OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: **April 2, 2024**

SUBJECT: **Cyclaniliprole**. Petition for New Greenhouse Uses on Lettuce and Cucumber and Amendment of Tolerances on Cucurbit Vegetables Crop Group 9. Summary of Analytical Chemistry and Residue Data.

PC Code: 026202
CAS No.: 1031756-98-5
Decision No.: 591152
Petition No.: 2E9037
Risk Assessment Type: NA
TXR No.: NA
MRID No.: See below

DP Barcode: D468364
Task Group No.: 00484698
Parent Case No.: 00482628
Registration No.: 71512-26
Regulatory Action: Section 2 Registration
Reg. Review Case No.: NA
40 CFR: 180.694

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Summary of Submitted Residue Chemistry Studies		
OCSPP 860 Series Guideline	MRID Number	Title
860.1500	52037601	Pike, T. (2022) Cyclaniliprole: Magnitude of the Residue on Lettuce (Greenhouse). Study Numbers: 12515; 12515.19-FLR03. Unpublished study prepared and submitted by Interregional Research Project Number 4. 175 p.
860.1500	52037602	Czechura, P. (2021) Cyclaniliprole: Magnitude of the Residue on Cucumber, Greenhouse. Study No. AAFC18-035R. Unpublished study prepared by the Pest Management Centre, Agriculture and Agri-Food Canada, Vineland, ON. 119 p.

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.

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1.0 Executive Summary

Cyclaniliprole (3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide) is an anthranilic diamide insecticide. It targets the activation of insect ryanodine receptors, impairing regulation of muscle contractions followed by paralysis.

Interregional Research Project No. 4 (IR-4) on behalf of the registrant ISK Biosciences Corporation (ISK) has submitted registrations for the use of cyclaniliprole on new greenhouse uses on lettuce and cucumber and amended tolerances on cucurbit vegetables crop group 9. There are established tolerances for residues in/on leafy vegetables 4-16 at 15 ppm and cucurbit vegetables at 0.15 ppm.

Proposed Use Profile

The end-use product (EP) relevant to this registration action is Cyclaniliprole 50SL Insecticide (EPA Reg. No. 71512-26). The product is marketed as soluble liquid (SL) formulations and contain 0.42 lb ai/gal (50 g ai/L). Cyclaniliprole 50SL Insecticide (EPA Reg. No. 71512-26) proposes a maximum of three applications at a maximum single application rate of 0.054 lb ai/A, with total maximum rate of 0.16 lb ai/A/year to greenhouse grown lettuce and at a maximum single application rate of 0.089 lb ai/A, with total maximum rate of 0.27 lb ai/A/year to greenhouse grown cucumber. The proposed preharvest intervals (PHIs) range from 0-days (cucumber) to 1-day (lettuce).

The nature of the residue in plants is adequately understood based on metabolism studies on apples, lettuce, and potatoes representing fruit, leafy, and root crops. Cyclaniliprole is the major residue in these crops. The nature of the residue in rotational crops is adequately understood based on confined and limited field rotational crop studies. HED has determined that the residue of concern for tolerance enforcement in plant commodities (primary and rotational crop) is cyclaniliprole (The Residues of Concern Knowledge-based Subcommittee (ROCKS) decision memo; D428093, I. Negrón-Encarnación, 31-JUL-2015).

The nature of the residue in livestock is adequately understood based on metabolism studies with lactating goats and laying hens. In both goats and hens, cyclaniliprole was a major residue. Metabolites NSY-28, YT-1284, and NSY-27 were found in both hens and goats (Refer to Appendix A for chemical names and structures). HED has determined that the residue of concern for tolerance enforcement in ruminant and poultry commodities is parent cyclaniliprole (ROCKS decision memo; D428093, I. Negrón-Encarnación, 31-JUL-2015).

Adequate enforcement methods are available for plants and livestock commodities. Both methods utilize a high-performance liquid chromatography (HPLC) method with tandem mass spectrometry detection (MS/MS). Cyclaniliprole is not recovered using the food drug administration (FDA) multi-residue methods. The enforcement method was used for data collection for the proposed crops.

Adequate storage stability data are available for residues of cyclaniliprole in five categories of plant commodity matrices. The intervals of demonstrated storage stability cover the actual intervals of frozen storage of samples from the crop field trials. Adequate cattle feeding study is available. No poultry feeding study was conducted and none is required to support the registered/proposed uses at this time. If a poultry feeding study is conducted in the future, then analysis for cyclopropanecarboxylic

acid (CPCA) is recommended.

There are no feedstuffs associated with this petition; therefore, the existing tolerances on ruminant commodities are adequate.

Adequate supporting field trial data on greenhouse grown lettuce and cucumber were submitted.

2.0 Regulatory Recommendations

There are no residue chemistry considerations that would preclude the establishment of permanent tolerances and registration for greenhouse uses on cucumber and lettuce.

The specific tolerance recommendations are discussed in Section 2.2.

2.1 Data Deficiencies/Data Needs

None

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate enforcement methods are available for plant and livestock commodities.

The enforcement method for plants (Method JSM0269) separately determines cyclaniliprole and its metabolite NK-1375 in/on crop commodities. Residues are extracted using acetonitrile and cleaned up by solid-phase extraction (SPE). Extracted residue levels are determined by LC-MS/MS. The limit of quantitation (LOQ) is 0.01 ppm for each analyte in each plant matrix.

The enforcement method for livestock commodities (Method JSM0277) separately determines cyclaniliprole and the four metabolites NK-1375, NSY-27, NSY-28 and YT-1284 (For chemical names, Refer to Appendix A). Residues are extracted using acetonitrile and cleaned up by liquid-liquid partition with hexane followed by SPE. Extracted residue levels are determined by LC-MS/MS. The method LOQ for all five analytes is 0.01 ppm in each matrix (liver, kidney, fat, muscle, milk, and eggs).

2.2.2 Recommended Tolerances

Tolerances are proposed for residues of the insecticide cyclaniliprole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only cyclaniliprole, 3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide, in or on the commodity.

The compliance statement is in accordance with the Final Guidance on Tolerance Expressions (D. Wilbur; 12-JUL-2022).

Table 2.2.2. Tolerance Summary for Cyclaniliprole.			
Commodity/Correct Commodity Definition	**Established/Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
Vegetable, leafy, group 4–16	15 Established No Tolerance is proposed	--	The established tolerance is appropriate
Vegetable, cucurbit, group 9	0.15 Established 0.3 Proposed	**0.3**	Based on the available data and OECD calculation

2.2.3 Revisions to Petitioned-For Tolerances

There are no revisions to the petitioned for tolerances.

2.2.4 International Harmonization

The tolerance definitions are harmonized among the U.S., Canada, and Codex for plant and livestock commodities.

There are Codex maximum residue limits (MRLs) established for residues on cucumber and squash (summer) at 0.05 ppm; and melons, pumpkin, squash (winter) at 0.1 ppm. For cucurbit vegetables group 9, no harmonization is possible for these commodities because decreasing the tolerance level to harmonize with the Codex MRL could put U.S. growers at risk of violative residues despite legal use of cyclaniliprole.

There are Codex MRLs established for residues on leafy greens subgroup (7 ppm), leaves of Brassicaceae Brassica (10 ppm), head Brassicas (0.7 ppm), and flowerhead Brassicas (0.8 ppm). For leafy greens subgroup 4-16 (15 ppm), no harmonization is possible for these commodities because decreasing the tolerance level to harmonize with the Codex MRL could put U.S. growers at risk of violative residues despite legal use of cyclaniliprole.

There are Canadian MRLs established for residues on cucurbit vegetables group 9 at 0.1 ppm and leafy vegetables at 10 ppm. This petition is being reviewed concurrently both by EPA and by PMRA Canada. PMRA is establishing MRLs on cucumber at 0.3 ppm and leaf lettuce at 15 ppm.

Refer to International Residue Limits table (Attachment C).

HED has determined that there is no toxicological concern from use of cyclaniliprole, tolerances are being established by the U.S. for trade purposes.

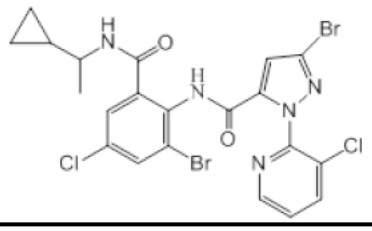
2.3 Label Recommendations

None.

3.0 Introduction

Cyclaniliprole is an anthranilic diamide insecticide that targets the activation of ryanodine receptors in insects, impairing regulation of muscle contractions followed by paralysis.

3.1 Chemical Identity

Table 3.1. Test Compound Nomenclature.	
Compound	Chemical Structure 
Common name	cyclaniliprole
Company experimental name	IKI-3106
IUPAC name	2′,3-dibromo-4′-chloro-1-(3-chloro-2-pyridyl)-6′-{[(1*RS*)-1-cyclopropylethyl]carbamoyl}pyrazole-5-carboxamide
CAS name	3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide
CAS #	1031756-98-5
End-use product/EP	Cyclaniliprole 50 SL [EPA Reg. No. 71512-26]

3.2 Physical/Chemical Characteristics

Cyclaniliprole (pure active ingredient; PAI) is not a volatile chemical since it has a low vapor pressure. It is more soluble in polar organic compounds as compared to nonpolar organic compounds. It is not very soluble in water.

Table 3.2. Physicochemical Properties of the Technical Grade Test Compound: Cyclaniliprole.			
Parameter	**Value**		**Reference (MRID)**
Molecular weight (g/mole)	602.11		49289301
Melting point/range	241 – 244 °C (PAI)		49289303
pH	5.9 (TGAI)		49289303
Relative density at 20°C	1.57 (TGAI)		49289303
Water solubility (20°C)	0.15 mg/L(PAI)		49289303
Solvent solubility (g/L at 20°C) (TGAI)	n-heptane xylene 1,2-dichloromethane acetone methanol n-octanol ethyl acetate	0.0001 0.20 4.4 10 4.0 1.5 3.6	49289303
Vapor pressure at 25 °C	2.4 x 10^{-6} Pa (1.8 x 10-8 torr) (PAI)		49289303
Dissociation constant (pK_a)	8.6 (PAI)		49289303
Octanol/water partition coefficient Log (K_{OW})	557 (log_{10} Pow = 2.7) (PAI)		49289303

3.3 Pesticide Use Pattern/Directions for Use (860.1200)

ISK Biosciences Corporation, the product registrant, is supporting registration of Cyclaniliprole 50SL Insecticide (EPA Reg. No. 71512-26). The EP is a SL formulation containing 0.42 lb ai/gal (50 g ai/L); and is to be applied as broadcast foliar sprays using ground, aerial, or chemigation equipment. The proposed uses are summarized in Table 3.3.1.

