Fenpicoxamid (305)

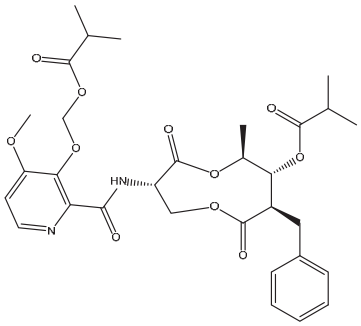
The first draft was prepared by Professor Mi-Gyung Lee, Andong National University, Republic of Korea

EXPLANATION

Fenpicoxamid is a picolinamide fungicide for the control of foliar diseases. It acts as a contact and residual protectant with limited systemic activity but some translaminar activity. The representative uses in Europe were for cereals for control of *Septoria tritici*. Fenpicoxamid is also registered for use on banana for the control of Black Sigatoka (*Mycosphaerella fijiensis*).

Fenpicoxamid was scheduled at the Forty-ninth Session of the CCPR for the evaluation of toxicology and residues for the first time by the 2018 JMPR. The Meeting received information from the manufacturer on metabolism (tomato, cabbage, wheat, lactating goat, laying hen), rotational crops (confined study), methods of residue analysis, storage stability (crop), environmental fate, and supervised trials and GAP information (banana).

IDENTITY

ISO common name:	Fenpicoxamid
Chemical name	
IUPAC:	(*3S,6S,7R,8R*)-8-benzyl-3-{3-[(isobutyryloxy)methoxy]-4-methoxypyridine-2-carboxamido}-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl isobutyrate
CAS:	[[4-methoxy-2- [[[(*3S,7R,8R,9S*)-9-methyl-8-(2-methyl-1- oxopropoxy)-2,6-dioxo-7-(phenylmethyl)-1,5- dioxonan-3-yl]amino]carbonyl]-3- pyridinyl]oxy]methyl 2-methylpropanoate
CAS Registry No.:	517875-34-2
CIPAC No.	991
Molecular formula:	$C_{31}H_{38}N_2O_{11}$
Structural formula:	
Molecular weight:	614.7 g/mol

PHYSICAL AND CHEMICAL PROPERTIES

Pure active ingredient

Chemical/physical property	Results	Reference
Appearance	White powder at 22°C	Moe, 2012, FAPC-G-12-29
Vapour pressure	2.0×10^{-7} Pa (1.5×10^{-9} mmHg) at 25 °C 1.2×10^{-7} Pa (8.9×10^{-10} mmHg) at 20 °C	Comb, 2012, NAFST-12-114
Melting point	158.3°C	Moe, 2012, FAPC-G-12-29
Octanol-water partition coefficient	At 20 °C by shake flask method: Log Kow, 4.2 ± 0.1 at pH 5 buffer, 4.4 ± 0.2 at pH 7 buffer and 4.3 ± 0.2 at pH 9 buffer.	Comb, 2012, NAFST-12-111
Solubility in water	At 20 °C, 0.031 mg/L in purified water, 0.031 mg/L at pH 5 buffer, 0.041 mg/L at pH 7 buffer and 0.029 mg/L at pH 9 buffer.	Comb, 2012, NAFST-12-110

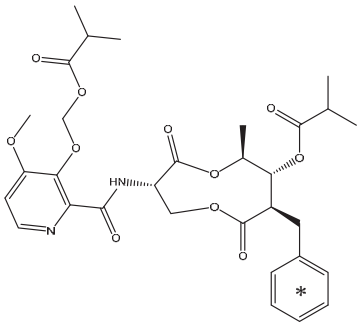
Chemical/physical property	Results	Reference
	Fenpicoxamid is not stable in water due to hydrolysis; therefore an accurate determination of solubility cannot be ascertained.	
Solubility in organic solvents (Conducted on technical grade fenpicoxamid, with a minimum purity of 85.4% w/w)	At 20 °C, 11 g/L methanol, >250 g/L acetone, 20 g/L xylene, >250 g/L 1,2-dichloromethane, 120 g/L ethyl acetate, 0.021 g/L n-heptane, and 0.14 g/L n-octanol. Fenpicoxamid is not stable in methanol.	Comb, 2012, NAFST-12-137
Relative density	1.21 at 20 °C	Comb, 2012, NAFST-12-113
Hydrolysis	Fenpicoxamid hydrolyses rapidly in water. DT_{50} = 7.1 days (pH 4, 25 °C) DT_{50} = 0.92 days (pH 7, 25 °C) DT_{50} = 0.024 days (pH 9, 25 °C)	Yoder and Jackson, 2013, report 120538
Aqueous photolysis	DT_{50} = 1.3 days (pH 7, 25 °C); DT_{50} (natural light, 40 °N) = 3.06 days	Blakeslee and Jackson, 2014, report 110422
Dissociation constant	pKa = 2.4 at 20 °C (Ka = 3.7×10^{-3})	Comb, 2012, NAFST-12-112
Thermal stability	Decomposition at 246.32 °C	Moe, 2012, FAPC-G-12-29

Formulations

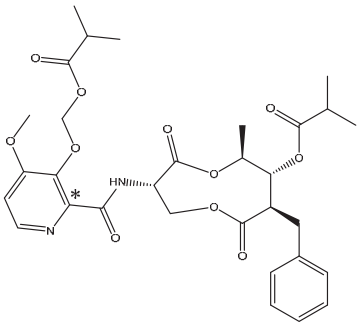
Specifications for fenpicoxamid have not been developed by the FAO. Fenpicoxamid (minimum purity, 750 g/kg) is formulated as GF-2925, a suspension concentrate (SC) containing 130 g ai/L.

METABOLISM AND ENVIRONMENTAL FATE

The fate and behaviour of fenpicoxamid in animals, plants and soils were investigated using fenpicoxamid labelled in the phenyl and pyridine rings.



