maximum ADI. The Meeting concluded that the long term intakes of residues of chlormequat chloride, when used in accordance with GAPs that have been considered by JMPR, are unlikely to pose a public health concern.

Short term dietary exposure

The International Estimated Short Term Intakes (IESTIs) of chlormequat chloride were calculated for food commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting. The results are shown in Annex 4 to the 2017 Report.

The ARfD for chlormequat chloride is 0.05 mg/kg bw (or 0.0388 mg/kg bw expressed as chlormequat cation).

The calculated IESTIs for chlormequat ranged from 0–100% of the ARfD for children, and 0–50% for the general population. The Meeting concluded that the short-term intake of residues of chlormequat chloride, when used in accordance with GAPs that have been considered by JMPR, are unlikely to pose a public health concern.

5.7 CYCLANILIPROLE (296)

TOXICOLOGY

Cyclaniliprole is the International Organization for Standardization (ISO)–approved common name for 2′,3-dibromo-4′-chloro-1-(3-chloro-2-pyridyl)-6′{[(1RS)-1-cyclopropylethyl]carbamoyl}pyrazole-5-carboxanilide (International Union of Pure and Applied Chemistry), with the Chemical Abstracts Service (CAS) number 1031756-98-5. Cyclaniliprole, an anthranilic diamide insecticide, is a ryanodine receptor modulator.

Cyclaniliprole has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed by the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All critical studies contained statements of compliance with good laboratory practice (GLP) and were conducted in accordance with relevant national or international test guidelines, unless otherwise indicated.

Biochemical aspects

In studies conducted using [^{14}C]cyclaniliprole, maximum plasma concentrations of radioactivity were reached at 24–120 hours after a single oral dose of 10 or 400 mg/kg body weight (bw) in rats and 6–48 hours after a single oral dose of 1 mg/kg bw in dogs. Based on the level of radioactivity in bile, urine, liver and carcass, gastrointestinal absorption in rats was estimated to be 11% in males and 9% in females at 10 mg/kg bw, and 2% in males and 5% in females at 400 mg/kg bw. In dogs, gastrointestinal absorption was approximately 40% following a single oral dose of 1 mg/kg bw. In rats, the majority of radioactivity was eliminated in faeces (>85%) within 48 hours, with relatively low levels excreted in urine (< 1%). Following a single oral dose of 10 mg/kg bw to rats, approximately 2% of radioactivity remained in tissues at 168 hours, with 31% remaining following repeated dosing. In both rats and dogs, the highest tissue concentrations of radioactivity were detected in whole blood and plasma. It was not possible to determine plasma elimination half-lives as plasma radioactivity did not decrease over the experimental period (up to 168 hours). Radioactivity in all other tissues decreased over time.

In rats, parent cyclaniliprole was the main compound identified in faeces and fat. Cyclaniliprole was also detected in plasma, liver and kidney; none was detected in bile or urine. The main plasma metabolite was 18-bromo-2-(3-bromo-1(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloroquinazolin-4(3*H*)-one (NSY-28; up to 98% of total tissue radioactivity). Low levels of the metabolites 3-bromo-*N*-(2-bromo-6-carbamoyl-4-chlorophenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (YT-1284) and 3-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamido)-5-chlorobenzoic acid (NSY-27) were detected in excreta and liver, with YT-1284 also detected in kidney and NSY-27 in plasma. The metabolite 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 (NK-1375) was detected only in fat.

Toxicological data

In rats, the oral and dermal median lethal dose (LD_{50}) values were greater than 2000 mg/kg bw, and the inhalation median lethal concentration (LC_{50}) was greater than 4.62 mg/L. Cyclaniliprole was not irritating to the skin of rabbits, but was slightly irritating to rabbit eyes. Cyclaniliprole did not induce skin sensitization in mice or guinea-pigs.

Evidence of limited toxicity was seen in repeated-dose studies. In mice, rats and dogs, the liver is the target organ, with dogs the most sensitive species.

In a 13-week study in mice, which tested dietary concentrations of 0, 200, 1200 or 8000 parts per million (ppm) cyclaniliprole (equal to 0, 27, 159 and 1023 mg/kg bw per day in males and 0, 34,

179 and 1350 mg/kg bw per day in females, respectively), the no-observed-adverse-effect level (NOAEL) was 8000 ppm (equal to 1023 mg/kg bw per day), the highest dose tested.

In a 28-day range-finding study in rats, which tested dietary concentrations of 0, 300, 1250, 5000 or 20 000 ppm cyclaniliprole (equal to 0, 26.4, 107, 426 and 1778 mg/kg bw per day in males and 0, 26.4, 113, 443 and 1800 mg/kg bw per day in females, respectively), the slight increase in liver weight observed at the highest dose was not considered adverse.

In a 90-day study of toxicity in rats, which tested dietary concentrations of 0, 600, 6000 or 20 000 ppm cyclaniliprole (equal to 0, 39.9, 402 and 1331 mg/kg bw per day in males and 0, 43.3, 467 and 1594 mg/kg bw per day in females, respectively), the NOAEL was 20 000 ppm (equal to 1331 mg/kg bw per day), the highest dose tested.

In a 90-day study of toxicity in dogs, which tested dietary concentrations of 0, 100, 1000 or 10 000 ppm cyclaniliprole (equal to 0, 2.68, 26.8 and 266 mg/kg bw per day in males and 0, 2.75, 26.9 and 270 mg/kg bw per day in females, respectively), the NOAEL was 100 ppm (equal to 2.68 mg/kg bw per day) based on a consistent increase in alkaline phosphatase activity, a slight but consistent decrease in albumin and increased liver weight at and above 1000 ppm (equal to 26.8 mg/kg bw per day).

In a 1-year study of toxicity in dogs, which tested dietary concentrations of 0, 50, 150, 1000 or 10 000 ppm cyclaniliprole (equal to 0, 1.29, 4.07, 27.2 and 259 mg/kg bw per day in males and 0, 1.47, 4.20, 27.6 and 288 mg/kg bw per day in females, respectively), the NOAEL was 150 ppm (equal to 4.07 mg/kg bw per day) based on a consistent increase in alkaline phosphatase activity, a slight but consistent decrease in albumin and increased liver weight at 1000 ppm (equal to 27.2 mg/kg bw per day).

The overall NOAEL for the 90-day and 1-year studies of toxicity in dogs was 150 ppm (equal to 4.07 mg/kg bw per day) based on increased alkaline phosphatase activity, reduced albumin and increased liver weight at 1000 ppm (equal to 26.8 mg/kg bw per day).

In a 78-week study of chronic toxicity and carcinogenicity in mice, which tested dietary concentrations of 0, 200, 1250 or 8000 ppm cyclaniliprole (equal to 0, 22.7, 140 and 884 mg/kg bw per day in males and 0, 31.6, 186 and 1316 mg/kg bw per day in females, respectively), no treatment-related increase in tumour incidences was observed. The NOAEL for chronic toxicity and carcinogenicity was 8000 ppm (equal to 884 mg/kg bw per day), the highest dose tested.

In a 1-year study of toxicity in rats, which tested dietary concentrations of 0, 200, 2000, 6000 or 20 000 ppm cyclaniliprole (equal to 0, 9.21, 89.6, 277 and 955 mg/kg bw per day in males and 0, 11.7, 117, 358 and 1213 mg/kg bw per day in females, respectively), the NOAEL was 20 000 ppm (equal to 955 mg/kg bw per day), the highest dose tested.

In a 104-week study of carcinogenicity in rats, which tested dietary concentrations of 0, 200, 2000, 6000 or 20 000 ppm cyclaniliprole (equal to 0, 7.93, 82.5, 249 and 834 mg/kg bw per day in males and 0, 10.3, 103, 306 and 1041 mg/kg bw per day in females, respectively), no treatment-related increase in tumour incidences was observed. The NOAEL for chronic toxicity was 6000 ppm (equal to 249 mg/kg bw per day) for follicular cell hypertrophy of the thyroid gland at 20 000 ppm (equal to 834 mg/kg bw per day). The NOAEL for carcinogenicity was 20 000 ppm (equal to 834 mg/kg bw per day), the highest dose tested.

The Meeting concluded that cyclaniliprole is not carcinogenic in mice or rats.

Cyclaniliprole was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that cyclaniliprole is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that cyclaniliprole is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study in rats, which tested dietary concentrations of 0, 500, 3000 or 20 000 ppm cyclaniliprole (equal to 0, 41.2, 245 and 1683 mg/kg bw per day in males

and 0, 45.6, 274 and 1835 mg/kg bw per day in females, respectively), the NOAELs for reproductive toxicity, parental toxicity and offspring toxicity were 20 000 ppm (equal to 1683 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats, which tested cyclaniliprole at gavage doses of 0, 100, 300 or 1000 mg/kg bw per day from gestation day 6 to 19, the NOAELs for maternal and embryo/fetal toxicity were 1000 mg/kg bw per day, the highest dose tested. In a developmental toxicity study in rabbits, which tested cyclaniliprole at gavage doses of 0, 100, 300 or 1000 mg/kg bw per day from gestation day 6 to 27, the NOAELs for maternal toxicity and embryo/fetal toxicity were 1000 mg/kg bw per day, the highest dose tested.

The Meeting concluded that cyclaniliprole is not teratogenic.

In an acute neurotoxicity study in rats, which tested cyclaniliprole at a single gavage dose of 0, 500, 1000 or 2000 mg/kg bw, the NOAELs for acute systemic toxicity and neurotoxicity were 2000 mg/kg bw, the highest dose tested.

In a 13-week neurotoxicity study in rats, which tested dietary concentrations of 0, 600, 3100 or 16 000 ppm cyclaniliprole (equal to 0, 40, 204 and 1085 mg/kg bw per day in males and 0, 49, 240 and 1279 mg/kg bw per day in females, respectively), the NOAELs for systemic toxicity and neurotoxicity were 16 000 ppm (equal to 1085 mg/kg bw per day), the highest dose tested.

The Meeting concluded that cyclaniliprole is not neurotoxic.

In a 28-day immunotoxicity study in female rats, which tested dietary concentrations of 0, 200, 1250 or 8000 ppm cyclaniliprole (equal to 0, 34, 209 and 1352 mg/kg bw per day, respectively), the NOAELs for systemic toxicity and immunotoxicity were 8000 ppm (equal to 1352 mg/kg bw per day), the highest dose tested.

The Meeting concluded that cyclaniliprole is not immunotoxic.

Toxicological data on metabolites and/or degradates

All relevant metabolites of cyclaniliprole detected in plants or livestock were also detected in rats.

The main residue in all commodities tested was parent cyclaniliprole, with the metabolite NK-1375 also detected in some plant commodities at 10–30% of total residues. While NK-1375 is formed in the rat, it was detectable only in fat at relatively low levels (4.2–5.9% of total tissue radioactivity). In an acute toxicity study in rats, the LD_{50} for NK-1375 was greater than 2000 mg/kg bw, while an Ames test indicated no evidence of in vitro mutagenicity. Structurally, NK-1375 is very similar to the parent; a structural comparison of NK-1375 with cyclaniliprole using Toxtree (version 2.6.13) identified no unique structural alerts that would not already be covered by the toxicity tests on the parent.