Table 3.3. Summary of Proposed Directions for Use of Cyclaniliprole.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate fl oz (lb ai/A)	Max. No. Applic. per Year	Max. Yearly Applic. Rate fl oz (lb ai/A)	RTI[1] days	PHI[2] days	Use Directions, and Limitations[3]
Greenhouse Lettuce[4]							
Post-emergence; Foliar, broadcast; Ground, air, or chemigation equipment	Cyclaniliprole 50 SL [71512-26] 0.42 lb ai/gal	16.4 (0.054) Or 0.38 fl oz/1000 sq ft 0.0012 lb ai/1000 sq ft	3	49.2 (0.16)	7 14- CA	1	In California no more than one application may be made from the onset of flowering until flowering is complete. Applications must be made when bees are not foraging, adhering to the above restrictions.
Greenhouse Cucumber							
Post-emergence; Foliar, broadcast; Ground, air, or chemigation equipment	Cyclaniliprole 50 SL [71512-26] 0.42 lb ai/gal	27.1 (0.089)	3	81.3 (0.27)	7 14- CA	0	Thorough coverage is essential to achieve best results. In New York State, do not apply more than 54 fl oz/Acre/ year (0.18 lb ai/Acre/year).
		(0.036-0.054) (Field grown)		(0.16) (Field grown)		1 (Field grown)	

[1] RTI = re-treatment interval.
[2] PHI = pre-harvest interval.
[3] Foliar application of this product is prohibited to a crop from onset of flowering until flowering is complete unless: (1) the application is being made in the time period between 2 hours prior to sunset until sunrise; or, (2) the application is being made at a time when the temperature at the application site is 50 degrees F or less. The restricted entry interval (REI) is 4 hours.
Performance may be enhanced when used with methylated seed oil (MSO) or other high quality adjuvants at a rate of 0.025% to 0.1% on a volume to volume basis.
[4] The use pattern for greenhouse lettuce is similar to field grown.

Conclusions. The proposed label is sufficient to assess the proposed use patterns and adequate to support registration.

4.0 Metabolite/Degradate Residue Profile

4.1 Nature of the Residue

Refer to Appendix A for chemical names and structures of parent and metabolites/degradates.

Conclusions of the metabolism of cyclaniliprole are provided below. For complete discussion of the metabolism summaries, see section 4.1 of D421034, N. Dodd, 09-DEC-2015.

4.1.1 Summary of Plant Metabolism (860.1300)

D421034, N. Dodd, 09-DEC-2015

Adequate metabolism studies for cyclaniliprole on three diverse crops (apples, lettuce and potatoes) is available. Two radiolabels, phenyl (^{14}C-Ph) and pyrazole (^{14}C-Pz) ring labels, were separately used on each crop. Cyclaniliprole is the major residue in apples, lettuce, and potatoes. The major metabolic pathway of cyclaniliprole in all three crops involves intramolecular cyclization resulting in the predominant metabolite NK-1375; the minor pathway is hydrolysis of the amino-cyclopropane bond yielding YT-1284, identified in apples and lettuce but not in potatoes. The residue of concern for the tolerance expression is parent (ROCKS; D428093, I. Negrón-Encarnación, 31-JUL-2015).

4.1.2 Summary of Livestock Metabolism (860.1300)

D421034, N. Dodd, 09-DEC-2015

Adequate metabolism studies are available in goats and hens. Two radiolabels, phenyl (^{14}C-Ph) and pyrazole (^{14}C-Pz) ring labels, were separately used on both goats and hens. The daily doses were orally administered at a rate of 10 ppm in the diet per day (MRBD=0.201 ppm; 50x the calculated dietary burden in dairy cattle).

In goats, cyclaniliprole was identified as a major (≥10% of the TRR) component in all edible matrices (both radiolabels). The metabolites NSY-28 and YT-1284 were also identified as major components in liver, kidney, and muscle. YT-1284 was also a major component in whole milk and the aqueous milk fraction. NSY-28 was a major metabolite with the Pz-label only in the milk aqueous fraction and fat. NSY-27 was detected as a minor (<10% TRR) metabolite in all liver, kidney, whole milk, and the aqueous milk fraction with both labels and in fat and milk fat with the Ph-label only; NSY-27 was not detected in muscle (both labels) or in fat and milk fat with the Pz-label. Other minor unidentified metabolites were detected, with each accounting for ≤8.6% of the TRR.

In hens, cyclaniliprole was detected as a major compound (>10% of the TRR) for both radiolabels in eggs, fat, skin, for the Ph-label only in muscle, and for the Pz-label only in liver. NSY-28 was a major metabolite in all tissues. YT-1284 was detected, depending on the sample and/or the label, as a minor (<10% of the TRR; eggs, liver, fat) and/or major (fat, skin, muscle) component. NSY-27 was detected at low levels in muscle and skin (both labels), and in excreta, eggs and fat ([^{14}C-Ph]-label only). Based on the results from the goat and hen studies, the majority of radioactive residues derived from the oral administration of cyclaniliprole to ruminants and poultry is largely excreted. Metabolism of cyclaniliprole in goats and hens proceeds via hydrolysis of the amino-cyclopropane bond yielding YT-1284. YT-1284 can either undergo hydrolysis at the carboxylic amide of the phenyl ring producing NSY-27, or alternatively intramolecular cyclization yielding NSY-28.

The residue of concern for the tolerance expression in ruminant and poultry commodities is parent (ROCKS; D428093, I. Negrón-Encarnación, 31-JUL-2015).

4.1.3 Summary of Confined Rotational Crops (860.1850)

D421034, N. Dodd, 09-DEC-2015

Adequate confined rotational crop study is available. The rotational crops carrots, lettuce, and wheat were planted 30, 120, and 365 days after application of [^{14}C-Ph]-cyclaniliprole in a 50SL formulation to sandy loam soil at the rate of 100 g ai/ha (0.089 lb ai/A, 0.33x the maximum yearly application rate for proposed crops). Since TRR in lettuce and carrots (foliage and roots) sown in soil aged for either 30 or 120 days were less than 0.01 ppm, residues in lettuce and carrots were not characterized further. Residues in wheat grain were not identified since TRR were ≤0.001 ppm at all PBIs. Residues found in wheat forage, hay, and straw were primarily cyclaniliprole and included a small amount of NK-1375. Since residues greater than 0.01 ppm were found in wheat forage, hay, and straw, limited field trials were conducted on wheat at 1x.

The residue of concern for the tolerance expression in rotational crops is parent (ROCKS; D428093, I. Negrón-Encarnación, 31-JUL-2015).

Although the study was conducted at 0.33x the maximum yearly rate for proposed crops and residues in carrots and lettuce (unlike wheat) were not studied in limited field accumulation in rotational crop studies, residues in lettuce and carrots (foliage and roots) were very low (≤0.002 ppm); therefore, a confined rotational crops study conducted at 1x the yearly proposed rate is not needed for carrots and lettuce.

4.1.4 Summary of Metabolites and Degradates

Refer to the summary table of parent and degradates in Appendix A.

4.2 Comparison of Metabolic Pathways

Metabolism in target plants (apples, lettuce, and potatoes) is similar. The major metabolic pathway of cyclaniliprole in all three crops involves intramolecular cyclization resulting in the predominant metabolite NK-1375; a minor pathway found in apples and lettuce is hydrolysis of the amino-cyclopropane bond yielding YT-1284. Cyclaniliprole was the major residue and NK-1375 was the major metabolite in all three plants. YT-1284 was found in apples and lettuce but was not found in potatoes.

Residues in rotational crops were low; the only identified metabolite in the rotational crop wheat was the plant metabolite NK-1375.

Metabolism in goats and hens is similar. Metabolism of cyclaniliprole in goats and hens proceeds via hydrolysis of the amino-cyclopropane bond yielding YT-1284. YT-1284 can either undergo hydrolysis at the carboxylic amide of the phenyl ring producing NSY-27, or alternatively intramolecular cyclization yielding NSY-28. Parent was a major residue in both goat and hen matrices. NSY-28 and YT-12184 were found as major metabolites in both goats and hens. NSY-27 was found as a minor metabolite in both goats and hens.

Metabolism in target plants and livestock (goats and hens) differs. The plant metabolite NK-1375 was not found in livestock. The livestock metabolites NSY-28 and NSY-27 were not found in plants.

4.3 Residues of Concern Summary and Rationale

ROCKS Decision Memo (D428093, I. Negrón-Encarnación, 31-JUL-2015)

As shown in Table 4.3 below, the Agency recommends parent cyclaniliprole only as the residue of concern to be included in the tolerance expression. Since there are no toxicological endpoints, a quantitative risk assessment will not be conducted; therefore, the Agency is not identifying residues of concern for risk assessment. Furthermore, the Agency does not have any hazard concern for metabolites and/or degradates of cyclaniliprole that may be found in drinking water, plants, and livestock. The Agency assumes that environmental metabolites and degradates that may be found in food and drinking water would have a similar mammalian hazard profile as compared to the parent compound and can therefore be excluded from a quantitative dietary risk assessment.

Table 4.3. Summary of Metabolites and Degradates Included in the Risk Assessment and Tolerance Expression.

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Not applicable[1]	Cyclaniliprole
	Rotational Crop	Not applicable[1]	Cyclaniliprole
Livestock	Ruminant	Not applicable[1]	Cyclaniliprole
	Poultry	TBD[2]	Not applicable
Drinking Water		Not applicable	Not Applicable

[1] This recommendation applies only to the uses proposed in this petition. Cyclopropane carboxylic acid (CPCA) is theoretically a potential residue of concern (only because of the lack of concern for the toxicity of the parent), but estimated exposures are likely to be low. To support the current petition, the risk assessment team should address this metabolite qualitatively.

[2] To be determined. No uses on poultry feed items are proposed. Since metabolism studies showed significant cleavage of the cyclopropane ring which may lead to formation of CPCA which is of potential toxicity concern, more information is needed if uses on poultry feed items are proposed in the future.

Rationale

Residues of Concern for Tolerance Enforcement: Parent cyclaniliprole was the predominant residue of observed in primary crops, rotational crops, and livestock. Based on this, HED recommends parent cyclaniliprole only as the residue of concern for tolerance enforcement.