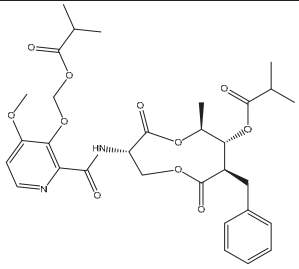
[Phenyl-UL-^{14}C]- fenpicoxamid

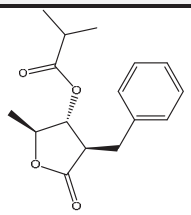
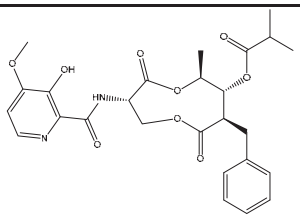
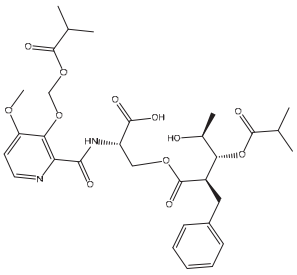
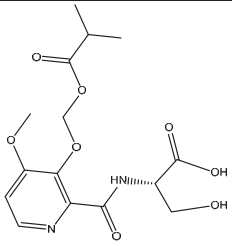
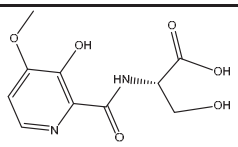
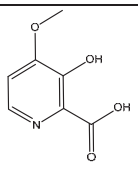


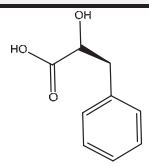
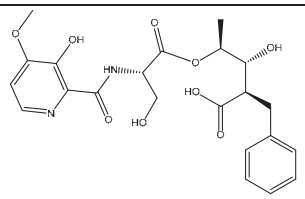
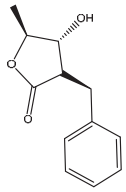
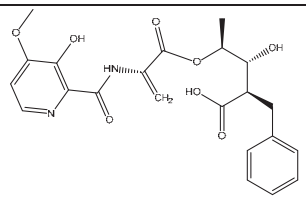
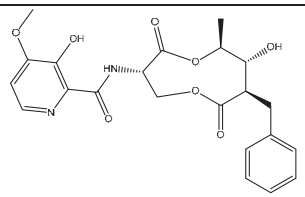
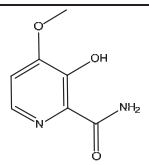
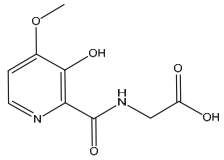
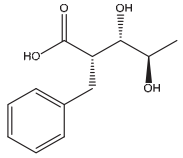
[Pyridine-2-^{14}C]- fenpicoxamid

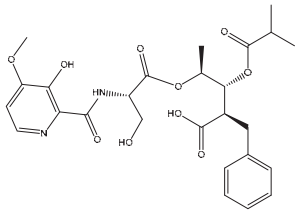
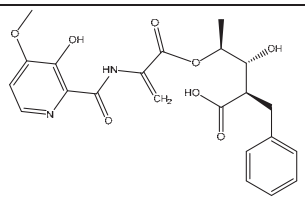
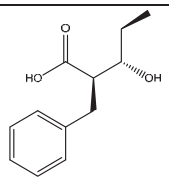
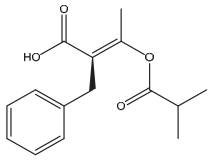
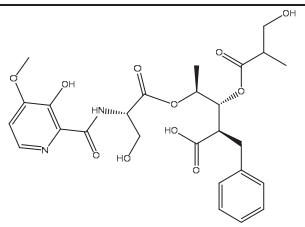
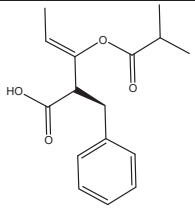
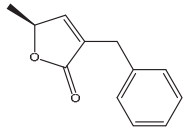
The chemical structures of the major degradation compounds arising from the metabolism of fenpicoxamid are presented in Table 1.

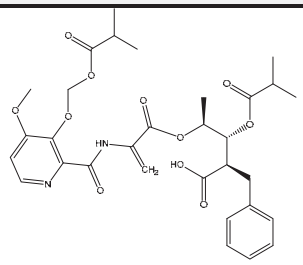
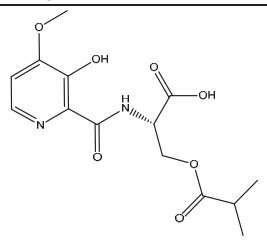
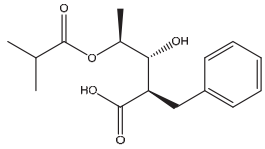
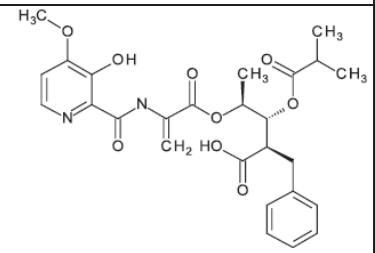
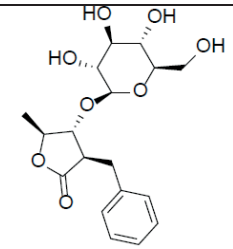
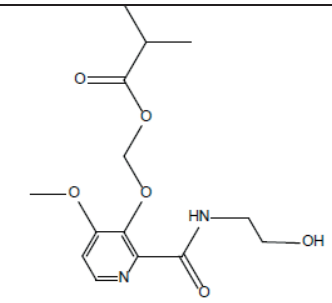
Table 1 Degradation compounds from metabolism of fenpicoxamid in plants, animals and the environment