Metabolites detected in livestock metabolism studies, YT-1284 and NSY-28, were also detected in rat metabolism studies and on this basis the ADI established for parent cyclaniliprole would adequately cover potential dietary exposure to these metabolites.

On this basis, the Meeting concluded that NK-1375 is likely to be of no greater toxicity than cyclaniliprole and therefore the acceptable daily intake (ADI) established for cyclaniliprole would cover potential dietary exposure.

Human data

No adverse events, including poisonings, have been reported in personnel involved in the manufacture of cyclaniliprole.

The Meeting concluded that the existing database on cyclaniliprole was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0.04 mg/kg bw based on the overall NOAEL of 4.07 mg/kg bw per day in 13-week and 1-year studies of toxicity in dogs for elevated alkaline phosphatase activity, reduced albumin and increased liver weight at 26.8 mg/kg bw per day, and using a 100-fold safety factor.

The ADI was established for the sum of cyclaniliprole and the metabolite, NK-1375, expressed as cyclaniliprole.

The Meeting concluded that it is not necessary to establish an acute reference dose (ARfD) for cyclaniliprole in view of its low acute toxicity and the absence of any other toxicological effects that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of cyclaniliprole

Species	Study	Effect	NOAEL	LOAEL
Mouse	Thirteen-week study of toxicity[a]	Toxicity	8 000 ppm, equal to 1 023 mg/kg bw per day[b]	–
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	8 000 ppm, equal to 884 mg/kg bw per day[b]	–
		Carcinogenicity	8 000 ppm, equal to 884 mg/kg bw per day[b]	–
Rat	Acute neurotoxicity study[c]	Toxicity	2 000 mg/kg bw[b]	–
	Twenty-eight day study of toxicity and immunotoxicity[a]	Toxicity, immunotoxicity	8 000 ppm, equal to 1 352 mg/kg bw per day[b]	–
	Thirteen-week study of neurotoxicity[a,d]	Toxicity, neurotoxicity	16 000 ppm, equal to 1 085 mg/kg bw per day	–
	One-year study of toxicity[a]	Toxicity	20 000 ppm, equal to 955 mg/kg bw per day[b]	–
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	6 000 ppm, equal to 249 mg/kg bw per day	20 000 ppm, equal to 834 mg/kg bw per day
		Carcinogenicity	20 000 ppm, equal to 834 mg/kg bw per day[b]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	20 000 ppm, equal to 1683 mg/kg bw per day[b]	–
		Parental toxicity	20 000 ppm, equal to 1 683 mg/kg bw per day[b]	–
		Offspring toxicity	20 000 ppm, equal to 1 683 mg/kg bw per day[b]	–
	Developmental toxicity	Maternal toxicity	1 000 mg/kg bw per	–

Species	Study	Effect	NOAEL	LOAEL
	study[c]		day[b]	
		Embryo/fetal toxicity	1 000 mg/kg bw per day[b]	–
Rabbit	Developmental toxicity study[c]	Maternal toxicity	1 000 mg/kg bw per day[b]	–
		Embryo/fetal toxicity	1 000 mg/kg bw per day[b]	–
Dog	Thirteen-week and 1-year studies of toxicity[a,d]	Toxicity	150 ppm, equal to 4.07 mg/kg bw per day	1 000 ppm, equal to 26.8 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake (ADI; applies to the sum of cyclaniliprole and NK-1375, expressed as cyclaniliprole)

0–0.04 mg/kg bw

Estimate of acute reference dose (ARfD)

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure. Results of mechanistic studies on the human relevance of increased alkaline phosphatase activity in dogs.

Critical end-points for setting guidance values for exposure to cyclaniliprole

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	T_{max}: 24–120 h (rats); 6–48 h (dogs). Gastrointestinal absorption: <10% in rats (10 mg/kg bw dose); 40% in dogs (1 mg/kg bw dose)
Dermal absorption	No data
Distribution	Widespread tissue distribution; highest levels in blood
Potential for accumulation	Unlikely to accumulate
Rate and extent of excretion	Slow elimination from plasma
Metabolism in animals	Limited
Toxicologically significant compounds in animals and plants	Cyclaniliprole, NK-1375
Acute toxicity	
Rat, LD_{50}, oral	>2 000 mg/kg bw
Rat, LD_{50}, dermal	>2 000 mg/kg bw
Rat, LC_{50}, inhalation	>4.62 mg/L
Rabbit, dermal irritation	Non-irritating

Rabbit, ocular irritation	Slightly irritating
Guinea-pig, dermal sensitization	Non-sensitizing
Mouse, dermal sensitization	Non-sensitizing
Short-term studies of toxicity	
Target/critical effect	Effects on liver, elevated alkaline phosphatase activity
Lowest relevant oral NOAEL	4.07 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Follicular cell hypertrophy of the thyroid gland
Lowest relevant NOAEL	249 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	No evidence of genotoxicity[a]
Reproductive toxicity	
Reproduction target/critical effect	No effect on reproduction
Lowest relevant parental NOAEL	1 683 mg/kg bw per day (rat)[b]
Lowest relevant offspring NOAEL	1 683 mg/kg bw per day (rat)[b]
Lowest relevant reproduction NOAEL	1 683 mg/kg bw per day (rat)[b]
Developmental toxicity	
Developmental target/critical effect	No evidence of developmental toxicity
Lowest maternal NOAEL	1 000 mg/kg bw per day (rat, rabbit)[b]
Lowest embryo/fetal NOAEL	1 000 mg/kg bw per day (rat, rabbit)[b]
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw (rat)[b]
Subchronic neurotoxicity NOAEL	1 085 mg/kg bw per day (rat)[b] Not neurotoxic
Other toxicological studies	
Immunotoxicity NOAEL	1 352 mg/kg bw per day (rat)[b]
	Not immunotoxic
Toxicological studies on NK1375	
Rat, LD_{50}, oral	>2 000 mg/kg bw per day
Genotoxicity	Not mutagenic in vitro
Human data	
	No adverse effects in manufacturing personnel

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

[b] Highest dose tested.

Summary

	Value	Studies	Safety factor
ADI[a]	0–0.04 mg/kg bw	Ninety-day and 1-year studies in dogs	100
ARfD	Unnecessary		

[a]Applies to cyclaniliprole + NK-1375, expressed as cyclaniliprole.

RESIDUE AND ANALYTICAL ASPECTS

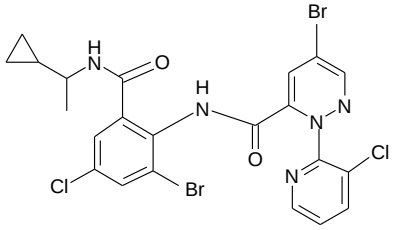
Cyclaniliprole (ISO common name) was scheduled for residue evaluation as a new compound by the 2017 JMPR at the 48th Session of the CCPR.

Cyclaniliprole is a broad-spectrum insecticide belonging to the diamide and pyrazole chemical classes of insecticides. Despite its structural similarity to some of the phenylpyrazole insecticides, this substance has a different mode of action, which it shares with other diamide insecticides. Diamides act at the ryanodine receptor, which is critical for muscle contraction.

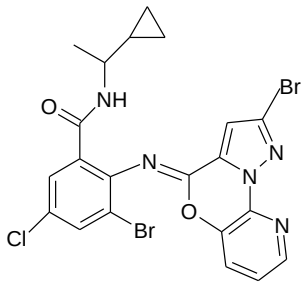
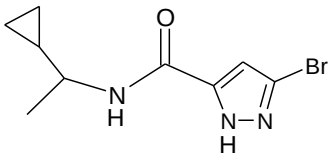
The Meeting received information from the manufacturer on identity, metabolism, environmental fate, storage stability, residue analysis, use patterns, residues resulting from supervised trials on pome fruit, stone fruit, grapes, brassica's, fruiting vegetables, leafy vegetables, soya beans, potato, almond, pecan, tea, fate of residue during processing, and livestock feeding studies.

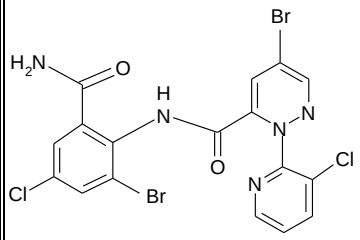
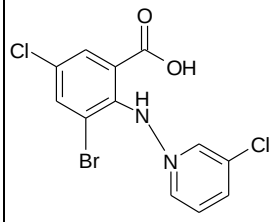
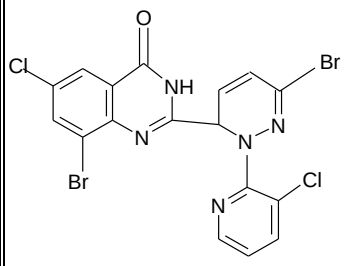
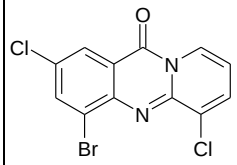
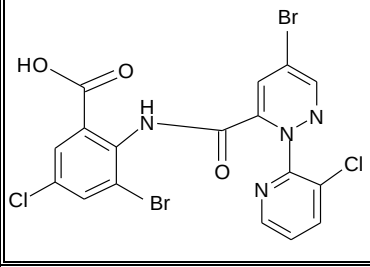
The IUPAC name for cyclaniliprole is 2',3-dibromo-4'-chloro-1-(3-chloro-2-pyridyl)-6'-{[(1*RS*)-1-cyclopropylethyl]carbamoyl}pyrazole-5-carboxanilide. The CA name is 3-bromo-*N*-[2-bromo-4-chloro-6-[[(1-cyclopropylethyl)amino]carbonyl]phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide.

Structural formula



Metabolites referred to in the appraisal by codes:

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 CF = 1.064 	YT-1327 3-bromo-*N*-(1-cyclopropylethyl)-1*H*-pyrazole-5-carboxamide 

YT-1284 3-bromo-*N*-(2-bromo-6-carbamoyl-4-chlorophenyl)-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide CF = 1.128 	BCPBA 3-bromo-5-chloro-2-((3-chloropyridin-2-yl) amino) benzoic acid 
NSY-28 8-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-yl)-6-chloroquinazolin-4(3*H*)-one CF = 1.165 	BPQO 4-bromo-2,6-dichloro-11*H*-pyrido[2,1-*b*]quinazolin-11-one 
NSY-27 3-bromo-2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamido)-5-chlorobenzoic acid CF = 1.125 	

Plant metabolism

The Meeting received plant metabolism studies for cyclaniliprole after foliar application on fruits (apples), leafy vegetables (lettuce) and root and tuber vegetables (potato).

The metabolism of ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole in commercially grown apples was studied following three foliar applications at 96–100 g ai/ha at a four-week interval. Total radioactive residues (TRR) in mature apples at DALA = 15 and 30 were 0.15 and 0.042 mg/kg eq for the phenyl label and 0.14 and 0.036 mg/kg eq for the pyrazole label, respectively. A high proportion of the residue remained on the surface of the fruit (59–92% TRR in surface wash; 5.3–29% TRR in peel; 2.3–12 % TRR in flesh). The residues in or on the fruit could be extracted by acetonitrile/water (> 89% TRR). The principal component of the residue was the parent compound

(40–50% TRR), followed by metabolite NK-1375 (23–29% TRR) and YT-1284 (1.0–3.9% TRR). A number of other metabolites were detected (0.3–4.9% TRR), but none reaching > 0.01 mg/kg eq in apple fruit.

