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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 25, 2012

Subject: **Cyantraniliprole**. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS).

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Petition No.: NA
Risk Assessment Type: NA
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From: Ideliz Negrón-Encarnación, ROCKS Alternate Secretary
Health Effects Division (HED) (7509P)

Through: Christine L. Olinger, ROCKS Co-Chair
Edward Scollon, ROCKS Co-Chair
HED (7509P)

To: Cyantraniliprole Risk Assessment Team
Risk Assessment Branch III (RAB III)
HED (7509P)

The ROCKS met on July 24, 2012 to discuss the residues of concern for the insecticide cyantraniliprole in crops, livestock and drinking water.

Team Members: Christopher Koper, Meghan Radtke, Steve Funk, Whang Phang, Leung Cheng, Paula Deschamp, and Thomas Harris.

ROCKS Members Attended: Elizabeth Holman, Katrina White, Ed Scollon, George Kramer, William Irwin, Chester Rodriguez, Brian Kiernan, Ray Kent, Greg Orrick, Dennis McNeilly and Ideliz Negrón.

Other Attendees: Jason Lutze (AU/APVMA); Nicolas Breysse and Gaelle Vial (FR/ANSES); Lata Koshy, Claire Stephenson and Mark Williams (UK/CRD); Louise Croteau, Barbara Martinovic Barrett, Stacie Stiege, Pierre Therriault and Monique Thomas (CA/PMRA).

Material Reviewed: Summary of toxicological, residue chemistry, and environmental fate data prepared by the cyantraniliprole risk assessment team.

Background

Cyantraniliprole is a second generation ryanodine receptor insecticide being jointly developed by DuPont and Syngenta. It is being reviewed as part of a global work share project. The crops proposed in the U.S. include berries, citrus, cotton, oilseeds, ornamentals, pome fruit, potatoes, stone fruit, tree nuts, turf, and various vegetables. Application methods include foliar spray, drip irrigation, soil drench and seed treatment. Metabolism studies were conducted on rice, cotton, tomato and lettuce as primary crops; lettuce, red beet, soybean and wheat as rotational crops; laying hens and lactating ruminants. In addition, soil and aquatic metabolism studies under aerobic and anaerobic conditions, aqueous photolysis and hydrolysis studies, and terrestrial field dissipation studies were conducted to understand the environmental fate of cyantraniliprole.

Committee Recommendation

Table 1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment[1]	Residues included in Tolerance Expression
Plants	Primary Crop	Cyantraniliprole	Cyantraniliprole
	Rotational Crop	Cyantraniliprole	Cyantraniliprole
	Processed Commodities	Cyantraniliprole and IN-J9Z38	Cyantraniliprole
Livestock	Ruminant	Cyantraniliprole, IN-N7B69, IN-MLA84, IN-MYX98, and/or IN-J9Z38[2]	Cyantraniliprole
	Poultry		Cyantraniliprole
Drinking Water		Cyantraniliprole and the degradates listed below[3]	Not Applicable

[1] Cyantraniliprole is 3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide. The names and chemical structures of the metabolites can be found in Appendix 1.
[2] Parent cyantraniliprole is recommended as residue of concern in all commodities along with the metabolites that are at significant amount in the commodity under consideration.
[3] IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97.

Summary of Briefing Materials Considered

Cyantraniliprole is an anthranilic diamide insecticide which acts through unregulated activation of ryanodine receptor (RyR) channels leading to calcium depletion and impaired regulation of muscle contraction. The major findings following repeated oral administration in rats, mice and dogs were changes in the liver, thyroid gland, and adrenal cortex. The thyroid toxicity observed was likely a result of increased hepatic enzyme activities and perturbation of the thyroid hormone homeostasis, and minor changes in the adrenal cortex were not considered biologically significant. Therefore, the primary mode of toxicity to mammals is hepatotoxicity. Cyantraniliprole was not observed to cause genotoxicity, neurotoxicity or immunotoxicity in rats and/or mice. No increase in tumor incidence was observed in adequately conducted carcinogenicity studies in rats and mice. Acute oral toxicity and mutagenicity studies are available for several metabolites including IN-JSE76, IN-PLT97, IN-F6L99 and IN-N5M09**.** While the acute studies did not indicate significant increases in toxicity for any of the metabolites, the primary mode of action for cyantraniliprole, liver toxicity, is not likely to manifest after a single exposure. However, in a 28-day feeding study with IN-JSE76 in rats, no adverse effects were observed up to the highest dose tested (20,000 ppm, equivalent to1445 mg/kg/day). Although this is still considered a short-term study, 28 days is sufficient to indicate potential hepatic injury. Therefore, assuming equal toxicity between parent and similarly structured metabolites/degradates is likely a conservative estimation.