Residues of Concern for Risk Assessment: Residues of concern in plants, livestock, and water were not selected for risk assessment purposes based on the absence of adverse effects at the highest doses tested in all of the required toxicity studies for cyclaniliprole, and the structural similarity of most degradates/metabolites with the parent compound. Those that retain all the rings of the parent compound are expected to have the same or lesser toxicity and similar hazard. Based on this, no quantitative assessment is necessary for parent or degradates/metabolites at this time.

It is noted that the cyclopropyl moiety is not present in YT-1284, NSY-27, and NSY-28. Because this moiety was not radiolabeled its fate could not be followed. Cyclopropane carboxylic acid is a potential degradate/metabolite of the cyclopropyl moiety. It has been reported to cause liver steatosis at 10 mg/kg/day in rats (D387448, J. Ryman, 18-APR-2012). The greatest exposure (on a relative basis) to YT-1284, NSY-27, and NSY-28 in any study was in the poultry metabolism study. However, no use has been proposed on any poultry feed items (at the initial registration). With respect to plants, cleavage metabolites in which the cyclopropyl moiety was cleaved were minor metabolites in primary crop metabolism studies. A back-calculation on a molecular weight basis to the molecular weight of the CPCA showed that the maximum exposure would be in the parts per trillion levels which is significantly lower than the population adjusted dose for CPCA (aPAD and cPAD are 0.0026 and 0.00087 mg/kg/day, respectively). With ruminants, the goat metabolism study did show potential for residues of these

degradates; however, the cattle feeding study, did not show detectable residues of the cleavage metabolites at least at a 2X feeding level (maximum reasonable dietary burden). There were detectable residues at the highest dose tested, which would indicate a potential concern if new registrations have feedstuff commodities associated which would significantly increase the ruminant dietary burden. With respect to drinking water, the cleavage metabolites were minor metabolites in the environmental fate studies for cyclaniliprole. The half-life for the parent is >381 days, so there is not likely to be significant exposure. In summary, no quantitative risk assessment considering the potential presence of CPCA is needed to support the currently proposed uses. The risk assessment team will address this metabolite qualitatively. In the future, if higher livestock dietary burdens are likely, then a quantitative risk assessment for CPCA may be needed.

5.0 Residue Profile

5.1 Residue Analytical Methods (860.1340)

5.1.1 Data Collection Methods

D421034, N. Dodd, 09-DEC-2015

Samples of lettuce and cucumber were analyzed for residues of cyclaniliprole and metabolite NK-1375 using a LC/MS/MS, Method JSM0269, with modifications. This method was previously deemed acceptable for tolerance enforcement (D421034, N. Dodd, 09-DEC-2015). The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.010 ppm for each analyte in lettuce and cucumber.

Acceptable method validation and concurrent recoveries were obtained from samples of lettuce and cucumber fortified with cyclaniliprole at 0.010-20 ppm and NK-1375 at 0.010-1.0 ppm, thus validating the method. The fortification levels were adequate to represent measured residue levels.

Method performance was evaluated during method validation (MV) and by use of concurrent recovery (CR) samples by fortifying greenhouse cucumbers with 0.01, 0.02 (MV only), 0.1 and 0.2 ppm cyclaniliprole and NK-1375. All recoveries were within the acceptable range of 70% to 120%; therefore, the method was considered valid for the analysis of cyclaniliprole and NK-1375 residues in cucumber matrices. The fortification levels did bracket the measured residues.

Conclusions. The method used for data collection has been adequately validated as data collection method. Acceptable method validation and concurrent recoveries for plant commodities have been demonstrated.

5.1.2 Multi-Residue Methods (860.1360)

49289349.der (includes MRID 49289350)

Cyclaniliprole was screened through multiresidue methods A and C. Cyclaniliprole was not sufficiently fluorescent (Protocol A) and was not chromatographable by gas chromatography (Protocol C). Because of the results with Protocols A and C, cyclaniliprole was not screened through Protocols D, E, and F. Cyclaniliprole was not screened through Protocol B since the chemical does not contain an acid or

phenol structure. Cyclaniliprole was not screened through Protocol G because the chemical does not contain a phenylurea or substituted urea structure.

Conclusions. The multiresidue methods (Protocols A through G) are not suitable for the analysis of cyclaniliprole.

5.1.3 Tolerance Enforcement Methods

The data collection method discussed in Section 5.1.1 (Method JSM0269 for plants) is an adequate enforcement method. For a complete discussion of the method performance and validation, see section 5.1.3 of D421034, N. Dodd, 09-DEC-2015.

Conclusions. Adequate enforcement methods are available to determine residues of cyclaniliprole in plant and livestock commodities.

5.1.4 Submittal of Analytical Reference Standards (860.1650)

An analytical reference standard for cyclaniliprole is available at the EPA National Pesticide Standards Repository with an expiration date of 01/17/2026 (email communication with Les Szabo, 09/19/2023).

5.2 Storage Stability (860.1380)

D421034, N. Dodd, 09-DEC-2015

The available storage stability data are adequate to support the storage conditions and durations of the greenhouse trials. The storage stability study on wine, oilseed rape seeds, grapes, lettuce, potatoes, broccoli, and dry beans showed that residues of cyclaniliprole and metabolite NK-1375 are stable for at least 18 months when stored at approximately -20ºC. The data therefore indicate that residues of cyclaniliprole are stable encompassing all five Organization for Economic Cooperation and Development (OECD) commodity categories: high water (lettuce, broccoli), high starch (potato), high protein (dry beans), high oil (oilseed rape seed), and high acid (grapes and wine) materials for up to 18 months when stored frozen (D421034, N. Dodd, 09-DEC-2015).

The cucumber samples were stored frozen a maximum of 541 days/18 months from harvest to extraction. Samples were analyzed on the day of extraction.

To support sample storage durations, a concurrent storage stability study was conducted using samples of lettuce; no 0-day recovery data were provided. The data demonstrate that residues of cyclaniliprole and NK-1375 are stable during frozen storage in/on lettuce for up to 25.5 months. These data are acceptable to support the storage conditions and durations of the samples from the submitted greenhouse trials.

Table 5.2. Summary of Storage Conditions.			
Matrix	**Storage Temperature (°C)**	**Actual Storage Duration[1]**	**Interval of Demonstrated Storage Stability**
Cucumber	≤-18	378-541 days (13-18 months)	Residues of cyclaniliprole and NK-1375 are stable during frozen storage for at least 18 months in commodities encompassing all five OECD commodity categories: lettuce and broccoli (high water); potato tubers (high starch); grapes and wine (high acid); dry bean seed (high protein); and canola seed (high oil).[3]
Lettuce	≤-18	588-764 days (19.3-25.1 months)	Residues of cyclaniliprole and metabolite NK-1375 are stable during frozen storage for at least 25.5 months in lettuce.[2]

[1] Interval from harvest to extraction. Samples were analyzed on the day of extraction (cucumber). Samples were analyzed within 0-2 days of extraction (lettuce).
[2] Concurrent storage stability study; refer to Table B.7.6.1.1-5b.
[3] D421034, N. Dodd, 09-DEC-2015.

Conclusions. Adequate storage stability data are available to support the storage conditions and intervals for samples in the current trials.

5.3 Residue Data

5.3.1 Crop Field Trials (860.1500)

52037601.der Lettuce
52037602.der Cucumber

Table 5.3.1.1. Summary of Residues from Lettuce Greenhouse Trials with Cyclaniliprole.											
Crop Matrix	**Analyte**	**Total Application Rate (lb ai/A) [g ai/ha]**	**PHI (days)**	**n[1]**	**Residues (ppm)**						
					Min.[2]	**Max.[2]**	**LAFT[3]**	**HAFT[3]**	**Median[3]**	**Mean[3]**	**SD[3]**
Head lettuce	Cyclaniliprole	0.148-0.160 [166-179]	1	2	0.923	2.88	1.12	2.68	1.90	1.90	1.10
	NK-1375			2	<0.010	0.037	<0.010	0.036	0.023	0.023	0.018
Leaf lettuce	Cyclaniliprole	0.166-0.169 [186-189]		2	3.41	7.94	3.43	7.94	5.69	5.69	3.19
	NK-1375			2	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
Head and leaf lettuce	Cyclaniliprole	0.148-0.169 [166-189]		4	0.923	7.94	1.12	7.94	3.05	3.79	2.93
	NK-1375			4	<0.010	0.037	<0.010	0.036	0.010	0.016	0.013

[1] n = Number of independent trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.010 ppm). N/A = Not applicable.

Lettuce

IR-4 has submitted residue data for cyclaniliprole on greenhouse-grown lettuce from four independent trials conducted in the United States and Canada during the 2019 growing season. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zones 1A (BC; 1 trial), 2 (MD; 1 trial), 6 (TX; 1 trial), and 12 (NS; 1 trial). Two trials each were conducted on head and leaf lettuce. Each trial consisted of one untreated plot and one treated plot reflecting three foliar broadcast applications of a 0.42 lb ai/gal (50 g ai/L) SL formulation of cyclaniliprole, made at 6- to 8-day retreatment intervals (RTIs), at 0.047-0.057 lb ai/A/application (53-64 g ai/ha/application) for total seasonal rates of 0.148-0.169 lb ai/A (166-189 g ai/ha). Applications were made using backpack sprayer equipment in spray

volumes of 44-56 gal/A (412-523 L/ha). An adjuvant (nonionic surfactant) was added to the spray mixture for each application at all trials. Duplicate treated samples of lettuce were harvested at a 1-day PHI. At one trial, samples were collected at additional PHIs of 0, 3, 7, and 13 days to assess residue decline. Following the last of three foliar broadcast applications totaling 0.148-0.169 lb ai/A, residues of cyclaniliprole and NK-1375 were 0.923-7.94 and <0.010-0.037 ppm, respectively, in/on greenhouse-grown lettuce at a 1-day PHI; the corresponding per-trial average residues were 1.12-7.94 and <0.010-0.036 ppm. Residues were higher in/on leaf lettuce than head lettuce. In the residue decline trial, average residues of cyclaniliprole in/on lettuce declined with increasing PHIs. Residues of NK-1375 were below the LOQ in/on lettuce at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

In recommending data requirements for greenhouse-grown cucumbers, the ChemSAC previously determined that for chemicals with no uses on the corresponding field-grown crops or for which the use patterns differ significantly between field and greenhouse uses, data depicting residues from 4 greenhouse sites with 4 samples per site are appropriate; for chemicals for which the field and greenhouse use patterns are similar, any of the following 3 study designs will generally be found to be appropriate: (1) residue data from 3 greenhouse sites with 2 samples per site; (2) residue decline data, encompassing the proposed PHI, from 2 greenhouse sites with 2 samples per time interval; and (3) residue data from 2 greenhouse sites with 4 samples per site (refer to Minutes of 11/16/2005 ChemSAC meeting).