Code	Chemical name	Chemical structure	Compound found in
Fenpicoxamid (XDE-777)	(*3S,6S,7R,8R*)-8-benzyl-3-{3-[(isobutyryloxy)methoxy]-4-methoxypyridine-2-carboxamido}-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl isobutyrate	 MW: 614.7	Tomato, cabbage, wheat (forage, hay, grain, straw), hen, goat, water (hydrolysis), rat, rotational crop (feed)

Code	Chemical name	Chemical structure	Compound found in
X12314005	(2S,3R,4R)-4-benzyl-2-methyl-5-oxotetrahydrofuran-3-yl 2-methylpropanoate	 MW: 276.3	Tomato, cabbage, wheat (forage, hay, straw), hen, goat, water (hydrolysis), rotational crop (feed), processing hydrolysis
X642188 (UK- 2A)	(3S,6S,7R,8R)-8-benzyl-3-{[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]amino}-6- methyl-4,9-dioxo-1,5-dioxonan-7-yl 2- methylpropanoate	 MW: 514.5	Tomato, cabbage, wheat (forage, hay, straw, grain), hen, goat, rat, rotational crop (food, feed), aerobic soil, soil phtolysis
Open-ring fenpicoxamid isomer (Unknown 1) (Met 632)	(2S)-3-[(2R,3R,4S)-2-benzyl-4-hydroxy-3- (2-methylpropanoyloxy)pentanoyl]oxy -2-[[4-methoxy-3-(2-methylpropanoyloxymethoxy)pyridine-2- carbonyl]amino] propanoic acid (or isomer) (proposed)	 or isomer (proposed) MW: 632.7	Tomato, cabbage, wheat (forage, hay, straw), hen, goat, water (hydrolysis)
X12335723	N-[(4-methoxy-3-{[(2-methylpropanoyl)oxy]methoxy}pyridin- 2-yl)carbonyl]-L-serine	 MW: 356.3	Wheat (straw), hen, goat, water (hydrolysis), , processing hydrolysis
X12264475	N-[(3-hydroxy-4-methoxypyridin-2-yl)carbonyl]serine	 MW: 256.1	Wheat (straw), hen, goat, water (hydrolysis), rotational crop (food, feed), aerobic soil, , processing hydrolysis
X696476	3-hydroxy-4-methoxypyridine-2-carboxylic acid	 MW: 169.1	Wheat (straw), hen, rotational crop (food, feed), aerobic soil

Code	Chemical name	Chemical structure	Compound found in
X129300	2-hydroxy-3-phenyl-propanoic acid	 MW: 166.2	Hen, goat
X12326349 (open-ring UK-2A diol)	2-benzyl-2,5-dideoxy-4-O-{N-[(3-hydroxy-4-methoxypyridin- 2-yl)carbonyl]-L-seryl}-L-arabinoic acid	 MW: 462.5	Hen, goat, rat
X11963422	(3R, 4R, 5S)-3-benzyl-4-hydroxy-3-methyldihydrofuran-2 (3H)-one	 MW: 206.2	Hen, goat, aerobic soil, rotational crop (feed), as glucose conjugate (X12526439), isomer of X11963422 in water (hydrolysis)
13495S-3S (isomer of X696872)	(2R,3R,4S)-2-benzyl-3-hydroxy-4-[2-[(3-hydroxy-4-methoxy-pyridine-2-carbonyl)amino]prop-2-enoyloxy]pentanoic acid	 MW: 444.4	Goat
X696872	N-[(3S, 7R, 8R, 9S)-7-benzyl-8-hydroxy-9-methyl-2,6-dioxo- 1,5-dioxonan-3-yl]-3-hydroxy- 4-methoxypyridine-2- carboxamide	 MW: 444.4	Hen, goat, rat, aerobic soil
X12313581	3-hydroxy-4-methoxypyridine-2-carboxamide	 MW: 168.2	Hen, aerobic soil
X763024	2-[(3-hydroxy-4-methoxy-pyridine-2-carbonyl)amino]acetic acid	 MW: 226.2	Hen, aerobic soil, rotational crop (food, feed)
X12399889	N,N-diethylethanaminium 2-benzyl-2,5- dideoxy-D-arabinonate	 MW: 224.3	Hen

Code	Chemical name	Chemical structure	Compound found in
X737057	2-benzyl-2,5-dideoxy-4-O-{N-[(3-hydroxy-4-methoxypyridin- 2-yl)carbonyl]-L-seryl}-3-O- (2-methylpropanoyl)-L-arabinoic acid	 MW: 532.6	Hen, goat, rat
X12402963	(2R,3R,4S)-2-benzyl-3-hydroxy-4-[2-[(3- hydroxy-4-methoxy-pyridine-2-carbonyl)amino]prop-2-enoyloxy]pentanoic acid	 MW: 444.4	Hen
PH-met 208	2-benzyl-3-hydroxypentanoic acid	 MW: 208.3	Hen
PH-met 262	(E)-2-benzyl-2-(isobutyryloxy)but-2-enoic acid	 or isomer MW: 262.3	Hen
Met 548	(2R,3R,4S)-2-benzyl-4-(((S)-3-hydroxy-2-(3- hydroxy-4-methoxypicolinamido)propanoyl)oxy)-3-((3- hydroxy-2-methylpropanoyl)oxy)pentanoic acid	 or isomer MW: 548.6	Hen, rat
pH-met 276 (open ring isomer of X12314005)	(Z)-2-benzyl-3-(2-methylpropanoyloxy)pent-3-enoic acid	 MW: 276.3	Hen, goat
X12019520	(5S)-3-benzyl-5-methylfuran-2(5H)- one	 MW: 188.2	Wheat (straw), hen, goat, water (hydrolysis), soil photolysis, processing hydrolysis