Metabolism studies were conducted with cyantraniliprole radiolabeled in the cyano group or in the carbonyl adjacent to the pyrazole ring. The metabolism of cyantraniliprole applied to rice, lettuce, cotton and tomato were similar after foliar and soil applications; cyantraniliprole was the major residue in addition to the formation of many minor metabolites. Results in crop field trials confirm parent as the predominant residue.

In addition to parent cyantraniliprole, several residues have also been identified in processing studies. Nature of the residue in processing studies showed formation of degradates IN-J9Z38, IN-N5M09, and IN-F6L99 under conditions of heat and/or hydrolysis. Magnitude of the residue studies showed formation of these degradates in certain processed commodities. For example, IN-J9Z38 was present in cooked spinach, orange oil, tomato paste, cotton seed oil, and cotton seed meal. Indeed, most of the cyantraniliprole was degraded to IN-J9Z38 in cooked spinach. IN-N5M09 and IN-F6L99 were each about 1 - 2% of the IN-J9Z38 concentration in cooked spinach. All three degradates were generated in apple sauce, with IN-J9Z38 approximating the concentration of cyantraniliprole and IN-N5M09 and IN-F6L99 each being <10 - 20% of the combined cyantraniliprole plus IN-J9Z38 concentration in the apple sauce. Degradates IN-N5M09 and IN-F6L99 were <LOQ (<0.01 ppm each) in commodities from processing studies with tomato, orange, plum, cottonseed, grapes, and olives.

In confined rotational studies, parent cyantraniliprole was the major residue present in soybean, wheat grain, lettuce, and beet root. Some metabolites were found at levels greater than 10% of the TRR only in livestock feedstuffs. In feedstuff commodities including wheat forage, hay, and straw, parent and IN-J9Z38 accounted for the majority of the residues. In soybean foliage, parent, IN-JSE76 and IN-MLA84 accounted for the majority of the residues. In field rotational crop studies, low levels of parent and metabolites were observed at the 30-day plant back interval except for animal feeds. In hay, forage, and straw of several crops, in addition to cyantraniliprole, significant amounts of metabolites such as IN-JCZ38, IN-J9Z39 and IN-MLA84 were also present. These metabolites are at significant levels in feedstuff commodities only.

Livestock metabolism studies were conducted on laying hens and lactating ruminants. For hens, most of the dose was excreted as unchanged parent compound (68-77% TRR). Residues in muscle, fat, and skin with fat were <0.01 ppm. Finite residues were found in eggs and liver. Cyantraniliprole, IN-HGW87, IN-J9Z38, and IN-MLA84 were major residues in eggs. However, feeding studies conducted by dosing laying hens at levels of 3, 10 and 30 mg/kg for 28 days show significant levels of parent cyantraniliprole and metabolites IN-MYX98, IN-J9Z38, and/or IN-MLA84 in eggs, muscle, liver and skin (with fat). For ruminants, cyantraniliprole was the major residue in milk, liver, kidney, muscle and fat. Also present in milk were 2 other major metabolites, IN-N7B69 and IN-MYX98. Feeding studies conducted with lactating cow at levels of 3, 10, 30 and 100 mg/kg for 28 days show significant levels of parent cyantraniliprole, and metabolites IN-N7B69, IN-J9Z38, IN-MLA84 and/or IN-MYX98 in cream, skim milk, muscle, liver, kidney and fat.

Cyantraniliprole's major routes of dissipation include alkaline-based hydrolysis (with DT_{50} values of 0.86 days at pH 9, 31 days at pH 7, and 222 days at pH 4), photodegradation in aqueous and moist soil environments (with DT_{50} values of 7.9 hours and 12.5 days, respectively), and aerobic and anaerobic biotransformation in terrestrial and aquatic environments (with DT_{50} values from 2.4 to 89 days). In terrestrial field studies, cyantraniliprole dissipated with DT_{50}s ranging from 3.4 to 44 days. Cyantraniliprole appears not to volatilize and is characterized as being moderately mobile. Some degradates are more mobile than the parent and some are less mobile than the parent. Based on laboratory studies, the major (≥10% of the applied) environmental degradates of cyantraniliprole include IN-J9Z38 (hydrolysis and biotransformation in aerobic and anaerobic soil and aquatic systems), IN-NXX69 (aqueous phototransformation), IN-QKV54 (moist soil phototransformation), IN-RNU71 (moist soil phototransformation), IN-JSE76 (aerobic soil biotransformation), IN-JCZ38 (aerobic soil biotransformation), and IN-K5A78 (aerobic soil biotransformation). IN-J9Z38 formed under both microbial mediated and abiotic processes. Major degradates that continued to increase over time to study termination in various fate studies include IN-J9Z38, IN-RNU71, IN-JSE76, IN-JCZ38, and IN-K5A78. It should be noted that additional aerobic soil biotransformation studies were conducted with transformation products. Degradate half-lives ranged from 3.5 to 1800 days, depending on transformation product and soil type. In addition, IN-K5A77, IN-K5A79, and IN-PLT97 were also detected in terrestrial field dissipation studies.