The lettuce field grown use pattern is similar to the greenhouse use pattern. Based on the greenhouse lettuce data, the recommended tolerance for residues in/on lettuce is 20 ppm. The maximum residue was 15.5 ppm. HED concludes that the existing established tolerance for residues of cyclaniliprole on vegetable, leafy, group 4–16 at 15 ppm is sufficient.

Table 5.3.1.2. Summary of Residues from Greenhouse Cucumber Trials with Cyclaniliprole.

Crop Matrix	Analyte	Total Application Rate (lbs ai/A) [g ai/ha]	PHI (days)	n	Residues (ppm)					
					Max.[1]	LAFT[2]	HAFT[2]	Median[2]	Mean[2]	SD[2]
Cucumber	Cyclaniliprole	(0.268-0.278) [300-312]	0	4	0.15	0.048	0.15	0.069	0.083	0.043
	NK-1375				<0.01	<0.01	<0.01	<0.01	<0.01	--
	Combined[3]				<0.16	<0.058	<0.16	<0.079	<0.093	0.043

[1] n = Number of independent trials.

[2] Values based on residues in individual samples.

[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.010 ppm). N/A = Not applicable.

Cucumber

Four independent residue trials for cyclaniliprole on greenhouse cucumbers were conducted in Canada encompassing NAFTA Growing Regions 5 (2 in ON), 11 (1 trial in BC) and 12 (1 trial in BC) during the 2018 and 2019 growing seasons. At each trial location, cyclaniliprole, formulated as IKI-3106 50 SL-A (equivalent to Cyclaniliprole 50 SL Insecticide PCP Reg. No. 32862), was applied as a foliar application at a rate of 98.5-106 g ai/ha (0.088-0.095 lb ai/A) for three applications with retreatment intervals of 6-8 days. The total seasonal application rate was 300-312 g ai/ha (0.267-0.278 lb ai/A). An adjuvant, MSO

or Hasten NT Ultra, was added at a rate of 0.25% v/v to the spray mixture for all applications. Cucumbers were harvested at a PHI of 0 days. In one trial, samples were collected at different time intervals (PHIs of 0, 1, 3, 7 and 13 days) to monitor residue decline. Following three foliar applications at a total seasonal rate of 300-312 g ai/ha (0.267-0.278 lb ai/A) with cucumbers harvested at a PHI of 0 days, individual sample (and per-trial average) residues of cyclaniliprole ranged from 0.04-0.15 ppm (0.048-0.15 ppm). Residues of NK-1375 were below the LOQ in/on all cucumber samples. Individual sample (and per-trial average) combined residues of cyclaniliprole and NK-1375 ranged from <0.05-<0.16 ppm (<0.058-<0.16 ppm).

In the residue decline trial, average residues of cyclaniliprole were the same between the 0 and 1 day PHIs then decreased from 0.080 ppm to <0.01 ppm in between PHIs of 1 and 13 days. Residues of NK-1375 were below the LOQ in/on cucumbers at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

The cucumber field grown use pattern is not similar to the greenhouse use pattern. The greenhouse use pattern had higher application rate and a more restrictive PHI. Based on the OECD MRL calculation procedure, the recommended tolerance is 0.3 ppm for cucurbit vegetables crop group 9.

Conclusions. The submitted lettuce and cucumber greenhouse data are adequate to fulfill data requirements. The greenhouse trials are considered scientifically acceptable and conducted at the proposed maximum application rates. There are sufficient data provided to determine appropriate tolerances and inform risk assessment.

5.3.2 Field Rotational Crops (860.1900)

D421034, N. Dodd, 09-DEC-2015

The field rotational studies conducted in the US at 1x indicate that quantifiable residues of cyclaniliprole (parent) may be found in the rotational crop wheat (forage and straw) at PBIs up to one year. The highest average field trial (HAFT) residues were 0.026 ppm in wheat forage and 0.182 ppm in wheat straw. No detectable residues (<0.005 ppm) were found in wheat grain.

5.3.3 Processed Food and Feed (860.1520)

There are no proposed uses that are relevant to this guideline topic.

5.3.4 Meat, Milk, Poultry and Eggs (860.1480)

D421034, N. Dodd, 09-DEC-2015

There are no proposed uses that are relevant to this guideline topic.

5.3.4.1 Dietary Burden

D421034, N. Dodd, 09-DEC-2015

There are no proposed uses that are relevant to this guideline topic.

The existing calculated dietary burden for dairy cattle based on the maximum reasonably balanced diet (*Table 1 Feedstuffs*, June 2008) is 0.20 ppm.

5.3.4.2 Estimated Secondary Residues in Livestock

D421034, N. Dodd, 09-DEC-2015

There are no livestock feedstuffs associated with the proposed greenhouse uses (cucumber and lettuce). The existing tolerances on ruminant commodities (fat, meat, meat byproducts of cattle, goat, horse, and sheep) are adequate.

5.3.5. Food Handling (860.1460)

There are no proposed uses that are relevant to this guideline topic.

5.3.6 Water, Fish, and Irrigated Crops (860.1400)

There are no proposed uses that are relevant to this guideline topic.

5.4 Food Residue Profile

The database indicates that residues of cyclaniliprole are likely to remain in the edible portion of treated crops as parent compound. Parent cyclaniliprole is present in cucumber and lettuce. Residues of cyclaniliprole concentrate in processed commodities of apple wet pomace, citrus oil, and potato wet peel.

6.0 Tolerance Derivation

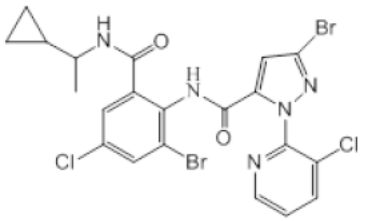
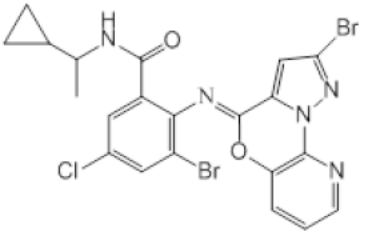
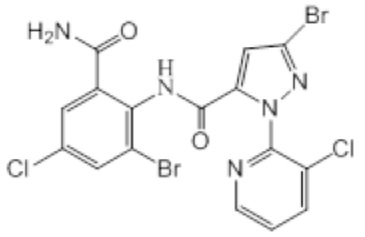
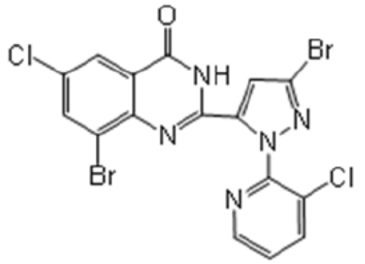
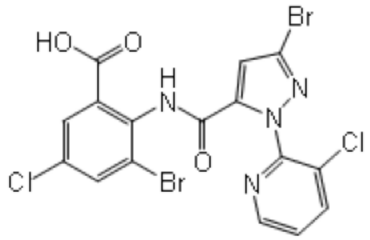
The recommended tolerance levels for plant commodities were obtained by use of the OECD MRL calculation procedure. Average residues of cyclaniliprole from greenhouse trials conducted according to the proposed label were used in the calculations. Details of the data sets and calculations are provided in Appendix D.

For greenhouse grown cucumber, the tolerance level estimate was 0.3 ppm.

For greenhouse grown lettuce, the tolerance level estimate was 20 ppm.

Appendix A. Tabular Summary of Metabolites

Table A.1. Summary Table of Parent and Metabolites/Degradates.

Common Name/ Code (ID No.)	Chemical Name	Chemical Structure
Cyclaniliprole IKI-3106	3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide	
NK-1375	3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide	
YT-1284	3-bromo-*N*-(2-bromo-6-carbamoyl-4-chlorophenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide	
NSY-28	8-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloroquinazolin-4(3*H*)-one	
NSY-27	3-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamido)-5-chlorobenzoic acid	

Appendix B. Field Trial Geographic Distribution

Table B.1. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	1A	2	3	4	5	6	7	8	9	10	11	12	
Greenhouse Cucumber	Submitted						2						1	1	4
	U.S. Req.[1]														
	Can. Req.[2]						2						1	1	4

[1] Guideline 860.1500 does not specify data requirements for greenhouse-grown crops.

[2] As per Table 1.2 of PMRA Regulatory Directive DIR2010-05 for cucumber, greenhouse, with the following note: As these crops are not grown outdoors, the zones in which the trials will be conducted are not relevant.

Table B.2. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1	1A	2	3	4	5	6	7	8	9	10	11	12	
Lettuce, greenhouse	Submitted		1	1				1						1	4
	U.S. Req.[1]														
	Can. Req.[2]						2							2	4

[1] Guideline 860.1500 does not specify data requirements for greenhouse-grown crops.

[2] As per Table 1.2 of PMRA Regulatory Directive DIR2010-05 for lettuce, greenhouse, with the following note: As these crops are not grown outdoors, the zones in which the trials will be conducted are not relevant.

Appendix C. International Residue Limits

Cyclaniliprole

Summary of US and International Tolerances and Maximum Residue Limits			
Residue Definition:			
US		Canada	Codex[1]
40 CFR 180.694 (a) cyclaniliprole, 3-bromo-N-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxamide		Cyclaniliprole: 3-bromo-N-[2-bromo-4-chloro-6- [[(1-cyclopropylethyl)amino]carbonyl] phenyl]-1-(3-chloro-2-pyridinyl)-1H- pyrazole-5-carboxamide	Plants: Cyclaniliprole
Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*		
	US	Canada	Codex
Vegetable, leafy, group 4–16	15	10 leafy vegetables (4-16) 15 leaf lettuce	7 Leafy greens subgroup 10 leaves of Brassicaceae Brassica 0.7 Head Brassicas 0.8 Flowerhead Brassicas
Vegetable, cucurbit, group 9	0.3	0.1 cucurbit vegetables group 9 0.3 cucumber (proposed)	0.05 cucumber, squash (summer) 0.1 melons, pumpkin, squash (winter)

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant. Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix D. OECD MRL Calculation Procedure Inputs/Outputs

Greenhouse grown data for lettuce and cucumber.