The metabolism of ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole in lettuce was studied following three foliar applications at 107–117 g ai/ha at a 10 days interval. Total radioactive residues (TRR) in mature lettuce at DALA = 8 and 15 were 0.76 and 0.39 mg/kg eq for the phenyl label and 0.76 and 0.37 mg/kg eq for the pyrazole label, respectively. A high proportion of the residue remained on the surface of the leaves (76–84% TRR in surface wash). The residues in or on the leaves could be extracted by acetonitrile/water (> 94% TRR). The principal component of the residue was the parent compound (59–78% TRR), followed by metabolite NK-1375 (13–22% TRR) and YT-1284 (0.3–0.6% TRR). A number of other metabolites were detected (0.2–2.2% TRR), but none reaching > 0.01 mg/kg eq.

The metabolism of ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole in potato was studied following three foliar applications at 40 g ai/ha/application at a 14 days interval. Total radioactive residues (TRR) in potato foliage at DALA = 8 and 15 were 2.4 and 1.8 mg/kg eq for the phenyl label and 3.0 and 1.6 mg/kg eq for the pyrazole label, respectively. A high proportion of the residue remained on the surface of the leaves (44–57% TRR in surface wash). The residues in or on the leaves could be extracted by acetonitrile/water (> 90% TRR). The principal component of the residue was the parent compound (60–67% TRR), followed by metabolite NK-1375 (13–15% TRR). A number of other metabolites were detected, but none higher than 3.9% TRR. Residues in potato tubers were not investigated, because concentrations were below the trigger value of 0.01 mg/kg eq.

In summary, the metabolism in crops after foliar application is similar. In fruits, leafy vegetables and root and tuber vegetables the parent compound represents the principal part of the residue, followed by metabolite NK-1375. Metabolism follows two pathways. The major pathway is cyclisation by reaction between an oxygen moiety and a chloride moiety, giving the compound NK-1375 (pathway 1). The minor pathway is N-de-alkylation of cyclaniliprole and loss of the 1-cyclopropylethyl group on the nitrogen atom in the amide moiety in the side chain yielding the corresponding primary amide YT-1284 (pathway 2).

In general, metabolism between plants and rat is not similar, though some NK-1375 was found in fat, it was not observed in any other animal tissues. The plant metabolite YT-1284 (minor metabolite 0.3–3.9% TRR) was found in animal commodities (6.0–19% TRR).

Fate in rotational crops

Metabolism of cyclaniliprole was investigated in one confined rotational crop study and two field rotational crops studies.

In the confined rotational crop study ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole was applied to bare sandy loam soil at a rate of 98–110 g ai/ha under indoor conditions. Rotational crops (wheat, lettuce and carrot) were sown at 30, 120 and 365-day plant back intervals (PBI). Total radioactivity in rotational crops were 0.001 mg/kg eq in lettuce, carrot root, carrot foliage and wheat grain at all pant back intervals, except for carrot foliage (0.002 mg/kg eq) at PBI 30 days. Total radioactivity in wheat forage was 0.018 mg/kg eq (PBI 30 days), 0.028 mg/kg eq (PBI 120 days) and 0.015 mg/kg eq (PBI 365 days). In wheat hay, total radioactivity decreased from 0.030 mg /kg eq (30-day PBI) to 0.017 mg/kg eq (365-day PBI). Total radioactivity in wheat straw decreased from 0.058 mg/kg eq (30-day PBI) to 0.029 mg/kg eq (365-day PBI).

In wheat forage, hay and straw parent was the principal component and ranged from 67% to 90% TRR at the three plant back intervals. Metabolite NK-1375 was found at a maximum of 14% TRR in forage (30-day PBI). NK-1375 in forage, hay and straw at other plant back intervals ranged from not detectable to 3.5% TRR.

From these data, the Meeting concluded that cyclaniliprole can be taken up from the soil under confined conditions even after long plant back intervals (365 days) in cereals, but it does not

lead to detectable residues in leafy vegetables or root and tuber vegetables. No additional metabolites were observed in confined rotational crops indicating the same metabolic pathway as primary crops.

The Meeting received two field rotational crop studies to investigate the actual uptake of residue from soil.

In the first field rotational crop study at three different locations in the EU cyclaniliprole was applied to tomatoes and peppers as primary crops with two applications of 40 g ai/ha, with an interval of 10–11 days. Wheat was planted as a rotational crop 29–32, 124–154 days after application. Cyclaniliprole was found at a maximum concentration equal to the LOQ of 0.01 mg/kg in four samples; twice in straw of wheat drilled at approximately 30 days after last application, once in straw of wheat drilled 124 days after last application and one in forage of wheat drilled 128 days after last application. In all other samples cyclaniliprole was below the LOQ of 0.01 mg/kg. NK-1375 was not detected in any of the samples.

In another field rotational crop study at six different locations in the USA cyclaniliprole was applied as foliar application to lettuce, soybean or wheat at 1x 300 g ai/ha. The last application was at BBCH 71–89 of the primary crops. The primary crops were mowed and plots were tilled or plots were disked before planting the rotational crop. The rotational crop wheat was sown 29–30, 119–127/147 or 263–366 days after application.

No residues of parent (< 0.01 mg/kg) were found in wheat grain. Parent was found in wheat forage and wheat straw at levels < 0.01–0.073 mg/kg (PBI 20–30 days), < 0.01–0.189 mg/kg (highest individual analytical value; PBI 119–127 days), and < 0.01–0.083 mg/kg (PBI 147–366 days). Metabolite NK-1375 was not found at levels > 0.01 mg/kg in any of the harvested commodities at any of the rotations, except in wheat straw at the 127 day plant back interval on one location in the USA.

The dose rate of 1×300 g ai/ha covers the current maximum seasonal rates.

The Meeting concluded that residues due to crop rotation are not expected in leafy vegetables, root and tuber vegetables, cereal grain and leaves of root and tuber vegetables. No data are available for oilseeds and pulses. Residue levels due to crop rotation in wheat forage and straw can be expected.

Animal metabolism

The Meeting received results of metabolism studies in laboratory animals (rats), lactating goats and laying hens.

Metabolism in laboratory animals was summarised and evaluated by the WHO panel of the JMPR in 2017.

One lactating goat per radiolabel was dosed orally once daily for five consecutive days with a capsule containing ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cylcaniliprole. The actual dose levels were 12.3 ppm and 11.2 ppm for the phenyl and pyrazole labelled cyclaniliprole, respectively. The total overall recoveries of radioactivity were 81–87% of the cumulative dose following sacrifice at 23 hours after the last dose for both labels. The majority of the radioactivity was recovered in the faeces (68/59% TAR, phenyl/pyrazole). The remainder of the dose was recovered in urine (5.1/6.6% TAR, phenyl/pyrazole), GI tract contents (5.4%/9.5% TAR), and cage wash (0.2%/0.3% TAR). Total recovered radioactivity in milk and tissues was 8.8%/6.0% TAR, respectively.

The highest radioactivity concentrations in edible tissues were found in the liver (1.5/1.3 mg/kg eq), fat (0.86/0.79 mg/kg eq), and kidneys (0.58/0.55 mg/kg eq) followed by muscle (0.12/0.12 mg/kg eq). Total radioactive residues in milk from the phenyl label dosed goat reached a plateau concentration of approximately 0.12–0.14 mg/kg eq by 96–119 hours after dosing. Total radioactive residues in milk from the pyrazole label dosed goat reached a plateau concentration of approximately 0.081–0.091 mg/kg eq following 72 hours after dosing.

Following solvent extraction with acetonitrile, residue extractabilities in tissues and milk ranged from 84% (kidney) to 100% (fat).

Parent was identified in milk and all goat tissues at levels of 71/58% TRR in milk (0.094/0.048 mg/kg eq), 33/30% TRR (0.48/0.40 mg/kg eq) in liver, 30/19% TRR (0.17/0.10 mg/kg eq) in kidney, 44/23% TRR (0.052/0.027 mg/kg eq) in muscle and 76/44% TRR (0.67/0.31 mg/kg eq) in fat. The most significant metabolites identified in all tissues and milk were NSY-28, ranging from 5.2% TRR (milk) to 53% TRR (kidney) and metabolite YT-1284, ranging from 6.0% TRR (fat) to 21% TRR (milk). Levels of NSY-28 in kidney (0.21–0.29 mg/kg eq), muscle (0.055 mg/kg eq) and liver (0.42 mg/kg eq) were higher than those of the parent compound. Other metabolites (including metabolite NSY-27) were found at levels below 10% TRR.

Five laying hens per radiolabel were dosed orally once daily for 14 consecutive days with a gelatine capsule containing ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole at mean daily doses in the dry feed of 11.03 and 10.8 ppm for the phenyl or pyrazole label, respectively. Hens were euthanized 12 hours after the last dose. Total recovered radioactivity amounted to 96% and 98% of the administered dose for the phenyl and pyrazole radiolabelled forms, respectively. The majority of the radioactivity was recovered in excreta (92%/93%, phenyl/pyrazole), while only low levels were found in eggs (2.0/2.5% TAR, phenyl/pyrazole) and tissues (0.8/0.7% TAR, phenyl/pyrazole).

The highest radioactivity concentrations were found in liver (1.7/1.5 mg/kg eq, phenyl/pyrazole), followed by fat (0.34/0.27 mg/kg eq, phenyl/pyrazole), skin (0.27/0.30 mg/kg eq, phenyl/pyrazole) and muscle (0.072/0.067 mg/kg eq, phenyl/pyrazole). Total radioactive residues in whole egg achieved a plateau concentration of 0.62–0.67 mg/kg eq after 8–9 days of dosing. Total radioactive residues in egg whites and egg yolk separately were not determined.

Following solvent extraction with acetonitrile, residue extractabilities were > 76% TRR for eggs and tissues.

Parent was identified at levels of 4.4–12% TRR (0.073–0.17 mg/kg eq) in liver, 9.7–16% TRR (0.006–0.011 mg/kg eq) in muscle, 21–23% TRR (0.15–0.16 mg/kg eq) in eggs, 44–58% TRR (0.15–0.16 mg/kg eq) in fat and 26–30% TRR (0.069–0.090 mg/kg eq) in skin. The most significant metabolite in all tissues and eggs was NSY-28 (54–63% TRR 0.38–0.42 mg/kg eq) in eggs, 63–56% TRR (0.82–1.0 mg/kg eq) in liver; 27–26% TRR (0.069–0.093 mg/kg eq) in fat; 38–47% TRR (0.10–0.14 mg/kg eq) in skin; 27–48% TRR (0.019–0.033 mg/kg eq) in muscle, followed by YT-1284 (4.0% TRR in eggs to 28% TRR in muscle). Levels of NSY-28 were higher than those of the parent compound in eggs, skin, muscle and liver.

In summary, metabolism observed in lactating goats and laying hens arose via N-de-alkylation of cyclaniliprole and loss of the 1-cyclopropylethyl group on the nitrogen atom in the amide moiety in the side chain yielding the corresponding primary amide, YT-1284. This metabolite is subjected to cyclization by reaction between two amide moieties in YT-1284 giving the quinazoline compound, NSY-28.