Code	Chemical name	Chemical structure	Compound found in
X12393285	2-Benzyl-2,5-dideoxy-4-O-(2-{[(4-methoxy-3-{[(2-methylpropanoyl)oxy]methoxy}pyridine-2-yl)carbonyl]amino}acryloyl)-3-O-(2- methylpropanoly)-L-arabinonic acid	 MW: 614.7	water (hydrolysis)
X12386481 (X481)	(S)-2-(3-hydroxy-4-methoxypicolinamido)-3-(isobutyryloxy)propanoic acid	 MW: 326.3	water (hydrolysis)
X12433979	(2R,3R,4S)-3-benzyl-3-hydroxy-4-(isobutyryloxy)pentanoic acid	 MW: 294.4	water (hydrolysis)
X12255349	2-benzyl-2,5-dideoxy-4-O-{2-[(3-hydroxy-4-methoxypyridine-2-yl)carbonyl)amino] acryloyl}-3-O-(2-methylpropanoyl)-L-arabinonic acid	 MW: 514.52	Soil photolysis
X12526439	(3R, 4R, 5S)-3-benzyl-4-hydroxy-3- HO methyldihydrofuran-2 (3H)-one	 MW: 368.38	Rotational crop (food, feed)
X12446477	({2-[(2-hydroxyethyl)carbarnoyl]-4-methoxypyridin-3-yl}oxy)methyl 2-methylpropanoate	 MW: 312.32	Aqueous photolysis

Plant metabolism

The Meeting received information on the fate of fenpicoxamid following foliar application on fruits (tomato), leafy vegetables (cabbage) and cereals (wheat).

Tomato

A study was conducted to investigate the metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in greenhouse grown tomato (*Lycopersicon esculentum* cv. Early Girl) following two foliar applications [Wu, 2013a, report 121003]. Application was made at *ca.* 30 days (BBCH 79) and 1 day (BBCH 88) before harvest, each at a rate of 300 g ai/ha (total seasonal rate of 600 g ai/ha) with ^{14}C-fenpicoxamid formulated as EC formulation. Mature fruit samples were collected 1, 7 and 14 days after the last application (DALA). Vine samples were sampled at 14 DALA only. Samples were weighed and stored frozen at below -10 °C. Total radioactive residue (TRR) was determined by combustion/LSC.

All fruit samples were rinsed in acetonitrile to remove surface residues within 34-46 days following collection. TRR in acetonitrile rinse and rinsed fruit were determined by LSC. The acetonitrile rinses were analysed by HPLC. Vine samples were not rinsed prior to combustion analysis.

Residues in rinsed fruit samples or vine samples were extracted twice with 0.1% H_3PO_4 in acetonitrile, followed by acetonitrile/water (1:1, v/v) both containing 0.1% H_3PO_4. Each extract was analysed by LSC. The pooled extracts were cleaned up by SPE and analysed by HPLC. Non-extracted residues remained in the post extraction solids (PES) after organic extraction were analysed by combustion. Characterisation of residue components by HPLC indicated that the same metabolites were observed in the mature tomato fruit as in the mature vines. Parent and three metabolic fractions (unknown 1 = open-ring fenpicoxamid isomer, X642188 and X12314005) were isolated from the PH-label treated tomato vine and identification was performed by LC-MS and/or LC-MS/MS. The results are shown in Tables 2-5.

TRR levels in mature tomato (1, 7 and 14 DALA) were in the range of 0.057-0.13 mg eq/kg. Radioactive residue levels in treated vines were significantly higher at *ca*. 3.0 mg eq/kg. Surface wash of fruit accounted for *ca*. 80-90% of the total radioactivity. No significant differences in TRR levels of fruit were appeared by the position of the ^{14}C label and over the time of fruit collection. Acetonitrile containing 0.1% H_3PO_4 extracted 88-94% (10-19% TRR) of the radioactivity from the all rinsed fruits.

The predominant radio-component in fruit was fenpicoxamid itself (89.5-96.8% TRR, 0.051-0.12 mg/kg). Surface wash contained only the parent compound (79.6-89.5% TRR). Metabolites X642188, an open-ring fenpicoxamid isomer and X12314005 were present each at very low levels of ≤0.7% TRR and at less than 0.001 mg/kg. There were additional 2 to 5 unidentified metabolites were found, each of them at concentrations < 0.001 mg eq/kg. In vines, parent was predominant residue and the metabolite patterns were similar to those of fruit.

A proposed metabolic pathway in tomato is shown in Figure 1. Fenpicoxamid is not significantly metabolised in tomatoes. The majority of the radioactive residue in mature tomato plants treated with foliar applications of fenpicoxamid is the unchanged parent. The metabolism of fenpicoxamid proceeds either with loss of the oxymethylisobutyrate group from the pyridine ring to form metabolite X642188 or with opening of the bislactone ring at one of two possible positions to give an open-ring fenpicoxamid isomer. Further metabolism resulted in cleavage of a phenyl ring fragment from the parent molecule to form metabolite X12314005. Based on the metabolic pathway, low levels of additional phenyl-fragment and pyridine-fragment metabolites are postulated, but not identified. None of the metabolites observed appeared to be present as conjugates.

Table 2 Total radioactive residues in tomato fruit and vines

Fraction	1 DALA		7 DALA		14 DALA	
	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg
Phenyl Label						
Acetonitrile fruit rinse	85.7	0.072	89.5	0.051	81.0	0.051
Rinsed fruit	14.3	0.012	10.5	0.006	19.0	0.012
Whole fruit	100.0	0.084	100.0	0.057	100.0	0.063
Vines					100.0	2.932
Pyridine Label						
Acetonitrile fruit rinse	85.9	0.110	79.6	0.090	83.9	0.078
Rinsed fruit	14.1	0.018	20.4	0.023	16.1	0.015
Whole fruit	100.0	0.128	100.0	0.113	100.0	0.093
Vines					100.0	3.052

Vine samples were only collected at 14 DALA and were not rinsed prior to combustion analysis.