Compound	Cyclaniliprole	Cyclaniliprole
Crop	Lettuce (Head/Leaf)	Cucumber
Region / Country	NAFTA (Greenhouse)	NAFTA (Greenhouse)
GAP	0.148-0.169 lb ai/A	0.268-0.278 lb ai/A
Total number of data (n)	4	4
Percentage of censored data	0%	0%
Number of non-censored data	4	4
Lowest residue	1.120	0.048
Highest residue	7.940	0.150
Median residue	3.055	0.069
Mean	3.793	0.084
Standard deviation (SD)	2.928	0.045
Correction factor for censoring (CF)	1.000	1.000
Proposed MRL estimate		
- Highest residue	7.940	0.150
- Mean + 4 SD	15.503	0.264
- CF x 3 Mean	11.378	0.252
Unrounded MRL	15.503	0.264
Rounded MRL	20	0.3
	High uncertainty of MRL estimate due to small dataset.	High uncertainty of MRL estimate due to small dataset.

Residues (mg/kg)		Residues (mg/kg)	
1.120		0.068	
2.680		0.150	
7.940		0.048	
3.430		0.070	

For greenhouse grown cucumber, the tolerance level estimate was 0.3 ppm.

For greenhouse grown lettuce the tolerance level estimate was 20 ppm.

The lettuce field grown use pattern is similar to the greenhouse use pattern. The greenhouse grown

lettuce data were included in the OECD MRL calculation procedure. Based on the greenhouse lettuce data, the highest recommended tolerance for residues in/on lettuce is 20 ppm.

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Lettuce (Greenhouse)

Document ID: MRID No. 52037601
PMRA No. 3407780

Report: Pike, T. (2022) Cyclaniliprole: Magnitude of the Residue on Lettuce (Greenhouse). Study Numbers: 12515; 12515.19-FLR03. Unpublished study prepared and submitted by Interregional Research Project Number 4. 175 p.

Guidelines: EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996)
PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials
PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements
OECD Guideline 509 Crop Field Trial (September 2009)

GLP Compliance: No deviations from GLP regulatory requirements were reported which would have an impact on the validity of the study.

Acceptability: The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 468364.

Scientific Integrity: 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.pdff. 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.

Evaluator: Meheret Negussie, Health Effects Division, Chemist Meheret Negussie

Secondary Evaluator: Robert Lanthier, MUAS, HED, PMRA

Note: This Data Evaluation Record (DER) was prepared under contract by PB&A/CSS Joint Venture (submitted 8/29/2023). The PB&A/CSS Joint Venture role does not include establishing Agency policies. The DER has been reviewed by HED and revised as necessary to reflect current Office of Pesticide Programs (OPP) policies.

EXECUTIVE SUMMARY

Interregional Research Project No. 4 (IR-4) has submitted residue data for cyclaniliprole on greenhouse-grown lettuce from four independent trials conducted in the United States and Canada during the 2019 growing season. Trials were conducted in North American Free Trade Agreement (NAFTA) Growing Zones 1A (BC; 1 trial), 2 (MD; 1 trial), 6 (TX; 1 trial), and 12 (NS; 1 trial). Two trials each were conducted on head and leaf lettuce.

Each trial consisted of one untreated plot and one treated plot reflecting three foliar broadcast applications of a 0.42 lb ai/gal (50 g ai/L) soluble concentrate (SL) formulation of cyclaniliprole, made at 6- to 8-day retreatment intervals (RTIs), at 0.047-0.057 lb ai/A/application (53-64 g ai/ha/application) for total seasonal rates of 0.148-0.169 lb ai/A (166-189 g ai/ha). Applications were made using backpack sprayer equipment in spray volumes of 44-56 gal/A (412-523 L/ha). An adjuvant (nonionic surfactant) was added to the spray mixture for each application at all trials. Duplicate treated samples of lettuce were harvested at a 1-day preharvest interval (PHI). At one trial, samples were collected at additional PHIs of 0, 3, 7, and 13 days to assess residue decline.

Samples were maintained frozen at the test sites, during shipping, and at the laboratory prior to analysis. The maximum storage interval for samples between harvest and extraction for analysis was 25.1 months. Samples were analyzed within 2 days of extraction. To support sample storage durations, a concurrent storage stability study was conducted using samples of lettuce. The data demonstrate that residues of cyclaniliprole and metabolite NK-1375 are stable during frozen storage in lettuce for at least 25.5 months. These data are acceptable to support the storage conditions and durations of the samples from the submitted greenhouse trials.

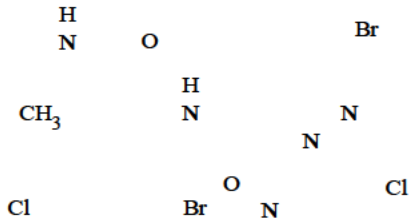
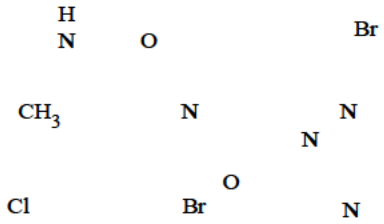
Samples were analyzed for residues of cyclaniliprole and metabolite NK-1375 using a high performance liquid chromatography method with tandem mass spectrometry detection (LC/MS/MS), Method JSM0269, with modifications. This method was previously deemed acceptable for tolerance enforcement (D421034, N. Dodd, 09-DEC-2015). The limit of quantitation (LOQ; determined as the lowest level of method validation, LLMV) was 0.010 ppm for each analyte in lettuce. Acceptable method validation and concurrent recoveries were obtained from samples of lettuce fortified with cyclaniliprole at 0.010-20 ppm and NK-1375 at 0.010-1.0 ppm. The fortification levels were adequate to represent measured residue levels.

Following the last of three foliar broadcast applications totaling 0.148-0.169 lb ai/A, residues of cyclaniliprole and NK-1375 were 0.923-7.94 and <0.010-0.037 ppm, respectively, in/on greenhouse-grown lettuce at a 1-day PHI; the corresponding per-trial average residues were 1.12-7.94 and <0.010-0.036 ppm. Residues were higher in/on leaf lettuce than head lettuce.

In the residue decline trial, average residues of cyclaniliprole in/on lettuce declined with increasing PHIs. Residues of NK-1375 were below the LOQ in/on lettuce at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Cyclaniliprole and Metabolite of Interest.	
Common name	Cyclaniliprole
Identity	3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide
CAS registry number	1031756-98-5
Molecular weight	602.11 g/mol
Company experimental name	IKI-3106
	
Common name	NK-1375
Identity	3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide
Molecular weight	565.65 g/mol
CAS registry number	Not available
	

B. Study Design

1. Test Procedure

Four greenhouse trials on lettuce (two trials each on head lettuce and leaf lettuce) were conducted with an SL formulation during the 2019 growing season. Trial locations by NAFTA growing zone are summarized in Table B.7.6.1.1-2. All trials were found to be independent based on the criteria described in 568_Criteria for Independence of Trials 4/23/2013 (EPA and PMRA).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.															
Crop	No. Trials	NAFTA Growing Zone													Total
		1	1A	2	3	4	5	6	7	8	9	10	11	12	
Lettuce, greenhouse	Submitted		1	1				1						1	4
	U.S. Req.[1]														
	Can. Req.[2]						2							2	4

[1] Guideline 860.1500 does not specify data requirements for greenhouse-grown crops.

[2] As per Table 1.2 of PMRA Regulatory Directive DIR2010-05 for lettuce, greenhouse, with the following note: As these crops are not grown outdoors, the zones in which the trials will be conducted are not relevant.

In recommending data requirements for greenhouse-grown tomatoes and cucumbers, the ChemSAC previously determined that, for chemicals with no uses on the corresponding field-grown crops or for which the use patterns differ significantly between field and greenhouse uses, data depicting residues from 4 greenhouse sites with 4 samples per site are appropriate. For chemicals for which the field and greenhouse use patterns are similar, any of the following 3 study designs will generally be found to be appropriate: (1) residue data from 3 greenhouse sites with 2 samples per site; (2) residue decline data, encompassing the proposed PHI, from 2 greenhouse sites with 2 samples per time interval; and (3) residue data from 2 greenhouse sites with 4 samples per site (refer to Minutes of 9/17/2008 ChemSAC meeting).

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3.

Table B.7.6.1.1-3. Study Use Pattern.								
Location: City, State/Province; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lb ai/A) [g ai/ha]	RTI (days)	Total Rate (lb ai/A) [g ai/ha]	Surfactant/ Adjuvant[2]
Head lettuce							
Agassiz, BC; 2019 (BC426)	0.42 lb ai/gal SL	1. Foliar broadcast; 10 true leaves	47 [441]	0.047 [53]	--	0.148 [166]	NIS
		2. Foliar broadcast; 10 leaves	51 [475]	0.051 [57]	6		
		3. Foliar broadcast; mature	50 [471]	0.050 [56]	8		
Salisbury, MD; 2019 (MD425)	0.42 lb ai/gal SL	1. Foliar broadcast; heads forming	44 [412]	0.055 [62]	--	0.160 [179]	NIS
		2. Foliar broadcast; nearly full mature heads	48 [449]	0.054 [61]	6		
		3. Foliar broadcast; marketable heads	45 [421]	0.051 [57]	6		

Table B.7.6.1.1-3. Study Use Pattern.							
Location: City, State/Province; Year (Trial ID)	End-use Product[1]	Method of Application; Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lb ai/A) [g ai/ha]	RTI (days)	Total Rate (lb ai/A) [g ai/ha]	Surfactant/ Adjuvant[2]
Leaf lettuce							
Kentville, NS; 2019 (NS427)	0.42 lb ai/gal SL	1. Foliar broadcast; 5 leaves	55 [510]	0.056 [63]	--	0.169 [189]	NIS
		2. Foliar broadcast; 8-10 leaves	54 [501]	0.055 [62]	7		
		3. Foliar broadcast; 12 leaves	56 [523]	0.057 [64]	7		
Weslaco, TX; 2019 (TX428)	0.42 lb ai/gal SL	1. Foliar broadcast; vegetative	47 [440]	0.055 [62]	--	0.166 [186]	NIS
		2. Foliar broadcast; vegetative	48 [449]	0.056 [63]	7		
		3. Foliar broadcast; vegetative	47 [440]	0.055 [62]	7		

[1] A 0.42 lb ai/gal (50 g ai/L) SL formulation of cyclaniliprole (Harvanta 50SL).
[2] NIS = Nonionic surfactant.