The major compounds identified in goat, hen tissues, milk or eggs are: parent and NSY-28, followed by YT-1284. Parent and NSY-28 comprise a significant part of the residue in tissues, milk and eggs. Significant additional contributions (> 10% TRR) are found for metabolite YT-1284 in all tissues and milk.

In general, metabolism between goat, hen and rat is similar.

Environmental fate in soil

The Meeting received information on aerobic metabolism in soil.

Aerobic metabolism and degradation in soil of ^{14}C-phenyl-cyclaniliprole or ^{14}C-pyrazole-cyclaniliprole was investigated in two studies at an application rate of 0.2 mg/kg, equivalent to a field rate of 150 g ai/ha in both studies. Cyclaniliprole was the major component at all times in both studies. The calculated DT_{50}s were > 692 days at 20 °C and 482–638 days at 35 °C.

The Meeting concluded that cyclaniliprole is very persistent.

Environmental fate in water-sediment systems

Not applicable.

Methods of analysis

The Meeting received description and validation data for analytical methods for the determination of cyclaniliprole related residues in plant and animal commodities.

The existing multi-residue method QuEChERS was submitted as an enforcement/monitoring method for the determination of parent compound and metabolite NK-1375 in plant commodities. The Meeting considers validation sufficient for plant commodities with high acid content, high water content, high starch content, high oil content. The LOQ was 0.01 mg/kg each for parent compound and metabolite NK-1375 in each matrix.

Several other LC-MS/MS methods were submitted for the determination of parent and its metabolite NK-1375 and degradation products BPQO, BCPBA and YT-1327 in plant material. Crop commodities were extracted with acetonitrile and cleaned up with SPE. The extraction efficiency of the residue analytical method was compared to the extraction efficiency of the analytical method used in the metabolism study. The extraction efficiency was 84% for total residues (cyclaniliprole and NK-1375) in surface washed lettuce. All analytical methods were considered fit for purpose with LOQs of 0.01 mg/kg for individual analytes. This procedure was not followed for the degradation products, but the submitted method was validated in several processed commodities derived from tomatoes and grapes.

A similar LC-MS/MS method was submitted for the determination of parent and its metabolites NK-1375, NSY-27, NSY-28 and YT-1284 in milk, eggs and animal tissues. Animal commodities were extracted twice with acetonitrile and subsequently partitioned against hexane. SPE clean-up is performed prior to LC-MS/MS analysis. The extraction efficiency of the residue analytical method was compared to the method used in the metabolism studies. The extraction efficiency for acetonitrile ranged from 70% to 93% in liver, milk and eggs as shown by a radio-validation study in goat milk and liver and hen egg and liver. The analytical method was considered fit for purpose with LOQs of 0.01 mg/kg for the individual analytes.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the storage stability of parent and metabolite NK-1375 in raw and processed plant commodities and of parent, NK-1375, NSY-27, NSY-28 and YT-1284 in animal commodities.

Storage stability studies showed that cyclaniliprole and metabolite NK-1375 were stable for at least 18 months at -20 °C in crop commodities representative of the high water, high acid, high starch, high protein and high oil commodity groups.

Cyclaniliprole and metabolite NK-1375 were stable for at least 18 months at -20 ºC in wine. No storage stability data were provided for the degradation products BPQO, BCPBA and YT-1327 found after some processing procedures.

Cyclaniliprole and the metabolites NK-1375, NSY-27, NSY-28 and YT-1284 were stable at -20 ºC for at least 39 days in bovine liver, kidney, muscle, and fat. Stability data in metabolism studies show that no further degradation occurs for another 2–3 months.

Definition of the residue

In primary crops (apple, lettuce and potato), parent compound represented the principal part of the residue in most crop commodities ranging from 40% TRR to 78% TRR (0.015–9.7 mg/kg eq). The major metabolite in these crops was NK-1375 with concentrations ranging from 13–29% TRR (0.009–0.113 mg/kg eq). Metabolite YT-1284 was observed in apples (1.0–3.9% TRR (0.001–0.006 mg/kg eq)) and lettuce (0.3–0.6% TRR (0.002–0.003 mg/kg eq)).

In confined rotational crops no residues (< 0.001 mg/kg eq) were found in lettuce, carrot and wheat grain. Parent was the principal component in wheat forage, hay and straw (67–90% TRR, 0.012–0.044 mg/kg eq). Metabolite NK-1375 was detectable at a lower but significant level only at 30 day PBI in forage (14% TRR, 0.003 mg/kg eq) and was less than 10% TRR in wheat hay and straw and other PBIs (<3.5% TRR, < 0.001 mg/kg eq). In field rotational crops with wheat in rotation on nine locations in the USA and EU, NK-1375 was found once at detectable levels in wheat straw (0.013 mg/kg).

Cyclaniliprole is found in every primary crop commodity and is considered suitable as marker compound. The Meeting noted that suitable analytical methods exist to measure cyclaniliprole and its metabolites in plant commodities. The Meeting decided to define the residue for enforcement/monitoring as parent only.

Apart from cyclaniliprole, NK-1375 was found at significant levels in primary crops (pome fruit, stone fruit, grapes, brassica's, fruiting vegetables, leafy vegetables, tea) if the application rate is high enough. In the majority of these crops the metabolite accounted for 10–30% of the total residue. The JMPR 2017 received toxicological data for the metabolite NK-1375, showing that this compound is no more toxic than parent and that it was detected in rat metabolism studies.

Processing studies showed that hydrolysis under very specific conditions can lead to the formation of degradation products YT-1327, BCPBA and BPQO and might be relevant for the residue definition for processed commodities formed after sterilisation. Processing studies in grapes, apples, peaches and tomatoes show that even at exaggerated application rates, residues of these degradation products were below the LOQ, except for tomato paste where residues of YT-1327, BCPBA and BPQO were found, each accounting for less than 3% of parent. Considering that these levels were found at 6.5 times the highest GAP, the resulting residues at the critical GAP would be expected to be below the LOQ in all kinds of processed commodities and need not to be considered for the residue definition for dietary risk assessment.

In addition to the parent compound, NK-1375 is the only compound which might be relevant for the plant residue definition for dietary risk assessment. The Meeting decided to define the residue for dietary risk assessment for plant commodities as parent and NK-1375.

In animal metabolism studies the major compounds identified in goat, hen tissues, milk or eggs are: parent, NSY-28 and YT-1284. Parent was identified at levels ranging from 9.7% TRR to 76% TRR (0.006–0.673 mg/kg eq) in the different animal commodities. Metabolite NSY-28 was identified at levels of 5.2–63% TRR (0.007–1.049 mg/kg eq) in hen and goat commodities. Metabolite YT-1284 was identified at levels of 4.0–28% TRR (0.011–0.25 mg/kg eq) in hen and goat tissues, eggs and milk. In dietary feeding studies with the maximum dietary feeding level (11.6 ppm) slightly below the median dietary burden (12 ppm feed), metabolite YT-1284 was either not detectable or below the LOQ at the highest dose level. NSY-28 was detected in liver (0.014–0.032 mg/kg), kidney and fat (< 0.01–0.014 mg/kg) at the 11.6 ppm feeding level, representing 23–56% of the total residue in liver and max 12% of the total residue in kidney and fat.

Cyclaniliprole parent is found in every animal commodity and is therefore a suitable marker compound. The Meeting decided to define the residue for enforcement as parent only.

The log K_{ow} for cyclaniliprole is 2.0–2.8. The goat and hen metabolism studies showed a tendency of the parent compound to partition into the fat tissues; levels of cyclaniliprole found in goat fat were at least 6 times higher than residues in goat muscle. A similar, even more pronounced pattern (ratio 13.5:1) is observed for hen fat and muscle. The ratio of parent found in the fat and aqueous fraction of milk was at least 53:1. The dairy feeding study also showed a tendency to partition into fat. The Meeting considers the residue to be fat soluble.

Apart from cyclaniliprole, metabolites NSY-28 and YT-1284 were found at significant levels in livestock commodities and were considered for their relevance for the residue definitions. Levels of YT-1284 ranged from 4 to 28% in the various animal tissues in the two metabolism studies, but was not detected in any tissues in the dairy feeding study and therefore not expected to contribute to the dietary intake. Though significant levels of NSY-28 are found in liver and fat the metabolite is not

expected to contribute significantly to the overall dietary intake via consumption of edible offal and fat in chronic intake assessment. Furthermore, the toxicity of these metabolites is considered to be covered by toxicity studies on cyclaniliprole since each of the metabolites was detected in the rat. The Meeting noted that suitable analytical methods exist to measure cyclaniliprole and its metabolites in animal commodities.

The Meeting decided to define the residue for dietary risk assessment for animal commodities as parent only.

The Meeting recommended the following residue definitions for cyclaniliprole:

Definition of the residue for compliance with the MRL for plant and animal commodities: *cyclaniliprole.*

Definition of the residue for dietary risk assessment for plant commodities: *cyclaniliprole + 3-bromo-2-((2-bromo-4H- pyrazolo[1,5-d]pyrido[3,2-b]-[1,4]oxazin-4-ylidene)amino)-5-chloro-N-(1-cyclopropylethyl)benzamide (NK-1375), expressed as cyclaniliprole equivalents.*

The molecular weight conversion factor to express NK-1375 in cyclaniliprole equivalents = 1.064.

Definition of the residue for dietary risk assessment for animal commodities: *cyclaniliprole*

The Meeting considers the residue to be fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised trials data for cyclaniliprole on apple, pear, cherry, plum, peach, apricot, nectarine, grapes, head cabbages, Brussels sprouts, broccoli, cauliflower, cucumber, summer squash, melon, tomato, pepper, lettuces, spinach, mustard greens, kale, soybeans, almond, pecan, and tea.

Residues for maximum residue estimation are expressed in mg cyclaniliprole/kg. Residues for dietary risk assessment include parent cyclaniliprole and metabolite NK1375. The totals (sum of the mean of parent and NK-1375) are expressed as parent equivalents by applying a conversion factor of 1.064 to NK-1375. Levels of NK-1375 are generally not detectable if parent concentrations are < 0.01 mg/kg. Field trials resulting in significant residue levels show a maximum contribution of NK-1375 of approximately 30% to the total residue. Therefore, if parent is at or below LOQ the metabolite is < 0.01 mg/kg and the total is calculated as < 0.01 mg/kg.

For several crops (pome fruit (USA), stone fruit (USA), brassica's (USA), cucurbits (USA) and peppers and tomatoes (EU) field trials were performed with and without the use of an adjuvant. These trials demonstrate that the adjuvant does not influence the residue level.

None of the submitted trials from Canada and the USA matched the critical GAPs from the USA with respect to number of applications, retreatment intervals, and/or application rates. However, for some trials, the total seasonal rates were within ±25% of the maximum seasonal rates allowed on the label and the PHIs matched. To explore whether these trials could be used to evaluate maximum residue levels, the Meeting developed a simple tool to compare anticipated residues from at-GAP use patterns with those from the use patterns used in the trials. The tool uses application rates, retreatment intervals, PHI, and half-life estimates to model residues in crops at harvest. If modeled residues were within ±25% for these scenarios, then the Meeting decided that the trials could be used to estimate maximum residue levels.