Table 3 Distribution of the radioactive residue in fruit and vines of ^{14}C-fenpicoxamid treated tomato plants following extraction

Sample	Fraction	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		% TRR	mg eq/kg	% TRR	mg eq/kg
Fruit (1 DALA)	Initial residue	100	0.084	100	0.128
	Acetonitrile rinse	85.7	0.072	85.9	0.110
	Extract 1[a]	13.0 (90.9)[b]	0.011	12.9 (91.7)	0.017
	Extract 2[a]	0.3 (1.8)	<0.001	0.2 (1.5)	<0.001
	Extract 3[a]	0.3 (2.3)	<0.001	0.6 (4.1)	<0.001
	Total extracted	99.3	0.083	99.6	0.128
	PES	0.7	<0.001	0.4	<0.001
Fruit (7 DALA)	Initial residue	100	0.057	100	0.113
	Acetonitrile rinse	89.5	0.051	79.6	0.090
	Extract 1[a]	9.4 (89.3)	0.005	17.6 (86.4)	0.020
	Extract 2[a]	<0.1 (0.02)	<0.001	0.4 (2.0)	<0.001
	Extract 3[a]	0.6 (5.4)	<0.001	1.2 (5.7)	0.001
	Total extracted	99.5	0.057	98.8	0.112
	PES	0.5	<0.001	1.2	0.001
Fruit (14 DALA)	Initial residue	100	0.063	100	0.093
	Acetonitrile rinse	81.0	0.051	83.9	0.078
	Extract 1[a]	16.2 (85.0)	0.010	13.9 (86.2)	0.013
	Extract 2[a]	0.6 (3.2)	<0.001	1.2 (7.3)	0.001
	Extract 3[a]	1.7 (9.2)	0.001	0.6 (4.1)	<0.001
	Total extracted	99.5	0.063	99.6	0.093
	PES	0.5	<0.001	0.4	<0.001
Vines (14 DALA)	Initial residue	100	2.932	100	3.052
	Acetonitrile rinse				
	Extract 1[a]	84.0	2.463	85.3	2.603
	Extract 2[a]	12.7	0.372	10.8	0.330
	Extract 3[a]	2.4	0.071	2.7	0.082
	Total extracted	99.1	2.907	98.8	3.014
	PES	0.9	0.025	1.2	0.037

[a] Extract 1, 2, 3 are organic solvent extracts for rinsed fruit: using acetonitrile/0.1% H_3PO_4 in extract 1 and 2, and using acetonitrile/water (1:1) both containing 0.1% H_3PO_4 in extract 3

[b] Values in parentheses are extraction percentages based on rinsed fruit.

Table 4 Distribution and identification of residues in tomato fruit and vines from plants treated with ^{14}C-[PH]-fenpicoxamid

Residue component	MW	Fruit (1 DALA)		Fruit (7 DALA)		Fruit (14 DALA)		Vines (14 DALA)	
		% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]
Initial residue		100	0.084	100	0.057	100	0.063	100	2.932
Total extracted		99.3	0.083	99.5	0.057	99.5	0.063	99.1	2.907
Fenpicoxamid	614.66	95.7 [85.7]	0.080 [0.072]	89.5 [89.5]	0.051 [(0.051)	92.5 [81.0]	0.058 [0.051]	87.9	2.577
X642188	514.52	0.1	<0.001	na	na	0.2	<0.001	1.0	0.025
X12314005	276.33	0.7	<0.001	na	na	0.6	<0.001	1.7	0.022
Open-ring fenpicoxamid isomer*	632.66	0.4	<0.001	na	na	0.5	<0.001	3.0	0.091
Total identified		96.9	0.081	89.5	0.051	93.8	0.059	93.6	2.744
Total characterised		1.1	0.001			2.6	0.002	1.6	0.047
		3 peaks each 0.2-0.7% TRR (≤ 0.001 mg eq/kg)				5 peaks each 0.2-1.2% TRR (≤ 0.001 mg eq/kg)		4 peaks each 0.2-0.6% TRR	
Total unextracted		0.7	<0.001	0.5	<0.001	0.5	<0.001	0.9	0.026
Accountability [b]		98.7	0.083	90	0.051	96.9	0.061	96.1	2.818

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted

[ ]: radioactivity detected in acetonitrile rinse

na: not analysed, due to <0.010 mg/kg in pooled extract of the 7 DALA rinsed fruit

*Proposed to be one of several possible open ring analogues of fenpicoxamid based on the analysis of LC-MS/MS with vine extracts

Table 5 Distribution and identification of residues in tomato fruit and vines from plants treated with ^{14}C-[PY]-fenpicoxamid

Residue component	MW	Fruit (1 DALA)		Fruit (7 DALA)		Fruit (14 DALA)		Vines (14 DALA)	
		% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]
Initial residue		100	0.128	100	0.113	100	0.093	100	3.052
Total extracted		99.6	0.127	98.8	0.112	99.6	0.093	98.8	3.014
Fenpicoxamid	614.66	96.8 [85.9]	0.124 [0.110]	96.7 [79.6]	0.109 [0.090]	95.1 [83.9]	0.088 [0.078]	92.2	2.814
X642188	514.52	0.2	<0.001	0.2	<0.001	0.2	<0.001	0.8	0.020
X12314005	276.33	-	-	-	-	-	-	-	-
Open-ring fenpicoxamid isomer	632.66	0.4	<0.001	0.5	<0.001	0.4	<0.001	2.4	0.072
Total identified		97.4	0.125	97.4	0.110	95.7	0.089	95.4	2.912
Total characterised		0.5	<0.001	0.5	<0.001	1.6	0.002	2.2	0.064
		3 peaks each 0.1-0.2% TRR (≤ 0.001 mg eq/kg)		2 peaks each 0.2-0.3% TRR (≤ 0.001 mg eq/kg)		5 peaks each 0.1-0.8% TRR (≤ 0.001 mg eq/kg)		7 peaks each 0.1-0.6% TRR	
Total unextracted		0.4	<0.001	1.2	0.001	0.4	<0.001	1.2	0.037
Accountability [b]		98.3	0.126	99.1	0.112	97.7	0.091	98.8	3.015