Post-meeting Note: Regarding TP (IN-NXX69), it is the opinion of the Canadian reviewer that it may be relevant for surface water modeling (although it is formed at pH 4 and perhaps pH 7 is more "environmentally relevant" but not for groundwater modeling since it is not a relevant pathway (not formed in soil).

Rationale

Parent cyantraniliprole was detected as a main residue in the metabolism studies, crop field trials and livestock feeding studies. Based on this, it is considered an appropriate marker for primary crops, rotational crops and livestock commodities and is recommended as the residue of concern (ROC) for tolerance enforcement. The following discussion is for the selection of the residue of concern for risk assessment purposes only.

Primary Crops: Metabolism studies show parent cyantraniliprole as a major residue in rice, lettuce, cotton and tomato, and IN-J9Z38 as a major residue in rice and lettuce. The crop field trials show the presence of several metabolites at levels below the limit of quantitation or at significantly lower amounts than parent cyantraniliprole. The ROCKS recommends inclusion of parent only for risk assessment purposes.

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

Processed Commodities: Although degradates IN-J9Z38, IN-N5M09, and IN-F6L99 were formed under conditions of heat and/or hydrolysis, in general, only IN-J9Z38 was observed at significant concentrations in a few processed commodities (e.g. cooked spinach, apple sauce). IN-N5M09 and IN-F6L99 were found at low levels in apple sauce and cooked spinach, but were absent (<LOQ) in a variety of other processed commodities. Based on this the ROCKS recommends parent cyantraniliprole and IN-J9Z38 as ROC.

Livestock: Feeding studies show that parent cyantraniliprole, IN-N7B69, IN-MLA84, IN-MYX98, and/or IN-J9Z38 are likely to be present in significant amount in some commodities. These metabolites are assumed to have similar toxicity to parent cyantraniliprole. The ROCKS recommends inclusion of parent cyantraniliprole for risk assessment purposes in all the commodities. In addition, inclusion of the metabolites that are significant levels in specific commodities (e.g. IN-N7B69, IN-MYX98 in milk; IN-MYX98 in muscle of poultry; IN-MLA84 and IN-MYX98 in liver; IN-MLA84, IN-N7B69, and IN-MYX98 in kidney) is recommended and should be considered on a matrix-specific basis.

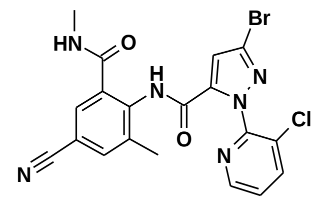
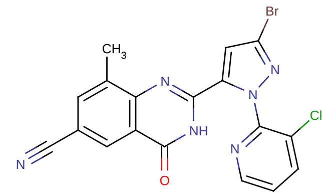
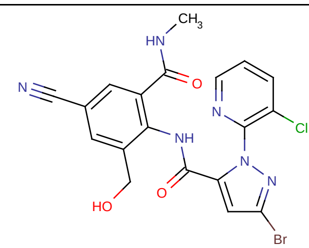
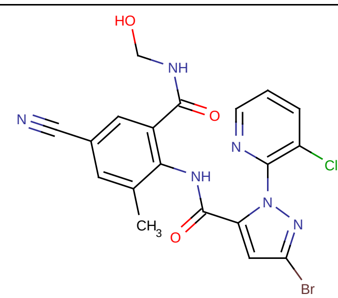
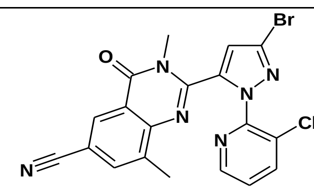
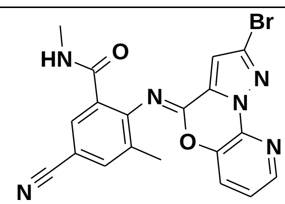
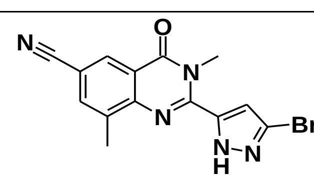
Water: Cyantraniliprole is likely to degrade extensively in the environment through several degradation routes to form IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97. These degradates were either major degradates in relevant laboratory studies, formed in the field, or both. In the absence of toxicity data and similar analogs, these degradates are considered no more toxic than the parent compound and a total residue approach is recommended for risk assessment purposes. Therefore, the recommended ROC in water include cyantraniliprole, IN-J9Z38, IN-NXX69, IN-QKV54, IN-RNU71, IN-JSE76, IN-JCZ38, IN-K5A78, IN-K5A77, IN-K5A79, and IN-PLT97.