In implementing the tool, the Meeting used the submitted residue decline trials to derive crop(group) specific median half-life estimates; at least three decline trials, each with at least 4 time points, with the first time point well above LOQ and the following two time points at least at or above the LOQ. If the decline data were not sufficient to derive a reasonably robust median half-life estimate, or total application rates were not within ±25% of the maximum seasonal rate allowed on the label, then the tool was not used to evaluate the suitability of the trials.

Pome fruit

Field trials involving apples and pears were performed in the USA and Canada, EU (the Netherlands, Germany, United Kingdom, France, Italy and Spain) and Australia. Field trials involving apples performed in the EU (2 × ca. 40 g ai/ha, RTI 13–15 days, PHI 14 days) and field trials involving apples performed in Australia (2×ca. 30–300 g ai/ha, interval 13–15 days, PHI 28 days) did not match any GAP.

The critical GAP for pome fruit is the GAP from the USA: 1×60 + 3×80 g ai/ha, to reach the seasonal maximum rate of 300 g ai/ha, 10-day RTI, 7-day PHI.

Field trials with apples or pears from USA and Canada (3×59–107 g ai/ha, RTI 13–15 days, PHI 7 days) differed from the critical GAP with regard to the number of applications, the application rate and the retreatment interval. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ of 12 days (n=16) for pome fruit, show that the expected residues are similar (2.3% deviation). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in apples in ranked order were (n=16): 0.013, 0.023, 0.027, 0.035, 0.037, 0.046, 0.049, 0.054, 0.054, 0.055, 0.058, 0.068, 0.068, 0.10, 0.10, and 0.13 mg/kg cyclaniliprole.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in apples were (n=16): 0.023, 0.033, 0.038, 0.046, 0.053, 0.056, 0.059, 0.065, 0.065, 0.067, 0.073, 0.079, 0.084, 0.12, 0.13, and 0.17 mg/kg parent equivalents.

For estimation of the maximum residue level the ranked order of cyclaniliprole residues in pears were (n=9): 0.037, 0.060, 0.069, 0.095, 0.097, 0.11, 0.13, 0.14, and 0.14 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in pears were (n=9): 0.051, 0.070, 0.081, 0.11, 0.12, 0.12, 0.14, 0.16, and 0.16 mg/kg parent equivalents.

The datasets of apples and pears are of the same population (Mann-Whitney test). The Meeting decided to combine the data to estimate a maximum residue level for pome fruit. The combined cyclaniliprole residues in apples and pears were (n=25): 0.013, 0.023, 0.027, 0.035, 0.037, 0.037, 0.046, 0.049, 0.054, 0.054, 0.055, 0.058, 0.060, 0.068, 0.068, 0.069, 0.095, 0.097, 0.10, 0.10, 0.11, 0.13, 0.13, 0.14, and 0.14 mg/kg.

For dietary risk assessment cyclaniliprole residues include metabolite NK-1375 and the combined data in apples and pears were (n=25): 0.023, 0.033, 0.038, 0.046, 0.051, 0.053, 0.056, 0.059, 0.065, 0.065, 0.067, 0.070, 0.073, 0.079, 0.081, 0.084, 0.11, 0.12, 0.12, 0.12, 0.13, 0.14, 0.16, 0.16, 0.17 mg/kg equivalents.

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.073 mg/kg parent equivalents for pome fruit.

The Meeting estimated a median residue of 0.060 mg/kg (parent only) for animal dietary burden calculations.

Stone fruit

Cherries

Field trials involving cherries were performed in the USA, Canada and Japan. Field trials in Japan (2×ca. 100 g ai/ha, interval 7 days, PHI 1–21 days) did not match any GAP.

The critical GAP for cherries is the GAP for stone fruit from the USA: 1×60 + 3×80 g ai/ha, to meet the maximum rate of 300 g ai/ha/season, 7-day RTI, 7-day PHI.

Field trials with cherries from the USA and Canada (3×100 g ai/ha, interval 6–8 days, PHI 7 days) differed from the critical GAP with regard to the number of applications and the application

rate. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ of 7.2 days (n=15 from various stone fruit crops) for stone fruit, show that the expected residues are similar (max +18.4% deviation). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in cherries in ranked order were (n=15): 0.010, 0.016, 0.082, 0.097, 0.13, 0.13, 0.14, 0.14, 0.18, 0.24, 0.28, 0.30, 0.33, 0.44 and 0.56 mg/kg.

Residue levels in the field trials from the USA and Canada were determined in flesh without stone. The Japanese trials on cherries show that the contribution of the pit to the weight of the whole fruit is approximately 10%. Correction of the residue levels using this weight/weight ratio would lead to the same maximum residue level.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 as measured in flesh were (n=15): 0.021, 0.027, 0.10, 0.11, 0.14, 0.14, 0.16, 0.17, 0.19, 0.26, 0.32, 0.34, 0.34, 0.48 and 0.61 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.9 mg/kg and an STMR of 0.17 mg/kg parent equivalents for the subgroup cherries.

Plums

Field trials involving plums were performed in the USA, Canada and EU (Netherland, Germany, United Kingdom, France, Italy and Spain). Field trials involving plums performed in the EU (2×ca. 40 g ai/ha, RTI 13–15 days, PHI 13–15 days) did not match any GAP.

The critical GAP for plums is the GAP for stone fruit from the USA: 1×60 + 3×80 g ai/ha, to reach a maximum rate of 300 g ai/ha/season, 7-day RTI, 7-day PHI.

Field trials with plums from USA and Canada (3×40–102 g ai/ha, interval 6–8 days, PHI 7 days) differed from the critical GAP with regard to the number of applications and the application rate. Comparison of application scenarios of the trials with the critical GAP using the tool described earlier and applying a calculated median $t_{1/2}$ of 7.2 days (n=15 from various stone fruit crops) for stone fruit show that the expected residues are similar (max +18.4% deviation). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in plums in ranked order were (n=7): 0.019, 0.019, 0.024, 0.056, 0.062, 0.065, and 0.091 mg/kg.

Residue levels were determined in flesh without stone. The residue data from field trials in Europe show that the ratio of the residue levels in flesh versus whole fruit range between 0.86 and 0.97. Though these ratios are based on very low residue levels, still an overestimation of approximately 10% is anticipated. Correction with this factor would lead to the same maximum residue level.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in plums were (n=7): 0.030, 0.03, 0.035, 0.067, 0.075, 0.076, and 0.11 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR value of 0.067 mg/kg parent equivalents for the subgroup plums.

Peaches (including apricots and nectarines)

Field trials involving peaches were performed in the USA and Canada. Field trials involving apricots and peaches were performed in the EU (Spain, Southern France, Italy, Germany, Hungary and Poland). Field trials involving apricots and peaches performed in the EU (2×ca. 40 g ai/ha, RTI 13–15 days, PHI 13–15 days) did not match any GAP.

The critical GAP for apricots, peaches, nectarines is the GAP for stone fruit from the USA: 1×60 + 3×80 g ai/ha, max rate of 300 g ai/ha/season, 7-day RTI, 7-day PHI.

Field trials with peaches from the USA and Canada (3×55–103 g ai/ha, RTI 6–8 days, PHI 7 days) differed from the critical GAP with regard to the number of applications and the application rate. Comparison of application scenarios of the trials with the critical GAP using the tool described earlier and applying a calculated median $t_{1/2}$ of 7.2 days (n=15 from various stone fruit crops) for stone fruit show that the expected residues are similar (max +18.4% deviation). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in peaches in ranked order were (n=12): 0.023, 0.041, 0.045, 0.050, 0.051, 0.054, 0.064, 0.081, 0.094, 0.11, 0.16, and 0.19 mg/kg.

Residue levels were reported on a flesh basis. The residue data from supervised field trials in Europe show that the weight ratio's flesh/whole fruit range between 0.85 and 0.96. Though these ratios are based on very low residue levels, still an overestimation of approximately 10% is anticipated. Correction with this factor would lead to the same maximum residue level.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in peaches were (n=12): 0.034, 0.056, 0.058, 0.061, 0.062, 0.065, 0.078, 0.092, 0.10, 0.12, 0.17, 0.20 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.0715 mg/kg parent equivalents for peach. The Meeting decided the maximum residue level and STMR can be extrapolated to the whole subgroup of peaches (including apricots and nectarines).

Grapes

Field trials involving grapes were performed in the USA, Canada, EU (Italy Spain, Greece, Germany, France), and Japan. The residue field trials involving table and wine grapes in the EU (2×ca. 35 g ai/ha, interval 13–15 days, PHI 3 days) did not match any GAP. Similarly residue field trials on grapes performed in Japan (2×ca. 80 g ai/ha, interval 7 days, PHI 1–21 days) did not match any GAP.

The critical GAP for grapes is the GAP for small fruit (vine climbing fruit) from the USA: 1×60 + 3×80 g ai/ha, to reach the maximum rate of 300 g ai/ha/season, 7-day RTI, 7-day PHI.

Field trials with grapes from the USA and Canada (3×97–105 g ai/ha, interval 6–8 days, PHI 7 days) differed from the critical GAP with regard to the number of applications and the application rate. Comparison of application scenarios of the trials with the critical GAP using the tool described earlier and applying a calculated median $t_{1/2}$ (n=15) of 11 days for grapes show that the expected residues are similar (max +13.9% deviation). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in grapes in ranked order were (n=15): 0.025, 0.044, 0.048, 0.076, 0.11, 0.12, 0.12, 0.14, 0.14, 0.16, 0.20, 0.24, 0.33, 0.39 and 0.51 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in grapes were (n=15): 0.036, 0.055, 0.059, 0.092, 0.13, 0.13, 0.15, 0.15, 0.17, 0.22, 0.25, 0.28, 0.44, 0.48, and 0.59 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.8 mg/kg and an STMR of 0.15 mg/kg parent equivalents for grapes.

The Meeting estimated a median residue of 0.14 mg/kg (parent only) for animal dietary intake calculations.

Leek

Though the Meeting received a GAP for leek, no supporting field residue trials were submitted.

Brassica vegetables (except Brassica leafy vegetables)

Flowerhead Brassicas

Field residue trials on broccoli were performed in the USA and Canada and in Europe (Germany, United Kingdom, France, Italy, and Spain). Residue trials on cauliflower were performed in Europe (Germany, the Netherlands, France, Italy, and Spain). The trials performed in the EU did not match any GAP.

The critical GAP flower head brassica's is the USA GAP for brassica's: 4×60 g ai/ha, max total rate of 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials with broccoli from the USA and Canada (3×61–87 g ai/ha, interval 6–8 days, PHI 1 day) differed from the critical GAP with regard to the number of applications and the application rate, but were comparable using the tool described earlier. Modelling with the calculated median $t_{1/2}$ of 1.8 days (n=5) for brassica's, show that the expected residues are similar (-8% to +22 % deviation, comparing the 3x60 and 3x80 g ai/ha/application patterns from the trials to the 4x60 g ai/ha/application GAP pattern). The Meeting concluded that the supervised residues trials could be used for estimation of a maximum residue level. Cyclaniliprole residues ranked order were (n=10): 0.11, 0.12, 0.18, 0.20, 0.34, 0.37, 0.41, 0.42, 0.47, and 0.66 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 were (n=10): 0.12, 0.13, 0.19, 0.23, 0.38, 0.38, 0.42, 0.49, 0.54, and 0.71 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 1.0 mg/kg and an STMR of 0.38 mg/kg parent equivalents for flower head brassicas.