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted

[ ]: radioactivity detected in acetonitrile rinse

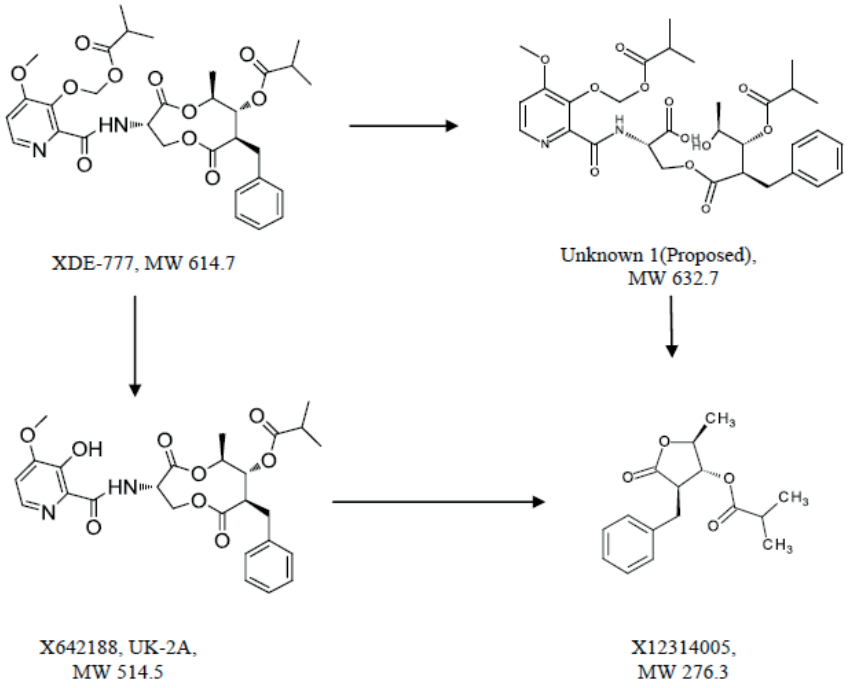


Figure 1 Proposed metabolic pathway in tomato and cabbage

Cabbage

A study was conducted to investigate the metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in outdoor grown cabbage (*Brassica oleracea* cv. Supreme Vantage) following two foliar applications at *ca.* 37 days (BBCH 41) and 7 days (BBCH 48)

before harvest [Wu, 2013b, report 121002]. Application was made, each at a rate of 300 g ai/ha (total seasonal rate of 600 g ai/ha) with ^{14}C-fenpicoxamid formulated as an EC formulation. Immature cabbage samples were collected 14 days after the first application and mature cabbage samples were collected 7 days after the last application. In collecting samples, cabbage whole plants were cut at the soil surface. For the mature samples, one set of samples were maintained with the wrapper leaves intact and a second set, the wrapper leaves were removed. TRR was determined by combustion/LSC.

Cabbage samples were extracted twice with 0.1% H_3PO_4 in acetonitrile, followed by 0.1% H_3PO_4 in acetonitrile/water (1:1, v/v). Each extract was analysed by LSC. The pooled extracts were cleaned up by SPE and analysed by HPLC. Unextracted residues remained in the PES after organic extraction were analysed by combustion. Parent and metabolites were isolated from the PH-label treated wrapper leaves sample and identification was performed by LC-MS. The results are shown in Tables 6-9.

TRR levels (both labels) in immature cabbage were in the range of 0.93-1.3 mg eq/kg. In mature cabbage heads with wrapper leaves, TRRs (both labels) were 0.42-0.51 mg eq/kg, while those in mature cabbage heads without wrapper leaves (0.066-0.12 mg eq/kg) were approximately one-fifth lower than in intact cabbage. Acetonitrile/0.1% H_3PO_4 extracted 87-94% of the total residues from cabbage samples.

Table 6 Total radioactive residues in cabbage

^{14}C-fenpicoxamid	Sample	TRR (mg eq/kg)
Phenyl label	Immature cabbage (14 days after 1st application)	1.275
	Mature, head with wrapper leaves (7 DALA) Mature, head without wrapper leaves (7 DALA) Mature, wrapper leaves (7 DALA)	0.508 0.119 1.619
Pyridine label	Immature cabbage (14 days after 1st application)	0.925
	Mature, head with wrapper leaves (7 DALA) Mature, head without wrapper leaves (7 DALA) Mature, wrapper leaves (7 DALA)	0.423 0.066 1.549

In all samples (immature cabbage, cabbage head with or without wrapper leaves, and wrapper leaves), unchanged parent was predominant accounting for *ca*. 68-96% of the TRR, and present at levels of 0.054-1.5 mg/kg. Minor metabolites, X642188, open ring analogue of fenpicoxamid and X12314005, were found at up to 5.4, 5.0 and 13.1% TRR, and present at up to 0.013, 0.058 and 0.030 mg/kg, respectively. An additional 3 to 10 unidentified metabolite fractions (<0.1-4.8% TRR) were also observed at ≤0.014 mg eq/kg except one fraction in immature cabbage (0.028 mg eq/kg). The metabolism pattern of fenpicoxamid was the same with that in tomato. See Figure 1 for the metabolic pathway in tomato.