Recommended Tolerance Expression

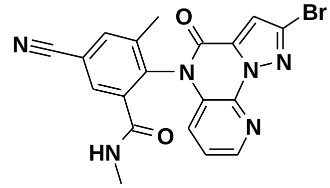
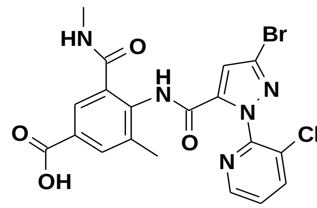
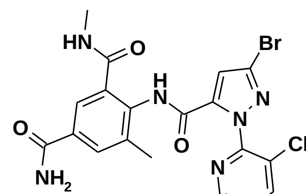
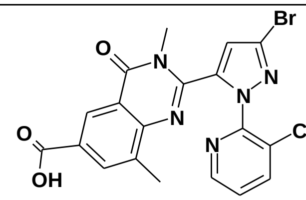
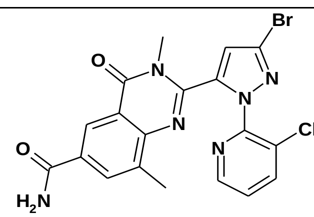
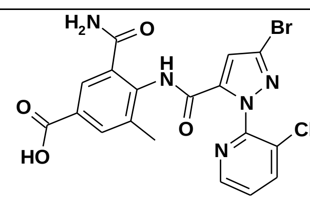
The ROCKS recommends the following language for the tolerance expression for plant and livestock commodities:

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

Appendix 1. Cyantraniliprole and it major metabolites/degradates.

Common Name	Chemical Name	Structure
Cyantraniliprole SYN545377 DPX-HGW86	CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-N-[4-cyano-2-methyl-6 [(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide	
IN-MLA84	CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarbonitrile	
IN-N7B69	CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-(hydroxymethyl)-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carbonitrile	
IN-MYX98	CAS Name: 3-Bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-[[(hydroxymethyl) amino]carbonyl]-6-[(methylphenyl]-1*H*-pyrazole-5-carboxamide	
IN-J9Z38	CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile	
IN-NXX69	CAS Name: 2-[[(4Z)-2-bromo-4H-pyrazolo[1,5-d]pyrido[3,2-b][1,4]oxazin-4-ylidene]amino]-5-cyano-N,3-dimethylbenzamide	
IN-QKV54	CAS Name: 2-(3-Bromo-1H-pyrazol-5-yl)-1,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarbonitrile	

Appendix 1. Cyantraniliprole and it major metabolites/degradates.

Common Name	Chemical Name	Structure
IN-RNU71	CAS Name: 2-(2-Bromo-4-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrazin-5(4H)-yl)-5-cyano-N,3-dimethylbenzamide	
IN-JSE76	CAS Name: 4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]carbonyl]amino]-3-methyl-5-[(methylamino)carbonyl]benzoic acid	
IN-JCZ38	CAS Name: 4-[[[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]carbonyl]amino]-N'3',5-dimethyl-1,3-benzenedicarboxamide	
IN-K5A78	CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarboxylic acid	
IN-K5A77	CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-3,4-dihydro-3,8-dimethyl-4-oxo-6-quinazolinecarboxamide	
IN-K5A79	CAS Name: 3-(Aminocarbonyl)-4-[[[3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]carbonyl]amino]-5-methylbenzoic acid	
IN-PLT97	CAS Name: 2-[3-Bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-1,4-dihydro-8-methyl-4-oxo-6-quinazolinecarboxylic acid