Head Brassicas

Field trials conducted on head cabbage were performed in the USA and Canada and in the EU (Germany, Northern and Southern France, Italy and Spain). The trials performed in the EU did not match any GAP.

The critical GAP for head cabbages is the USA GAP for brassicas: 4×60 g ai/ha, max total rate of 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials with head cabbages from the USA and Canada (3×61–102 g ai/ha, RTI 6–8 days, PHI 1 day) differed from the critical GAP with regard to the number of applications and the application rate, but were comparable using the tool described earlier. Modelling with the calculated median $t_{1/2}$ of 1.8 days (n=5) for brassicas, show that the expected residues are similar (max -8% to +22 % deviation up to the 3×80 g ai/ha, comparing the 3x60, 3x80 and x3x100 g ai/ha/application patterns from the trials to the 4×60 g ai/ha/application GAP pattern). The Meeting concluded that the supervised residues trials up to 3×80 g ai/ha/application could be used for maximum residue estimation. Cyclaniliprole residues in head cabbages in ranked order were (n=8): < 0.01, < 0.01, 0.014, 0.027, 0.082, 0.15, 0.32, and 0.39 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in head cabbages were (n=8): < 0.01, < 0.01, 0.025, 0.038, 0.094, 0.17, 0.34, and 0.42 mg/kg parent equivalents.

The Meeting estimated a maximum residue level for head cabbages of 0.7 mg/kg and an STMR of 0.066 mg/kg parent equivalents.

Residue trials on Brussels sprouts were performed in Europe (Germany, the Netherlands, United Kingdom, France, Italy, and Greece). The trials performed in the EU did not match any GAP.

Fruiting vegetables, Cucurbits

Cucumber and summer squash

Residue trials were conducted on cucumbers and summer squash in the USA and Canada.

The critical GAP for fruiting vegetables, cucurbits is the GAP from the USA for "cucurbit vegetables"; 4×60 g ai/ha, max 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials from the USA and Canada with cucumbers (3×76–84 g ai/ha, RTI 6–8 days, 1-day PHI) and summer squash (3×77–83, interval 6–8 days, PHI 1 day) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval, but were comparable using the tool described earlier. Modelling with the calculated median $t_{1/2}$ of 2.4 days (n=3) for cucurbits, show that the expected residues are similar (max +18%). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in cucumbers in ranked order were (n=9): < 0.01, < 0.01, 0.011, 0.013, 0.014, 0.018, 0.019, 0.024, and 0.025 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in cucumber were (n=9): < 0.01, < 0.01, 0.022, 0.024, 0.025, 0.029, 0.030, 0.035, and 0.036 mg/kg parent equivalents.

For estimation of the maximum residue level the ranked order of cyclaniliprole residues in summer squash were (n=9): < 0.01, < 0.01, 0.014, 0.016, 0.026, 0.028, 0.028, 0.033, and 0.046 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in summer squash were (n=9): < 0.01, < 0.01, 0.025, 0.027, 0.037, 0.039, 0.040, 0.043 and 0.057 mg/kg parent equivalents.

Since the datasets of cucumber and summer squash are similar, the Meeting decided to combine the two datasets of cucumber and summer squash.

For estimation of the maximum residue level the ranked order of the combined cyclaniliprole residues in cucumber and summer squash were (n=18): < 0.01, < 0.01, < 0.01, < 0.01, 0.011, 0.013, 0.014, 0.014, 0.016, 0.018, 0.019, 0.024, 0.025, 0.026, 0.028, 0.029, 0.033, and 0.046 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in cucumber and summer squash were (n=18): < 0.01, < 0.01, < 0.01, < 0.01, 0.022, 0.024, 0.025, 0.025, 0.027, 0.029, 0.030, 0.035, 0.036, 0.037, 0.039, 0.040, 0.043, and 0.057 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.06 mg/kg and an STMR of 0.028 mg/kg parent equivalents for the subgroup of fruiting vegetables, cucurbits – cucumbers and summer squash.

Melons, pumpkins and winter squashes

Residue trials were conducted on melons in the USA and Canada.

The critical GAP for melons is the GAP from the USA for "cucurbit vegetables"; 4×60 g ai/ha, maximum 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials from the USA and Canada with melons (3×76–85, 6–8 day RTI, 1-day PHI) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ (n=3) of 2.4 days for cucurbits, show that the expected residues are similar (max +18 % deviation). The Meeting concluded that the supervised residue trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in melons in ranked order were (n=10): 0.014, 0.017, 0.023, 0.039, 0.040, 0.042, 0.044, 0.051, 0.071, and 0.087 mg/kg.

In the absence on data on melons without peel residue levels used for estimation of the STMR and HR for melons are based on whole fruit. For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in melon were (n=10): 0.024, 0.028, 0.033, 0.050, 0.055, 0.055, 0.058, 0.063, 0.081, and 0.099 mg/kg parent equivalents for whole fruit.

The Meeting estimated a maximum residue level of 0.15 mg/kg and an STMR of 0.055 mg/kg parent equivalents for the subgroup of fruiting vegetables, cucurbits – melons, pumpkins and winter squash.

Fruiting vegetables, other than Cucurbits

Indoor field trials involving application of cyclaniliprole on tomato and sweet pepper were performed in the EU (2×ca. 40 g ai/ha, interval 10–12 days, PHI 1–7 days). The indoor field trials did not match any GAP and were not further considered.

Tomatoes (outdoor)

Field trials involving outdoor applications of cyclaniliprole on tomatoes were performed in the EU, USA and Canada, and Japan. Trials performed in the EU (2×ca. 40 g ai/ha, 10–12 day RTI, 1–7 days PHI) and trials performed in Japan (2×111–141 g ai/ha, 7-day RTI, 1–21 day PHI) did not match any GAP.

The critical GAP for tomatoes is the USA GAP for "fruiting vegetables"; 4×60 g ai/ha, max 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials with tomatoes, including cherry tomatoes, from the USA and Canada (3×60–97 g ai/ha, 6–8 day RTI, 1-day PHI) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ of 12 days (n=12) for tomatoes, show that the expected residues are similar (-23% to + 3% deviation of GAP, comparing both the 3×60 and 3×80 g ai/ha/application patterns from the trial to the 4×60 g ai/ha/application GAP pattern). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in tomato in ranked order were (n=22): 0.011, 0.013, 0.016, 0.018, 0.019, 0.024, 0.024, 0.025, 0.026, 0.027, 0.029, 0.030, 0.032, 0.032, 0.034, 0.037, 0.038, 0.040, 0.042, 0.043, 0.070, and 0.076 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 were (n=22): 0.022, 0.024, 0.029, 0.029, 0.030, 0.035, 0.035, 0.036, 0.036, 0.037, 0.040, 0.041, 0.042, 0.043, 0.045, 0.048, 0.049, 0.051, 0.053, 0.053, 0.080 and 0.10 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.041 mg/kg parent equivalents for cherry tomatoes and tomatoes.

The Meeting estimated a median residue of 0.0295 mg/kg (parent only) for animal dietary intake calculations.

The USA critical GAP for fruiting vegetables, other than cucurbits also covers egg plants. The Meeting decided the data could be used to extrapolate the maximum residue level and the STMR of tomato to the subgroup of eggplants.

Chili pepper, indoor

The critical GAP for chili pepper in the Republic of Korea is for 2 applications at 45 g ai/ha, 10 day RTI, 3-day PHI.

One indoor field trial with cyclaniliprole on chili peppers (2×45 g ai/ha, 7-day RTI, 3-day PHI) performed in the Republic of Korea matched this GAP within 25%. Cyclaniliprole residues in chili peppers are (n=1): 0.040 mg/kg.

The Meeting considered the data insufficient for estimating a maximum residue level for chili pepper based on these data.

Peppers (field)

Field trials involving outdoor applications of cyclaniliprole on sweet peppers were performed in the EU (n=16) and USA and Canada (n=12). The trials performed in the EU (2x ca 40 g ai/ha, 10–12 day RTI, 1–7 day PHI) did not match any GAP.

The critical GAP for sweet peppers is the USA GAP for "fruiting vegetables"; 4×60 g ai/ha, max 240 g ai/ha/season, 5-day RTI, 1-day PHI.

Field trials with bell (9 field trials) and non-bell (3 field trials) peppers from the USA and Canada (3×60–82 g ai/ha, 6–8 day RTI, 1-day PHI) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ of 6.0 days (n=10) for peppers, show that the expected residues are similar (-20% to +7% deviation of GAP, comparing both the 3×60 and 3×80 g ai/ha/application patterns to the GAP pattern of 4×60 g ai/ha/application). The Meeting concluded that the supervised residues trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in peppers and non-bell peppers in ranked order were (n=12): 0.014, 0.019, 0.025, 0.041, 0.046, 0.048, 0.057, 0.068, 0.072, 0.077, 0.098, and 0.10 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 in sweet bell and non-bell peppers were (n=12): 0.025, 0.029, 0.035, 0.051[NB], 0.056, 0.059, 0.067[NB], 0.083, 0.094[NB], 0.096, 0.11, and 0.12 mg/kg parent equivalents.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.063 mg/kg parent equivalents for the subgroup peppers (excluding martynia, okra and roselle).

Chili peppers, dried

Based on the estimated maximum residue level of 0.2 mg/kg for the subgroup peppers (excluding Martynia, okra and Roselle) and applying a default processing factor of 10, the Meeting estimated a maximum residue level of 2 mg/kg for peppers, chili, dried, together with an STMR of 0.63 mg/kg parent equivalents (0.063 mg/kg×10).

Leafy vegetables

Leafy greens

Residue trials were conducted on head and leafy lettuce, spinach in the USA and Canada.

The critical GAP for lettuce, head, lettuce, leafy and spinach is the USA GAP for leafy vegetables (non-brassica's) of 4×60 g ai/ha, max 240 g ai/ha/season, 5 day-RTI, 1-day PHI. Field trials with lettuce, head (3×61–86 g ai/ha, 6–8 day RTI, 1-day PHI), lettuce, leafy (3×61–100 g ai/ha, 6–9 day RTI, 1-day PHI), and spinach (3×60–81 g ai/ha, 6–8 day RTI, 1-day PHI) from USA and Canada differed from the critical with regard to the number of applications, and/or the application rate and the retreatment interval. The available decline data were insufficient to estimate a median half-life and to use the tool described earlier to conclude whether the residue trials support the critical GAP (i.e. residues ± 25%).

The Meeting did not estimate a maximum residue level and STMR for leafy vegetables, subgroup leafy greens.

Brassica leafy vegetables

Field trials from Japan on Chinese cabbage (2×50–73, 6–8 day RTI, 1-day PHI) could not be matched to the Korean GAP of 2×45 g ai/ha, 10-day RTI, 14-day PHI. Field trials involving kale were

conducted in the EU (2×25 g ai/ha, RTI 13–14 days, PHI 13/14 days). The trials could not be matched to any GAP.