Lettuce was grown in greenhouses using practices representative of greenhouse production and under typical growing conditions. The plants were grown in commercial potting mix or vermiculite, and were irrigated by drip or continuous (hydroponic system) irrigation, or by hand. Temperatures on the days of application were reported for each trial site as follows: 19-26 °C for BC426; 84-104 °F (29-40 °C) for MD425; 16-20 ºC for NS427; and 79-91 °F (26-33 ºC) for TX428. Overall temperatures were reported to be “normal”; relative humidity ranges in the greenhouses were not provided.

Sample Handling and Preparation

Duplicate untreated and treated samples of lettuce were collected at a 1-day PHI, except at Trial MD425, where untreated samples were collected the day before treated samples. At Trial TX428, samples were collected at additional PHIs of 0, 3, 7, and 13 days to assess residue decline. Samples were placed into frozen storage within ~14 minutes of harvest and were stored frozen (<-18 °C) at the test sites prior to shipment via freezer truck or courier (on dry ice) to the analytical laboratory, Food and Environmental Toxicology Laboratory (Gainesville, FL). At the laboratory, samples were homogenized in the presence of dry ice and stored frozen (*ca*. -30 °C) until extraction for analysis.

2. Description of Analytical Procedures

Samples were analyzed for residues of cyclaniliprole and metabolite NK-1375 using LC/MS/MS Method JSM0269, with modifications. This method was previously deemed acceptable for tolerance enforcement (D421034, N. Dodd, 09-DEC-2015). A complete description of the method was included in

the submission. Minor modifications were reported, including elimination of the solid-phase extraction cleanup step.

Briefly, samples of lettuce were extracted twice with ACN, first by mechanical shaking for 30 minutes, then by hand shaking. The extracts were collected by centrifugation, combined, and adjusted to volume with ACN, then filtered through a 0.45-µm PTFE filter for LC/MS/MS analysis. The following ion transitions were monitored for quantitation: *m/z* 602.0 → 284 for cyclaniliprole and *m/z* 565.9 → 498 for NK-1375.

The LOQ (based on the LLMV) was 0.010 ppm for each analyte in lettuce. The limit of detection (LOD) and LOQ were calculated statistically by multiplying the standard deviation (in ppm) of six samples fortified at the LLMV by the appropriate $t_{0.99}$ value, with the calculated LOQ being 3x the LOD. The calculated LOD and LOQ, respectively, were 0.0053 and 0.0160 ppm for cyclaniliprole and 0.0025 and 0.0076 ppm for NK-1375. The LOD was not used in reporting results.

II. RESULTS AND DISCUSSION

Method performance was evaluated by use of method validation and concurrent recovery samples of lettuce fortified with cyclaniliprole at 0.010-20 ppm and NK-1375 at 0.010-1.0 ppm. Recoveries were within the acceptable range of 70-120%; therefore, the method is considered valid for the determination of residues of cyclaniliprole and NK-1375 in lettuce (Table B.7.6.1.1-4). The fortification levels were adequate to represent the measured residues. Concurrent recoveries were not corrected for apparent residues in controls.

The detector response was linear (coefficient of determination, r^2 ≥0.9827) within the range of 0.25-4.0 ng/mL. Representative chromatograms of control samples, fortified samples, and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined. Apparent residues of cyclaniliprole and NK-1375 in/on controls were below the LOQ (<0.010 ppm).

Table B.7.6.1.1-4. Summary of Method Validation and Concurrent Recoveries of Cyclaniliprole and NK-1375 from Lettuce.

Matrix	Analyte	Fortification Level (ppm)	Sample Size (n)	Recoveries[1] (%)	Mean ± Std. Dev. (%)
Method Validation					
Lettuce	Cyclaniliprole	0.010-20	10	74-118	92 ± 13
	NK-1375	0.010-1.0	10	78-111	91 ± 8
Concurrent Recoveries					
Lettuce	Cyclaniliprole	0.010-20	6	87-111	101 ± 11
	NK-1375	0.010-1.0	6	79-100	93 ± 8

[1] Concurrent recoveries were not corrected for apparent residues in controls.

The maximum storage interval for samples between harvest and extraction for analysis was 25.1 months (Table B.7.6.1.1-5a). Samples were analyzed within 2 days of extraction. To support sample storage durations, a concurrent storage stability study was conducted using samples of lettuce; no 0-day recovery data were provided. The data demonstrate that residues of cyclaniliprole and NK-1375 are stable during frozen storage in/on lettuce for up to 25.5 months (Table B.7.6.1.1-5b). These data are acceptable to support the storage conditions and durations of the samples from the submitted greenhouse trials.

Table B.7.6.1.1-5a. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Lettuce	≤-18	588-764 days (19.3-25.1 months)	Residues of cyclaniliprole and metabolite NK-1375 are stable during frozen storage for at least 25.5 months in lettuce.[2]

[1] Interval from harvest to extraction. Samples were analyzed within 0-2 days of extraction.

[2] Concurrent storage stability study; refer to Table B.7.6.1.1-5b.

Table B.7.6.1.1-5b. Stability of Residues of Cyclaniliprole and NK-1375 in Lettuce During Frozen Storage (-20 °C).

Commodity	Analyte	Spike Level (ppm)	Storage Interval	Fresh Fortification Recoveries (%) [Average]	Stored Sample Recoveries[1] (%)	Mean Recovery (%)	Corrected % Recovery[2]
Lettuce	Cyclaniliprole	0.50	777 days (25.5 months)	99, 136, 95 [110]	136, 148, 129	138	125
	NK-1375	0.10		95, 91 [93]	108, 109, 111	109	118

[1] Each recovery is the average of replicate analyses.

[2] Corrected for average recovery in freshly fortified samples.

The results from the submitted greenhouse trials are presented in Table B.7.6.1.1-6 and summarized in Table B.7.6.1.1-7. Following foliar applications of cyclaniliprole at a total rate of 0.148-0.169 lb ai/A, residues of cyclaniliprole and metabolite NK-1375 were 0.923-7.94 and <0.010-0.037 ppm, respectively, in/on greenhouse-grown lettuce harvested at a 1-day PHI. Higher residues of cyclaniliprole were observed in/on leaf lettuce than head lettuce, with overall average residues in/on leaf lettuce 3x higher than on head lettuce. Quantifiable residues of NK-1375 were only observed in/on head lettuce samples from one trial.

In the residue decline trial, average residues of cyclaniliprole in/on lettuce declined between the 0- and 13-day PHIs (Figure B.7.6.1.1-1). Residues of NK-1375 were below the LOQ in/on lettuce at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

Table B.7.6.1.1-6. Residue Data from Lettuce Greenhouse Trials with Cyclaniliprole.[1]							
Location: City, State/Province; Year (Trial ID)	Zone	Crop; Variety	Rate (lb ai/A) [g ai/ha]	Matrix	PHI (days)	Residues[2] (ppm) [Average]	
						Cyclaniliprole	NK-1375
Head lettuce							
Agassiz, BC; 2019 (BC426)	1A	Alexandria R2 (Butterhead)	0.148 [166]	Plants w/o roots	1	1.31, 0.923 [1.12]	<0.010[3], <0.010 [<0.010]
Salisbury, MD; 2019 (MD425)	2	Cegolaine (Bibb)	0.160 [179]	Plants w/o roots	1	2.88, 2.47 [2.68]	0.037, 0.035 [0.036]
Leaf lettuce							
Kentville, NS; 2019 (NS427)	12	New Red Fire M.I.	0.169 [189]	Plants w/o roots	1	7.94, 7.94 [7.94]	<0.010, <0.010 [<0.010]
Weslaco, TX; 2019 (TX428)	6	Tropicana	0.166 [186]	Plants w/o roots	0	3.99, 3.77 [3.88]	<0.010[3], <0.010 [<0.010]
					1	3.45, 3.41 [3.43]	<0.010, <0.010 [<0.010]
					3	2.67, 2.01 [2.34]	<0.010, <0.010 [<0.010]
					7	0.840[3], 0.889 [0.865]	<0.010, <0.010 [<0.010]
					13	0.220, 0.516 [0.368]	<0.010, <0.010 [<0.010]

[1] A 0.42 lb ai/gal (50 g ai/L) SL formulation of cyclaniliprole (Harvanta 50SL) was used.

[2] The LOQ was 0.010 ppm for each analyte. Per-trial averages were calculated by the study reviewer using the LOQ for all residues reported as <LOQ.

[3] Mean of replicate injections.

Figure B.7.6.1.1-1. Cyclaniliprole Residues in/on Lettuce at Various PHIs.

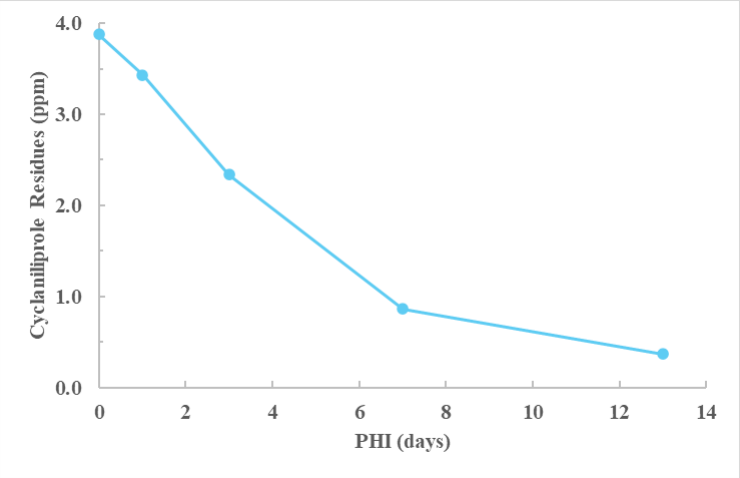


Table B.7.6.1.1-7. Summary of Residues from Lettuce Greenhouse Trials with Cyclaniliprole.