Table 7 Distribution of the radioactive residue in cabbage of ^{14}C-fenpicoxamid treated plants following extraction

Sample	Fraction	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		% TRR	mg eq/kg	% TRR	mg eq/kg
Immature plants	Initial residue	100	1.275	100	0.925
	Extract 1[a]	93.7	1.194	91.2	0.843
	Extract 2[a]	4.4	0.056	5.0	0.046
	Extract 3[a]	1.4	0.017	2.3	0.021
	Total extracted	99.4	1.267	98.5	0.911
	PES	0.60	0.008	1.5	0.014
Mature head with wrapper leaves	Initial residue	100	0.508	100	0.423
	Extract 1[a]	91. 8	0.466	88.2	0.373
	Extract 2[a]	5.7	0.029	7.5	0.032
	Extract 3[a]	2.0	0.010	3.3	0.014
	Total extracted	99.5	0.505	99.0	0.419
	PES	0.5	0.003	1.0	0.004
Mature head without wrapper leaves	Initial residue	100	0.119	100	0.066
	Extract 1[a]	91.9	0.109	86.6	0.057
	Extract 2[a]	4.0	0.005	5.2	0.003
	Extract 3[a]	3.2	0.004	5.7	0.004
	Total extracted	99.1	0.118	97.6	0.064

Sample	Fraction	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		% TRR	mg eq/kg	% TRR	mg eq/kg
	PES	0.90	0.001	2.5	0.002
Wrapper leaves	Initial residue	100	1.619	100	1.549
	Extract 1[a]	91.1	1.475	90.7	1.405
	Extract 2[a]	6.9	0.112	5.8	0.089
	Extract 3[a]	1.4	0.023	2.8	0.043
	Total extracted	99.4	1.610	99.2	1.537
	PES	0.6	0.009	0.8	0.012

[a] Extract 1, 2, 3 are organic solvent extracts: using 0.1% H_3PO_4 in acetonitrile in extract 1 and 2, and using 0.1% H_3PO_4 in acetonitrile/water (1:1) in extract 3.

Table 8 Distribution and identification of residues in cabbage from plants treated with ^{14}C-[PH]- fenpicoxamid

Residue component	MW	Immature cabbage		Head with wrapper leaves		Head without wrapper leaves		Wrapper leaves	
		% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]
Initial residue		100	1.275	100	0.508	100	0.119	100	1.619
Total extracted		99.4	1.267	99.5	0.505	99.1	0.118	99.4	1.609
Fenpicoxamid	614.66	91.3	1.164	68.0	0.345	73.3	0.087	90.1	1.459
X642188	514.52	1.2	0.013	1.4	0.006	5.4	0.005	0.9	0.012
X12314005	276.33	1.8	0.010	13.1	0.030	3.4	0.002	2.2	0.016
Open-ring fenpicoxamd isomer*	632.66	1.9	0.025	5.0	0.026	3.9	0.005	3.5	0.058
Total identified		96.2	1.227	87.5	0.445	86.0	0.102	96.7	1.566
Total characterised		3.2	0.041	11.9	0.060	13.2	0.016	2.8	0.045
		3 peaks each 0.4-2.2% TRR (≤0.028 mg eq/kg)		7 peaks each 1.2-2.8% TRR (≤0.014 mg eq/kg)		10 peaks each <0.1-4.8% TRR (≤0.0057 mg eq/kg)		4 peaks 3ach 0.5-0.8% TRR (≤0.013 mg eq/kg)	
Total unextracted		0.6	0.008	0.5	0.003	0.9	0.001	0.6	0.010
Accountability [b]		100	1.275	99.9	0.507	100	0.119	100	1.621

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted.

*The component was thought to be a different isomer of fenpicoxamid.

Table 9 Distribution and identification of residues in cabbage from plants treated with ^{14}C-[PY]- fenpicoxamid

Residue component	MW	Immature cabbage		Head with wrapper leaves		Head without wrapper leaves		Wrapper leaves	
		% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]	% TRR	mg eq/kg [a]
Initial residue		100	0.925	100	0.423	100	0.066	100	1.549
Total extracted		98.5	0.911	99.0	0.419	97.6	0.064	99.2	1.537
Fenpicoxamid	614.66	95.7	0.885	96.2	0.407	81.6	0.054	96.3	1.492
X642188	514.52	1.2	0.009	nd	nd	2.3	0.001	1.0	0.013
X12314005	276.33	-	-	-	-	-	-	-	-
Open-ring fenpicoxamid isomer	632.66	1.5	0.014	2.0	0.009	3.9	0.003	1.9	0.030
Total identified		98.4	0.910	98.2	0.415	87.8	0.058	99.2	1.537
Total characterised				0.8	0.003	9.8	0.006		
				1 peak 0.8% TRR (≤0.0034 mg eq/kg)		4 peaks each 1.9-3.0% TRR (≤0.002 mg eq/kg)			
Total unextracted		1.5	0.014	1.0	0.004	2.4	0.002	0.8	0.012
Accountability [b]		99.9	0.924	100	0.423	100	0.066	100	1.549

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted.

nd: not detected

Wheat

A study was conducted to investigate the metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in outdoor grown wheat (Ultra) following two foliar applications [Ma and Jackson, 2013, report 110334]. Applications were made at *ca.* BBCH 32 and BBCH 65, each at a rate of 133 g ai/ha (total seasonal rate of 266 g ai/ha) as an SC formulation containing 87% w/w formulation blank (GF-2807) and 13% w/w radiolabelled test material. Immature wheat forage samples were collected at BBCH 49, *ca.* 28 days after the first application. Immature wheat hay samples were collected at BBCH 77, *ca.* 24 days after the last application. The harvested hay samples were weighed and placed in a greenhouse to dry. Four days later the dried hay samples were collected and weighed again, then stored frozen until processing. Mature grain and straw were collected at BBCH 89, *ca.* 78 days after the last application. The heads were placed in a grain thresher to separate grain and chaff. Chaff was added to straw. Samples were weighed and stored frozen. TRR was determined by combustion/LSC.

