetables, trees, container stock)	448	No-R	0.021	lb ai/gallon solution	300	gallons solution	0.0353	560
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Nursery (ornamentals, vegetables, trees, container stock)	448	No-R	0.021	lb ai/gallon solution	300	gallons solution	0.0353	560
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Landscaping, trees/shrubs/bushes	8.68	No-R	0.021	lb ai/gallon solution	1000	gallons solution	0.00228	8,700
Liquid, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.9	No-R	0.31	lb ai/acre	5	acres	0.0000369	540,000
Liquid, Mechanically-pressurized Handgun, Broadcast (foliar)	Field crop, typical	8.68	No-R	0.013	lb ai/gallon solution	1000	gallons solution	0.00141	14,000
Liquid, Mechanically-pressurized Handgun, Drench/Soil-/Ground-directed	Field crop, typical	8.68	No-R	0.018	lb ai/gallon solution	1000	gallons solution	0.00195	10,000
Loader/Applicator									

Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Granule, Belly grinder, Broadcast	Industrial/commercial (tires, rail yards, junk yards, etc.)	80.6	No-R	0.087	lb ai/acre	1	acres	0.0000876	230,000
Granule, Belly grinder, Broadcast	Barn/Feedlot	80.6	No-R	0.087	lb ai/acre	0.2	acres	0.0000175	1,100,000
Granule, Belly grinder, Broadcast	Exterior Building Components (e.g., foundations, perimeters, door/window frames, etc.)	80.6	No-R	0.087	lb ai/acre	1	acres	0.0000876	230,000
Granule, Cup, Broadcast	Industrial/commercial (tires, rail yards, junk yards, etc.)	12.5	No-R	0.000002	lb ai/square foot	43560	square feet	0.0000136	1,500,000
Granule, Cup, Broadcast	Warehouse	12.5	No-R	0.000002	lb ai/square foot	43560	square feet	0.0000136	1,500,000
Granule, Cup, Broadcast	Barn/Feedlot	12.5	No-R	0.000002	lb ai/acre	0.2	acres	6.25E-11	320,000,000,000
Granule, Cup, Broadcast	Exterior Building Components (e.g., foundations, perimeters, door/window frames, etc.)	12.5	No-R	0.000002	lb ai/square foot	43560	square feet	0.0000136	1,500,000
Granule, Rotary spreader, Broadcast	Industrial/commercial (tires, rail yards, junk yards, etc.)	10	No-R	0.08712	lb ai/acre	5	acres	0.0000545	370,000
Granule, Spoon, Ground/soil-directed	Industrial/commercial (tires, rail yards, junk yards, etc.)	121	No-R	0.000002	lb ai/square foot	43560	square feet	0.000131	150,000
Granule, Rotary spreader, Broadcast	Poultry house (whole-house treatment of litter, walls, etc.)	10	No-R	0.08712	lb ai/acre	5	acres	0.0000545	370,000
Granule, Rotary spreader, Broadcast	Barn/Feedlot	10	No-R	0.08712	lb ai/acre	0.2	acres	0.00000218	9,100,000

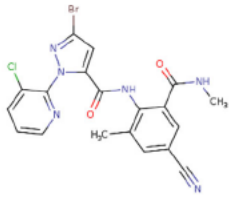
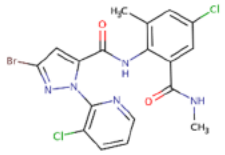
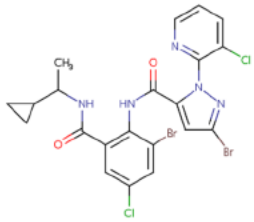
Table C.4. Occupational Handler Non-Cancer Exposure and Risk Estimates for Cyantraniliprole.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
								Dose (mg/kg/day)	MOE (LOC = 30)
Granule, Spoon, Ground/soil-directed	Barn/Feedlot	121	No-R	0.08712	lb ai/acre	0.2	acres	0.0000264	750,000
Granule, Spoon, Ground/soil-directed	Exterior Building Components (e.g., foundations, perimeters, door/window frames, etc.)	121	No-R	0.000002	lb ai/square foot	43560	square feet	0.000131	150,000

Link to table C.5 Cyantraniliprole_USEPA-OPP-HED_Seed Treatment and Planting Exposure_March2022

VIII. APPENDIX D

Table D.1. Structurally Similar Chemicals

Chemical Name	CAS #	Structure	Similarity to Cyantraniliprole (%)	pKa	logK	Vapor Pressure	Target Organ
Cyantraniliprole	736994-63-1			8.8 ± 1.38	1.94 + 0.11 at 20°C	5.13 x 10^{-15} Pa at 20°C	Thyroid
Chlorantraniliprole	500008-45-7		96	10.88 ± 0.71	Deionized Water 589 pH 4 588 pH 7 721 pH 9 654	6.3 x 10^{-12} Pa @ 20°C, 2.1 x 10^{-11} Pa @ 25°C	None - Chronic dietary only based on chronic mouse (935 mg/kg/day)
Cyclaniliprole	1031756-98-5		87	8.6	557 (log_{10} = 2.7)	2.4X10^{-6} Pa	None - qualitative risk assessment conducted

All tables are based on the most up-to-date information available at the time of the HASPOC meeting and are subject to change.