Crop Matrix	Analyte	Total Application Rate (lb ai/A) [g ai/ha]	PHI (days)	n[1]	Residues (ppm)						
					Min.[2]	Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Head lettuce	Cyclaniliprole	0.148-0.160 [166-179]	1	2	0.923	2.88	1.12	2.68	1.90	1.90	1.10
	NK-1375			2	<0.010	0.037	<0.010	0.036	0.023	0.023	0.018
Leaf lettuce	Cyclaniliprole	0.166-0.169 [186-189]		2	3.41	7.94	3.43	7.94	5.69	5.69	3.19
	NK-1375			2	<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
Head and leaf lettuce	Cyclaniliprole	0.148-0.169 [166-189]		4	0.923	7.94	1.12	7.94	3.05	3.79	2.93
	NK-1375			4	<0.010	0.037	<0.010	0.036	0.010	0.016	0.013

[1] n = Number of independent trials.
[2] Values based on residues in individual samples.
[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.010 ppm). N/A = Not applicable.

III. CONCLUSIONS

The lettuce greenhouse trials are considered scientifically acceptable. Following foliar broadcast applications of cyclaniliprole at a total rate of 0.148-0.169 lb ai/A, residues of cyclaniliprole and

metabolite NK-1375 were 0.923-7.94 and <0.010-0.037 ppm, respectively, in/on greenhouse-grown lettuce harvested at a 1-day PHI.

In the residue decline trial, average residues of cyclaniliprole in/on lettuce declined between the 0- and 13-day PHIs. Residues of NK-1375 were below the LOQ in/on lettuce at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

An acceptable method was used for residue quantitation, and adequate storage stability data were submitted to support sample storage durations and conditions for all analytes.

REFERENCES

D421034, N. Dodd, 09-DEC-2015

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Greenhouse Cucumbers

Document ID: MRID No. 52037602
PMRA No. 3299678

Report: Czechura, P. (2021) Cyclaniliprole: Magnitude of the Residue on Cucumber, Greenhouse. Study No. AAFC18-035R. Unpublished study prepared by the Pest Management Centre, Agriculture and Agri-Food Canada, Vineland, ON. 214 p.

Guidelines: EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996)
PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials
PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements
OECD Guideline 509 Crop Field Trial (September 2009)

GLP Compliance: No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

Acceptability: The study is considered scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document, DP# 468364.

Scientific Integrity: 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.pdff. 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.

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EXECUTIVE SUMMARY

Four independent residue trials for cyclaniliprole on greenhouse cucumbers were conducted in Canada encompassing North American Free Trade Agreement (NAFTA) Growing Regions 5 (2 in ON), 11 (1 trial in BC) and 12 (1 trial in BC) during the 2018 and 2019 growing seasons.

At each trial location, cyclaniliprole, formulated as IKI-3106 50 SL-A (equivalent to Cyclaniliprole 50 SL Insecticide PCP Reg. No. 32862), was applied as a foliar application at a rate of 98.5-106 g a.i./ha

(0.088-0.095 lb a.i./A) for three applications with retreatment intervals of 6-8 days. The total seasonal application rate was 300-312 g a.i./ha (0.267-0.278 lb a.i./A). An adjuvant, MSO or Hasten NT Ultra, was added at a rate of 0.25% v/v to the spray mixture for all applications. Cucumbers were harvested at a preharvest interval (PHI) of 0 days. In one trial, samples were collected at different time intervals (PHIs of 0, 1, 3, 7 and 13 days) to monitor residue decline.

All samples were maintained frozen at the testing facility, during shipping to the laboratory, and were stored frozen until analysis. The maximum storage interval for samples between harvest and extraction was 541 days/18 months. Samples were analyzed on the day of extraction. Residues of cyclaniliprole and metabolite NK-1375 have been shown to be stable during frozen storage (-20°C) for at least 18 months in commodities encompassing all five Organization for Economic Cooperation and Development (OECD) commodity categories: lettuce and broccoli (high water); potato tubers (high starch); grapes and wine (high acid); dry bean seed (high protein); and canola seed (high oil) (D421034, N. Dodd, 09-DEC-2015; PMRA# 2444537). Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

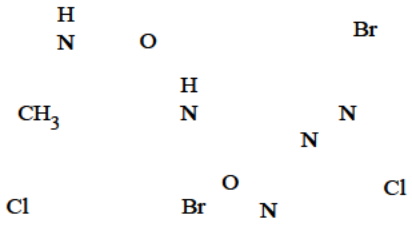
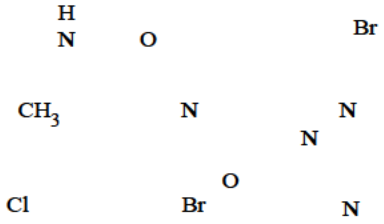
Samples in the current study were analyzed using a modified version of Method JSM0269, a high performance liquid chromatography method with tandem mass spectrometry detection (LC/MS/MS) to determine residues of cyclaniliprole and metabolite NK-1375. Acceptable method validation and concurrent recoveries were reported for cucumber samples fortified with cyclaniliprole and NK-1375 at 0.01, 0.02 (MV only), 0.1 and 0.2 ppm, thus validating the method. The limit of quantitation (LOQ) was 0.01 ppm per analyte.

Following three foliar applications at a total seasonal rate of 300-312 g a.i./ha (0.267-0.278 lb a.i./A) with cucumbers harvested at a PHI of 0 days, individual sample (and per-trial average) residues of cyclaniliprole ranged from 0.04-0.15 ppm (0.048-0.15 ppm). Residues of NK-1375 were below the LOQ in/on all cucumber samples. Individual sample (and per-trial average) combined residues of cyclaniliprole and NK-1375 ranged from <0.05-<0.16 ppm (<0.058-<0.16 ppm).

In the residue decline trial, average residues of cyclaniliprole were the same between the 0 and 1 day PHIs then decreased from 0.080 ppm to <0.01 ppm in between PHIs of 1 and 13 days. Residues of NK-1375 were below the LOQ in/on cucumbers at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Cyclaniliprole and Metabolite of Interest.	
Common name	Cyclaniliprole
Identity	3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide
CAS registry number	1031756-98-5
Molecular weight	602.11 g/mol
Company experimental name	IKI-3106
	
Common name	NK-1375
Identity	3-bromo-2-((2-bromo-4*H*-pyrazolo[1,5-*d*]pyrido[3,2-*b*]-[1,4]oxazin-4-ylidene)amino)-5-chloro-*N*-(1-cyclopropylethyl)benzamide
Molecular weight	565.65 g/mol
CAS registry number	Not available
	

B. Study Design

1. Test Procedure

A total of four independent greenhouse trials in/on cucumbers were conducted with a suspension formulation during the 2018 and 2019 growing seasons (Table B.7.6.1.1-2). It is noted that the Criteria for Determining Independence of Crop Field Trials were revised January 2021 and variety is no longer one of the primary criteria that infer independence. However, as these residue trials were conducted in 2018 and 2019, trial independence was assessed against the criteria that were current at the time the trials were initiated - Criteria for Independence of Crop Field Trials (November 2014). Independent spray mixtures were prepared at each trial location. See Table B.7.6.1.1-2b for the independence assessment for Trial ID # 009 and 012.

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.															
Crop	No. Trials	NAFTA Growing Zone													Total
		1	1A	2	3	4	5	6	7	8	9	10	11	12	
Greenhouse Cucumber	Submitted						2						1	1	4
	U.S. Req.[1]														
	Can. Req.[2]						2						1	1	4

[1] Guideline 860.1500 does not specify data requirements for greenhouse-grown crops.
[2] As per Table 1.2 of PMRA Regulatory Directive DIR2010-05 for cucumber, greenhouse, with the following note: As these crops are not grown outdoors, the zones in which the trials will be conducted are not relevant.

In recommending data requirements for greenhouse-grown tomatoes and cucumbers, the ChemSAC previously determined that, for chemicals with no uses on the corresponding field-grown crops or for which the use patterns differ significantly between field and greenhouse uses, data depicting residues from 4 greenhouse sites with 4 samples per site are appropriate. For chemicals for which the field and greenhouse use patterns are similar, any of the following 3 study designs will generally be found to be appropriate: (1) residue data from 3 greenhouse sites with 2 samples per site; (2) residue decline data, encompassing the proposed PHI, from 2 greenhouse sites with 2 samples per time interval; and (3) residue data from 2 greenhouse sites with 4 samples per site (refer to Minutes of 9/17/2008 ChemSAC meeting).

Table B.7.6.1.1-2b. Independent Trial Determination[1]			
Crop	Trial Nos.	Differences	Decision
Greenhouse cucumbers	009 and 012	Independently prepared tank mixes were used at each site. Location: Harrow, ON Timing: 1st application January 23, 2019 (009) 1st application January 15, 2019 (012) Variety: Verdon RZ (large variety) (009), Picowell RZ (small variety) (012)	Trials were independent since independent spray mixtures were used and different varieties of cucumbers were used in each trial.

[1] All assessments are based on the replicate trial guidance presented in Criteria for Independence of Crop Field Trials November 2014.

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3.

Table B.7.6.1.1-3. Study Use Pattern.							
Location: City, Province; Year (Trial AAFC18-035R-)	End-use Product/ Formulation (% ai)	Method of Application/ Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lbs a.i./A) [g a.i./ha]	Retreatment Interval (days)	Total Rate (lbs a.i./A) [g a.i./ha]	Surfactant/ Adjuvant
Harrow, ON; 2019 (009)	IKI-3106 50 SL-A/ Suspension (4.59%)	1. Foliar broadcast/ maturing fruit	97 [904]	(0.089) [100]	-	(0.268) [300]	MSO (0.25% v/v)
		2. Foliar broadcast/ maturing fruit	98 [913]	(0.090) [101]	6		
		3. Foliar broadcast/ mature fruit	96 [895]	(0.088) [98.9]	6		
Agassiz, BC; 2018 (010)	IKI-3106 50 SL-A/ Suspension	1. Foliar broadcast/ mature fruit on lower trusses, flowers on upper trusses	79 [742]	(0.095) [106]	-	(0.278) [312]	Hasten NT Ultra (0.25% v/v)

Table B.7.6.1.1-3. Study Use Pattern.							
Location: City, Province; Year (Trial AAFC18-035R-)	End-use Product/ Formulation (% ai)	Method of Application/ Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lbs a.i./A) [g a.i./ha]	Retreatment Interval (days)	Total Rate (lbs a.i./A) [g a.i./ha]	Surfactant/ Adjuvant
	(4.59%)	2. Foliar broadcast/ commercially mature fruit on middle trusses	79 [743]	(0.095) [106]	7		
		3. Foliar broadcast/ commercially mature fruit on middle trusses	75 [700]	(0.089) [99.5]	6		
Summerland, BC; 2018 (011)	IKI-3106 50 SL-A/ Suspension (4.59%)	1. Foliar broadcast/ fruiting	85 [794]	(0.088) [98.5]	-	(0.275) [308]	Hasten NT Ultra (0.25% v/v)
		2. Foliar broadcast/ fruiting	90 [841]	(0.094) [105]	7		
		3. Foliar broadcast/ mature (fruiting)	89 [835]	(0.093) [104]	7		
Harrow, ON; 2019 (012)	IKI-3106 50 SL-A/ Suspension (4.59%)	1. Foliar broadcast/ immature fruit	102 [952]	(0.089) [99.8]	-	(0.268) 301]	MSO (0.25% v/v)
		2. Foliar broadcast/ mature fruit	102 [954]	(0.089) [100]	6		
		3. Foliar broadcast/ mature fruit	103 [960]	(0.090) [101]	8		

Greenhouse cucumbers were grown and maintained according to typical agricultural practices. Drip irrigation was used at all trial locations. No unusual conditions within the greenhouses were reported during the study.