The critical GAPs for Chinese cabbage and for kale fall within the USA GAP for brassicas (cole) leafy vegetables: 4×60 ga ai/ha, max 240 g ai/ha/season, 5-day RTI, 1-day PHI. No field trials on Chinese cabbage or kale according to this USA GAP were performed.

The critical GAP for mustard greens is the USA GAP for leafy vegetables (non-brassica's): 4×60 g ai/ha, max 240 g ai/ha/season, 5 day-RTI, 1-day PHI.

Field trials with mustard greens from the USA and Canada (3×60–81 g ai/ha, 6–8 day RTI, 1-day PHI) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval. Comparison of application scenarios of the trials with the critical GAP, using the tool described earlier and applying a calculated median $t_{1/2}$ of 2.5 days (n=7) for leafy vegetables, show that the expected residues are similar (-12% to +17% deviation of GAP, comparing both the 3×60 and 3×80 g ai/ha/application patterns to the 4×60 g ai/ha/application of the critical GAP). The Meeting concluded that the supervised residue trials could be used for estimation of the maximum residue level.

Cyclaniliprole residues in mustard greens were (n=5): 1.4, 3.0, 4.0, 4.1, and 5.9 mg/kg.

For the estimation of the dietary intake the ranked order of cyclaniliprole residues including metabolite NK-1375 were (n=5): 1.5, 3.5, 4.3, 4.4, and 6.2 mg/kg equivalents.

The Meeting estimated a maximum residue level of 15 mg/kg and an STMR of 4.3 mg/kg equivalents for mustard greens. The Meeting estimated a median and highest residue value of 4.0 and 6.5 mg cyclaniliprole/kg (highest individual value), respectively for mustard greens for livestock dietary burden calculations. The Meeting decided to extrapolate the maximum residue levels, STMR, median and highest residue value to the whole subgroup of brassica leafy vegetables.

Legume vegetables (soya bean, green)

Field trials (three trials) involving soya bean, immature (with pods) were conducted in Japan (2×38–50 g ai/ha, RTI 7 days, PHI 1–21 days). Without a supportive GAP the trials were not further considered.

Pulses (soya bean, dry)

Field trials involving soya bean, dried (six trials) were conducted in Japan (2×38–49 g ai/ha, RTI 6–8 days, PHI 1–21 days). Without a supportive GAP the trials were not further considered.

Tree nuts

Field trials involving almonds and pecans were performed in the USA.

The critical GAP for tree nuts is the USA GAP of 1×60 + 3×80 g ai/ha, to reach the max of 300 g ai/ha/season, 10 day-RTI, 30-day PHI.

Field trials with almonds and pecans from the USA and Canada (3×99–105 g ai/ha, 13–15 day RTI, 30-day PHI) differed from the critical GAP with regard to the number of applications, and/or the application rate and the retreatment interval. The available decline data were insufficient to estimate a median half-live and to use the tool described earlier to conclude whether the residue trials support the critical GAP (i.e. residues ± 25%).

The Meeting did not estimate a maximum residue level and STMR for almonds and pecans.

Tea

Field trials involving tea (six trials) were conducted in Japan (1×171–199 g ai/ha, PHI 3–21 days). Without a supportive GAP the trials were not further considered.

Animal feeds

Almond hulls

Field trials involving almond hulls were performed in the USA.

The critical GAP for tree nuts in the USA and Canada is for 3×80 and 1×60 g ai/ha, to reach the seasonal maximum rate of 300 g ai/ha at 10 day intervals and a PHI of 30 days.

Field trials with almonds and pecans from USA and Canada (3×99–105 g ai/ha, 13–15 day RTI, 30-day PHI) differed from the critical with regard to the number of applications, and/or the application rate and the retreatment interval. The available decline data were insufficient to estimate a median half-live and subsequently use the tool described earlier to conclude whether the residue trials support the critical GAP (i.e. residues ± 25%).

The Meeting did not estimate a median and highest residue for almond hulls.

Rotational crops

Based on results of the confined and field rotational crop studies the Meeting concluded that residues are not expected in leafy vegetables, root and tuber vegetables, cereal grain and leaves of root and tuber vegetables. No data are available for oilseeds and pulses.

The Meeting did not estimate maximum residue levels for rotational crops for human consumption.

Wheat (forage and straw)

Though the results of the confined and field rotational crops studies indicate that no residues occur in rotational crops for human consumption, the Meeting concluded that residues can be expected in wheat forage and wheat straw and decided to estimate median and highest residues for wheat forage and wheat straw.

Residue levels in wheat forage were highest at a plant back interval of 120 days. Furthermore, the USA label includes a plant back restriction of 30 days, indicating the 120 days represents the most realistic situation. Concentrations of cyclaniliprole in ranked order were (n=6): < 0.01 (4×), 0.019, and 0.026 mg/kg as received. For dietary burden calculation, NK-1375 does not need to be taken into account.

The Meeting estimated a median and highest residue level of 0.01 and 0.026 mg/kg on an as received basis for wheat forage.

Residue levels in wheat straw were highest at a plant back interval of 120 days (n=6): 0.011, 0.020, 0.024, 0.071, 0.12, 0.18 mg/kg cyclaniliprole as received.

The Meeting estimated a maximum residue level for wheat straw and fodder of 0.45 mg/kg (dw) based on a dry matter content of 88%. The Meeting estimated a median and highest residue of 0.0475 and 0.18 mg/kg (parent only) on an as received basis. Conversion to dry matter based on the dry matter content of 88% results in a median and highest residue level of 0.054 (dw) and 0.20 mg/kg (dw) (parent only), respectively for wheat straw and fodder.

These values for wheat forage and wheat straw and fodder were extrapolated to all other grain forages, straws and fodders in the group cereal grains.

Fate of residues during processing

High temperature hydrolysis

Degradation of [^{14}C] cyclaniliprole was studied under hydrolytical conditions at high temperatures in sterile aqueous buffers at pH4, 5 and 6 for periods of up to 60 minutes. Data showed that cyclaniliprole is not degraded during simulation of pasteurisation (pH 4, 90°C, for 20 minutes). Data do show, however, that cyclaniliprole partly degrades into BPQO (11 %TAR) and YT-1327 (11%

TAR) under baking, boiling and brewing conditions (pH 5, 100°C, for 60 minutes). During sterilisation conditions (pH 6, 120 °C, for 20 minutes) BCPBA (23% TAR), BPQO (16% TAR) and YT-1237 (44% TAR) is formed. Though the hydrolysis study indicates that degradation products can be formed under specific processing conditions, these findings were not supported in the processing studies, except for tomato puree, where residues were found at concentrations up to 3% of the parent compound. The processing study was performed at an exaggerated dose level. The breakdown products are not expected to be detectable under normal use conditions.

Residues in processed commodities

Processing studies were undertaken for apples, peaches, tomatoes, plums, grapes, and tea. Two types of processing studies were performed; processing studies with spiked samples and with incurred residues. The spiked samples were not considered relevant for derivation of processing factors. The estimated processing factors derived from processing studies with incurred residues in combination with the estimated maximum residue levels and STMRs from supervised trials proposed STMR-Ps and median-P residues are summarised in the table below. MRLs in processed commodities are only proposed where they are higher than the MRL in the raw commodity. For estimation of the STMR-P the processing factors are based on parent + metabolite NK-1375. For MRL derivation and dietary burden calculation the processing factors are based on parent only (separate table).

Commodity	PF residue: parent + NK-1375	PF (median or best estimate)	STMR in RAC	STMR-P
Apples			0.073	
- juice, past.	0.13, < 0.33, < 0.5	< 0.33 (median, n=3)		0.024
Plums			0.067	
- dried prunes	3.7 [a]	3.7 (n=1)		0.25
Grapes			0.15	
- must	0.63 , 0.63, 0.71, 0.86	0.67 (median n=4)		0.10
- juice after pasteurisation	0.20, 0.12, 0.33, 0.38, 0.50, 0.71	0.36 (median, n=6)		0.54
- stored wine	0.14, 0.20 , < 0.33, 0.38, 0.040, 0.50	0.355 (median, n=6)		0.053
- raisins	< 0.14, 0.14, < 0.020, 0.50, 0.75, 0.75	[a]		[a]
Tomatoes			0.041	
- canned	< 0.14, < 0.17, < 0.2, < 0.5, < 0.5	0.2 (median, n=5)		0.008
- paste [b]	0.49, 0.50, 0.67, 1.57, 1.8, 2.5	1.12 (median, n=6)		0.046
- juice, pasteurised	< 0.5, 0.17, 0.8, 1.14, 1.5	0.8 (median, n=6)		0.033
- dried tomatoes	3, 3.2, 3.3, 5, 6	3.3 (median, n=5)		0.14

PF based on total cyclaniliprole; STMR-P is used for the long-term and short-term dietary exposure estimates and are based on the residue definition for dietary risk assessment.

[a] PF for raisins was not considered suitable without a plausible explanation why dilution instead of concentration occurred

[b] Values include PFs derived in European studies defining the processed product as puree. Since evaporation was used to concentrate the volume about 3 times, it was scaled under paste.

Commodity	PF residue: parent only	PF (median/best estimate)	Median residue in RAC	Median
Apple, wet pomace	3. 2	3.2 (n=1)	0.060	0.19
Grape, wet pomace	1.0, 1.17, 1.20, 1.64, 1.71, 3.0, 4.67, 8.0	1.7 (median n=8)	0.14	0.24
Grape, dry pomace	0.83, 3.07, 3.07, 2.83	3.1 (median, n=4)	0.14	0.43
Plums, dried	3.7	3.7 (n=1)	-	-
Tomato, dried	3.33, 3.75, 3.8, 4, 5.5	3.8 (median, n=5)	-	-

Tomato, wet pomace	0.67	0.67 (n=1)	0.0295	0.020
Tomato, dry pomace	22	22 (n=1)	0.0295	0.65

Median-P residues based on total cyclaniliprole, are used for dietary burden calculation

Total cyclaniliprole was shown to concentrate in prunes and dried tomatoes as well as in wet and dry pomace of apples and grapes. Despite the drying process, no concentration was observed in raisins. No clarification was provided. Since no breakdown of the compound is expected and drying of plums do lead to the expected increase in residue concentrations, the Meeting decided not to estimate an MRL or STMR for raisins.

The Meeting estimated a maximum residue level of 0.8 mg/kg (0.2 mg/kg×3.7=0.74 mg/kg) for prunes. The Meeting estimated a maximum residue level of 0.4 mg/kg (0.1 mg/kg×3.8 = 0.38 mg/kg) for dried tomatoes, using the processing factors based on parent only.

Animal feedstuffs

Livestock dietary burden

The Meeting estimated the dietary burden of cyclaniliprole in livestock on the basis of the diets (US/CAN, EU, Australia and Japan) listed in the OECD Feed Table 2013. Calculation from highest residue and median values (some bulk commodities) provide the levels in feed suitable for estimating maximum and highest residue levels while calculation from median values for feed is suitable for estimating STMR values for animal commodities

Some processed and forage commodities do not appear in the Recommendations Table (because no maximum residue level is needed), but they are used in estimating livestock dietary burdens. Those commodities are included in the list below. Almond hulls (AB0660) and soya beans were not included in the dietary burden calculation since they could not be matched to a GAP. In the rotational crops studies residues of cyclaniliprole were detected in wheat straw and forage. For the dietary burden calculation, these levels were widely extrapolated to the straw/hay (dry feed commodities) and forage (wet feed commodities) of the whole group of cereals grain crops. The input was based on the intake of parent only.