Sample Handling and Preparation

Duplicate untreated and treated cucumber samples were harvested from each trial location on the day of the last application (PHI = 0 day). Untreated samples were collected prior to treated samples or by different personnel. Greenhouse cucumbers were hand-picked from a minimum of 12 different areas of the plots avoiding plot edges and ends except at Trial ID# 011 and 012 where all areas of the plots were sampled including edges. A minimum of 12 (large fruit) or 24 (small fruit) were collected and all sample sizes were greater than the minimum target weight of 2 kg. Samples were placed in frozen storage within 22 minutes of sample collection and stored frozen generally < -22°C with actual temperatures fluctuating up to -11°C due to normal variation such as door opening, until shipment to the analytical laboratory. Samples were shipped frozen to the analytical laboratory.

All samples arrived frozen and in good condition at the PMC Analytical Chemistry Lab, Vineland, ON. Upon receipt, samples were placed in freezers with temperatures generally < -18°C with actual temperatures fluctuating up to -9.8°C due to normal variation such as door opening or activity in the freezers. Samples were macerated by homogenizing with dry ice using a Robot Coupe processor. Samples were only removed from frozen storage when needed for maceration and extraction.

2. Description of Analytical Procedures

Samples of greenhouse cucumbers were analyzed for residues of cyclaniliprole and metabolite NK-1375 using LC/MS/MS Method JSM0269, with modifications. This method was previously deemed acceptable for data gathering and enforcement in plant matrices (D421034, N. Dodd, 09-DEC-2015

; Study – PMRA # 2399092, Review – PMRA # 2517825). A complete description of the method was included in the study report. Modifications included changes to equipment, solvent quantities, and centrifugation speed and timing were made at several steps, removal of the SPE cleanup step, change to the composition of mobile phase A and modification of the instrument operating parameters for the LC/MS/MS available in the lab.

Briefly, samples of cucumbers were extracted with acetonitrile (ACN), with shaking for 30 minutes. The extract was collected following centrifugation and an aliquot was diluted with water for LC/MS/MS analysis. The LOQ, based on the lowest limit of method validation (LLMV), was 0.01 ppm for each analyte. The limit of detection (LOD) was calculated by multiplying the standard deviation recovery measurements at the LLMV by the one-tailed t-statistic (% confidence not reported) for 12 replicates for each analyte; the LOQ was calculated as 3 times the LOD. The calculated LODs and LOQs were 0.0008 and 0.0023 ppm for cyclaniliprole and 0.0010 ppm and 0.0029 ppm for NK-1375.

II. RESULTS AND DISCUSSION

Method performance was evaluated during method validation (MV) and by use of concurrent recovery (CR) samples by fortifying greenhouse cucumbers with 0.01, 0.02 (MV only), 0.1 and 0.2 ppm cyclaniliprole and NK-1375. All recoveries were within the acceptable range of 70% to 120%; therefore, the method was considered valid for the analysis of cyclaniliprole and NK-1375 residues in cucumber matrices. The fortification levels did bracket the measured residues.

The detector response was linear (coefficient of determination, r^2 >0.997) within the range of 0.1-5 ng/mL. Representative chromatograms of control samples, fortified samples and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined. Residues in controls were below the LOQ (<0.01 ppm for each analyte). Metabolites were not expressed in parent equivalents since residues were below the LOQ.

The field residue samples were stored frozen a maximum of 541 days/18 months from harvest to extraction (Table B.7.6.1.1-5). Samples were analyzed on the day of extraction. Acceptable storage stability data are available indicating that residues of cyclaniliprole and NK-1375 are stable during frozen storage (-20°C) for at least 18 months in commodities encompassing all five OECD commodity categories: lettuce and broccoli (high water); potato tubers (high starch); grapes and wine (high acid); dry bean seed (high protein); and canola seed (high oil) (D421034, N. Dodd, 09-DEC-2015; Study – PMRA# 2444537 and Review – PMRA# 2517826). These data are acceptable to support the storage conditions and durations of the samples from the submitted greenhouse trials.

Table B.7.6.1.1-5. Summary of Storage Conditions.			
Matrix (RAC)	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Cucumber	≤-9.8	378-541 days (13-18 months)	Residues of cyclaniliprole and NK-1375 are stable during frozen storage for at least 18 months in commodities encompassing all five OECD commodity categories: lettuce and broccoli (high water); potato tubers (high starch); grapes and wine (high acid); dry bean seed (high protein); and canola seed (high oil).[2]

[1] Interval from harvest to extraction. Samples were analyzed on the day of extraction.
[2] D421034, N. Dodd, 09-DEC-2015. PMRA# 2444537 reviewed with PMRA# 2517826.

The results from the submitted greenhouse trials are presented in Table B.7.6.1.1-6 and summarized in Table B.7.6.1.1-7. The results from these trials showed that when harvested 0 days after the last of three foliar applications at a seasonal rate of [0.268-0.278] lbs a.i./A (300-312 g a.i./ha), residues of cyclaniliprole ranged from 0.04-0.15 ppm. Residues of NK-1375 were below the LOQ (<0.01 ppm) in/on all cucumber samples. Combined residues of cyclaniliprole and NK-1375 in/on cucumbers were <0.058-<0.16 ppm.

In the residue decline trial, average residues of cyclaniliprole were the same between the 0 and 1 day PHIs then decreased from 0.080 ppm to <0.01 ppm in between PHIs of 1 and 13 days. Residues of NK-1375 were below the LOQ in/on cucumbers at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

Table B.7.6.1.1-6. Residue Data from Greenhouse Cucumber Trials with Cyclaniliprole.									
Location: City, Province; Year (Trial AAFC18-035R-)	Region	Crop/ Variety	Matrix	End-Use Product	Rate (lbs ai/A) [g a.i./ha]	PHI (days)	Residues (ppm) [Average]		
							Cyclaniliprole	NK-1375	Total[1]
Harrow, ON; 2019 (009)	5	Cucumber/ Verdon RZ	Fruit	IKI-3106 50 SL-A	(0.268) [300]	0	0.065, 0.070 [0.068]	<0.01, <0.01 [<0.01]	<0.075, <0.080 [<0.078]
Agassiz, BC; 2018 (010)	11	Cucumber/ Picowell RZ	Fruit	IKI-3106 50 SL-A	(0.278) [312]	0	0.14, 0.15 [0.15]	<0.01, <0.01 [<0.01]	<0.15, <0.16 [<0.16]
Summerland, BC; 2018 (011)	12	Cucumber/ Verdon RZ	Fruit	IKI-3106 50 SL-A	(0.275) [308]	0	0.056, 0.04 [0.048]	<0.01, <0.01 [<0.01]	<0.066, <0.05 [<0.058]
Harrow, ON; 2019 (012)	5	Picowell RZ	Fruit	IKI-3106 50 SL-A	(0.268) [301]	0	0.071, 0.068 [0.070]	<0.01, <0.01 [<0.01]	<0.081, <0.078 [<0.080]
						1	0.065, 0.075 [0.080]	<0.01, <0.01 [<0.01]	<0.075, <0.085 [<0.080]
						3	0.067, 0.062 [0.065]	<0.01, <0.01 [<0.01]	<0.077, <0.072 [<0.075]
						7	0.025, 0.023 [0.024]	<0.01, <0.01 [<0.01]	<0.035, <0.033 [<0.034]
						13	<0.01, <0.01 [<0.01]	<0.01, <0.01 [<0.01]	<0.02, <0.02 [<0.02]

[1] Total = Cyclaniliprole + Metabolite NK-1375 [which corresponds to the residue definition for risk assessment purposes].

Table B.7.6.1.1-7. Summary of Residues from Greenhouse Cucumber Trials with Cyclaniliprole.										
Crop Matrix	Analyte	Total Application Rate (lbs a.i./A) [g a.i./ha]	PHI (days)	n	Residues (ppm)					
					Max.[1]	LAFT[2]	HAFT[2]	Median[2]	Mean[2]	SD[2]
Cucumber	Cyclaniliprole	(0.268-0.278) [300-312]	0	4	0.15	0.048	0.15	0.069	0.083	0.043
	NK-1375				<0.01	<0.01	<0.01	<0.01	<0.01	--
	Combined[3]				<0.16	<0.058	<0.16	<0.079	<0.093	0.043

[1] n = Number of independent trials.

[2] Values based on residues in individual samples.

[3] Values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values <LOQ are assumed to be at the LOQ (0.010 ppm). N/A = Not applicable.

III. CONCLUSIONS

The greenhouse cucumber trials are considered scientifically acceptable. The results of the study showed that following foliar application of cyclaniliprole as IKI-3106 50 SL-A at a total application of (0.268-0.278 lb a.i./A) 300-312 g a.i./ha with cucumber samples collected at PHIs of 0 days, average cyclaniliprole residues ranged from 0.048-0.15 ppm. Residues of NK-1375 were below the LOQ (<0.01 ppm) in/on all cucumber samples. Average combined residues of cyclaniliprole and NK-1375 in/on cucumbers were <0.058-<0.16 ppm.

In the residue decline trial, average residues of cyclaniliprole were the same between the 0 and 1 day PHIs then decreased from 0.080 ppm to <0.01 ppm in between PHIs of 1 and 13 days. Residues of NK-1375 were below the LOQ in/on cucumbers at all sampling intervals; therefore, residue decline could not be assessed for the metabolite.

Adequate storage stability data are available to support sample storage durations and conditions.

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