Codex classification	Commodity	Median residue (-P) (mg/kg) [a]	Highest residue (-P) (mg/kg) [a]
AB 0226	Apple pomace, wet (median 0.060 mg/kg ×PF 3.2)	0.19	-
AB 0269	Grape pomace, wet (median 0.14 mg/kg ×PF 1.7)	0.24	-
AV 0480	Kale forage (leaves) – based on the median and highest residue for brassica leafy vegetables (based on mustard greens dataset)	4.0	6.5
AB – no code	Tomato pomace, wet (median of 0.0295×PF 0.67 (n=1)) [a b]	0.020	-
AF – no code	Barley forage (30% DM)	0.01	0.026
AS 0640	Barley, hay (88% DM)	0.0475	0.18
AS 0641	Barley, straw (89% DM)	0.0475	0.18
AF/AS – no code	Corn, field, forage/silage (40% DM)	0.01	0.026
AS 0645	Corn, field, stover (83% DM)	0.0475	0.18
AF – no code	Corn, pop, stover (83% DM)	0.0475	0.18
AF – no code	Corn, sweet, forage (48% DM)	0.01	0.026
AF – no code	Maize (corn, sweet, stover) (83% DM)	0.0475	0.18
AF – no code	Millet, forage (30% DM)	0.01	0.026
AF – no code	Millet, hay (85% DM)	0.0475	0.18
AF 0646	Millet, straw (90% DM)	0.0475	0.18
AF 0647	Oat, forage (30% DM)	0.01	0.026
AS 0647	Oat, hay (90% DM)	0.0475	0.18
AF – no code	Oat, straw (90% DM)	0.0475	0.18
AS0469	Rice, straw (90% DM)	0.0475	0.18
AF0650	Rye, forage (30% DM)	0.01	0.026
AS0650	Rye, straw (88% DM)	0.0475	0.18
AF0651	Sorghum, grain, forage (35% DM)	0.01	0.026

AS – no code	Sorghum, grain, stover (88% DM)	0.0475	0.18
AF – no code	Triticale, forage (30% DM)	0.01	0.026
AF – no code	Triticale, hay (88% DM)	0.0475	0.18
AF – no code	Triticale, straw (90% DM)	0.0475	0.18
AF 0654	Wheat forage (25% DM)	0.01	0.026
AS 0654	Wheat, hay (88% DM)	0.0475	0.18
AS 0654	Wheat, straw (88% DM	0.0475	0.18

[a] levels for cereal straw, hay, and forage are presented on as received basis.

[b] Using the STMR-P of 0.76 mg/kg for tomato, dry pomace and assuming 80% for the dry matter content does not lead to a different outcome of the dietary burden calculation.

The dietary burden calculation of cyclaniliprole for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the livestock diets from US/CAN, EU, Australia and Japan in the OECD Feed Table 2013.

		Livestock dietary burden for cyclaniliprole (based on cyclaniliprole parent only) ppm of dry matter diet			
		USA/CAN	EU	Australia	Japan
Max	beef cattle	0.033	8.8	0.49	-
	dairy cattle	0.12	8.8	18	0.043
	poultry – broiler	-	-	-	-
	poultry – layer	-	0.015	-	-
Mean	beef cattle	0.0086	5.9	0.37	-
	dairy cattle	0.066	5.8	11	0.015
	poultry – broiler	-	-	-	-
	poultry – layer	-	0.05	-	-

Based on the calculations in the above table the Australian diets resulted in the highest maximum or mean beef or dairy cattle dietary burdens and would normally be used for maximum residue level estimates for mammalian meat and milk. The intake is driven by intake via kale (brassica leafy vegetables). No use on kale (or any other leafy vegetables) is included in the Australian registration application (under evaluation). Furthermore, the anticipated Australian orchard uses preclude rotational crops. For dietary burden calculation of the Australian diets only apple pomace was included. The European dietary burden was set at zero intake, because no uses in Europe are anticipated (active substance was withdrawn). As such no dietary burden for poultry is estimated for any diet, The remaining dietary burden is shown in the table below.

		Livestock dietary burden for cyclaniliprole (based on parent only), ppm of dry matter diet			
		USA/CAN	EU	Australia	Japan
Max	beef cattle	0.033	-	0.095	-
	dairy cattle	0.12 [a]	-	0.048	0.043
	poultry – broiler	-	-	-	-
	poultry – layer	-	-	-	-
Mean	beef cattle	0.009	-	0.095[c]	-
	dairy cattle	0.066 [b]	-	0.048	0.015
	poultry – broiler	-	-	-	-
	poultry – layer	-	-	-	-

[a] Highest maximum beef or dairy cattle dietary burden suitable for maximum residue level estimates for mammalian meat and milk.

[b] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian milk.

[c] Highest mean beef cattle dietary burden suitable for STMR estimates for mammalian meat

Residues in animal commodities

The Meeting received a lactating dairy cow feeding study, which provided information on likely residue in animal tissues and milk from cyclaniliprole residues in animal diets.

Fifteen lactating Friesian cows were administered cyclaniliprole orally twice daily via capsules for 28–31 consecutive days at a feeding level of 0, 1.2, 3.5 and 11.6 ppm, corresponding with actual mean dose levels of 0, 4.9, 14 and 49 mg/animal/day (equivalent with 0, 0.0075, 0.021, and 0.075 mg/kg bw/day, respectively).

Cyclaniliprole-derived residues above the limit of quantitation were found only incidentally in whole milk samples. Residues were generally below the limit of quantitation (< 0.01 mg/kg) throughout the treatment and depuration periods. No residues of cyclaniliprole were detected above the limit of quantitation (0.01 mg/kg) in any samples taken on Days 21 and 28 in skimmed milk. Dose-related quantifiable residues were found in cream in samples taken on Days 21 and 28 and comprised of parent compound only. The mean values were 0.02 mg/kg and 0.078 mg/kg in the mid and highest dose group while the was 0.011 mg/kg at the lowest feeding level (1.2 ppm).

Concentrations of cyclaniliprole at the lowest feeding level of 1.2 ppm were either not detectable (muscle) or < 0.01 mg/kg, except for kidney, where a concentration of 0.011 mg/kg cyclaniliprole was found in one of the three animals. Concentrations of cyclaniliprole at the highest feeding level of 11.6 ppm were highest in liver (max 0.14 mg/kg) followed by fat (0.12 mg/kg), kidney (0.11 mg/kg), and muscle (0.032 mg/kg). Residues of NK-1375, NSY-27, and YT 1284 were either not detected or below the LOQ of < 0.01 mg/kg in all tissues and milk. Metabolite NSY-28 was found only in liver (11.6 ppm dose level) at 0.014–0.032 mg/kg and in kidney and subcutaneous fat at 0.014 mg/kg of one cow.

The results of the depuration group indicate that the total cyclaniliprole residues accumulate and slowly decline after the administration of the cyclaniliprole has stopped.

No laying hen study was submitted.

Animal commodities maximum residue level concentrations

Mammals

Dietary burden calculations demonstrate that the highest (0.12 ppm) and mean (0.066 ppm) dietary intake from beef and dairy cows is lower than the lowest intake levels (1.2 ppm) used in the dietary feeding study. Mean and highest residue levels observed in whole milk, muscle, liver and fat are either not detectable or below the LOQ of 0.01 mg/kg. At the 1.2 ppm feeding level of the feeding study some residues were observed in milk fat and kidney. These tissues were therefore considered for maximum residue and STMR calculation by extrapolation. The high and mean residues in the tissues and milk were calculated by extrapolating the maximum dietary burden (0.12 ppm) or median dietary burden (0.066 ppm) from the relevant feeding level (1.2 ppm cyclaniliprole) from the dairy cow feeding study, using the highest or median tissue and milk (fat) concentrations.

	Feeding level (ppm) for milk residues	Residues (mg/kg) in milk cream [a]	Feed level (ppm) for tissue residues	Residues (mg/kg) in			
				Muscle	Liver	Kidney	Fat
MRL beef of dairy cattle							
Feeding study [b]	1.2	0.015	1.2	ND	< 0.01	0.011	< 0.01
Dietary burden and high residue estimate	0.12	0.0019	0.12	< 0.01	< 0.01	0.0011	< 0.01
STMR beef or dairy cattle							
Feeding study [c]	1.2	< 0.01	1.2	ND	< 0.01	0.010	< 0.01
Dietary burden and median	0.066	0.0006	0.095	0	0.0008	0.0008	0,0008

residue estimate							

ND = not detectable

[a] Residues were detected in milk cream only. No residues were found in skimmed milk. Based on the default fat content of 4%, the STMR for mammalian milk was estimated at 0.000024 mg/kg (0.04 × 0.0006 mg/kg)

[b] highest residue for tissues and mean residues for milk

[c] mean residues for tissues and mean residues for milk

The Meeting estimated maximum residue levels of 0.01* mg/kg for mammalian milk, meat (based on fat), liver, kidney and fat. Though cyclaniliprole is fat soluble, residues in milk cream in the dietary feeding study are at max 0.015 mg/kg at the 1.2 ppm feeding level, indicating that a maximum residue level for milk fat of 0.01* mg/kg is sufficient as well. The Meeting estimate an STMRs of 0.0006 mg/kg for mammalian milk fat and 0.0008 mg/kg for liver, kidney and fat. The STMR for mammalian muscle was set at 0 mg/kg. Based on the default fat content of 4%, the STMR for mammalian milk was estimated at 0.000024 mg/kg (0.04 × 0.0006 mg/kg).

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

The Meeting recommended the following residue definitions for cyclaniliprole.

For plants and animals: Definition of the residue for compliance with the MRL for plant and animal commodities: *cyclaniliprole.*

Definition of the residue for dietary risk assessment for plant commodities: *cyclaniliprole + 3-bromo-2-((2-bromo-4H- pyrazolo[1,5-d]pyrido[3,2-b]-[1,4]oxazin-4-ylidene)amino)-5-chloro-N-(1-cyclopropylethyl)benzamide (NK-1375), expressed as cyclaniliprole equivalents.*

The molecular weight conversion factor to express NK-1375 in cyclaniliprole equivalents = 1.064.

Definition of the residue for dietary risk assessment for animal commodities: *cyclaniliprole*

The Meeting considers the residue to be fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The current Meeting established an ADI of 0–0.04 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for cyclaniliprole were calculated for the 17 GEMS/Food cluster diets using STMRs estimated by the current Meeting for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3 to the 2017 Report.

The calculated IEDIs were 0–7% of the maximum ADI of 0.04 mg/kg bw.

The Meeting concluded that the long-term dietary exposure of residues to cyclaniliprole from uses considered by the current Meeting is unlikely to present a public health concern.

Short-term dietary exposure

The 2017 Meeting determined that establishment of an acute reference dose is unnecessary for cyclaniliprole. The Meeting therefore concluded that the short-term dietary exposure to residues of cyclaniliprole, resulting from uses that have been considered by the JMPR, is unlikely to present a public health concern.