Samples were extracted three times under accelerated solvent extraction (ASE): extraction once with 0.1% H_3PO_4 in acetonitrile at 50 °C and twice with acetonitrile/water/H_3PO_4 (50:50:0.1, v/v/v) at 50 °C. Extracts were pooled and analysed by LSC and HPLC. Prior to HPLC analysis, pooled extracts were cleaned up by SPE using acetonitrile as an eluting solvent. For straw and grains, SPE cartridge was rinsed with water/acetonitrile (90:10) after applying sample extract to cartridge (combined eluates, SPE load/wash) and then eluted with acetonitrile (SPE eluant). Unextracted residue in straw (PES) was subjected to pectin extraction, lignin extraction and acid-detergent fibre isolation. Metabolites were isolated from the straw tissues and identified by LC-MS and LC-MS/MS. The results are shown in Table 10-11.

Table 10 Total radioactive residues in wheat

Sample	TRR	Solvent extraction [a]		PES	
	mg eq/kg	%TRR	mg eq/kg	%TRR	mg eq/kg
Phenyl Label					
Forage (28 days after 1st appl.)	0.539	110	0.595	1.4	0.008
Hay (24 days after 2nd appl.)	7.823	90	7.005	0.6	0.047
Straw (78 days after 2nd appl.)	4.192	102	4.264	1.9	0.078
Grain (78 days after 2nd appl.)	0.016	97	0.015	34	0.005
Pyridine Label					
Forage (28 days after 1st appl.)	0.990	103	1.018	2.1	0.021
Hay (24 days after 2nd appl.)	2.961	104	3.091	1.2	0.036
Straw (78 days after 2nd appl.)	4.877	101	4.931	4.0	0.193
Grain (78 days after 2nd appl.)	0.019	50	0.010	37	0.007

[a] Three extracts (ACN/H_3PO_4 100:0.1 at 50 °C, ACN/H_2O/H_3PO_4 50:50:0.1 at 50 & 70 °C) were pooled. Extraction percentage by each extraction was not reported.

TRR levels in wheat samples (both labels) were 0.54-0.99 mg eq/kg in forage, 3.0-7.8 mg eq/kg in hay, 4.2-4.9 mg eq/kg in straw and 0.016-0.019 mg eq/kg in grain.

ASE procedure using acetonitrile and additionally 50% aqueous acetonitrile extracted 90-110% of total radioactivity in forage, hay, and straw, while 50-97% of the TRR in grain was extracted, remaining 34-37% TRR (0.005-0.007 mg eq/kg) in the PES.

In forage, parent was the major compound accounting for 85.1-98.1% TRR (0.53-0.84 mg/kg) in both labels. Low levels of X642188 (1.1-3.4% TRR, 0.005-0.029 mg/kg), open-ring fenpicoxamid isomer (1.2-1.8% TRR, 0.007-0.019 mg/kg) and X12314005 (1.4% TRR, 0.003 mg/kg) were present in forage. Besides, no other single component accounted for more than 3.5% TRR (0.035 mg eq/kg).

In hay, parent was the major compound (79.1-87.2% TRR, 2.6-6.2 mg/kg) in both labels. Low levels of X642188 (0.8-1.9% TRR, 0.048-0.050 mg/kg), open-ring fenpicoxamid isomer (1.5-1.9% TRR, 0.059-0.12 mg/kg) and X12314005 (1.5% TRR, 0.054 mg/kg) were present in hay. Similar to PY-labelled straw, a peak eluting at solvent front accounted for 3.3% TRR (0.099 mg eq/kg) in PY-labelled hay. The nature of this residue was demonstrated as multi-component in straw. Besides, no other single component accounted for more than 1% TRR (0.07 mg eq/kg) in hay.

Table 11 Distribution and identification of residues in wheat treated with ^{14}C-fenpicoxamid

Residue component	MW	%TRR (mg eq/kg)[a]							
		Forage		Hay		Straw		Grain	
		PH	PY	PH	PY	PH	PY	PH	PY
TRR		0.539	0.990	7.823	2.961	4.192	4.877	0.016	0.019
Total extracted		110 (0.595)	103 (1.018)	90 (7.005)	104 (3.091)	102 (4.264)	101 (4.931)	97 (0.015)	50 (0.010)
Fenpicoxamid	614.66	98.1 (0.529)	85.1 (0.842)	79.1 (6.191)	87.2 (2.582)	82.7 (3.462)	75.6 (3.687)	38.3 (0.006)	21.4 (0.004)
X642188	514.52	1.1 (0.005)	3.4 (0.029)	0.8 (0.050)	1.9 (0.048)	nd	1.9 (0.076)	nd	0.8 (<0.001)
X12264475[*†]	256.21	-	nd	-	nd	-	2.0 (0.041)	-	2.9 (<0.001)
X696476[*†]	169.13	-	nd	-	nd	-	1.4 (0.019)	-	nd
X12335723[†]	356.33	-	nd	-	nd	-	1.7 (0.049)	-	nd
X12019520[*]	188.22	nd	-	nd	-	0.5 (0.006)	-	5.5 (<0.001)	-
Open-ring fenpicoxamid isomer	632.66	1.2 (0.007)	1.8 (0.019)	1.5 (0.119)	1.9 (0.059)	1.7 (0.072)	1.3 (0.066)	nd	nd
X12314005	276.33	1.4 (0.003)	-	1.5 (0.054)	-	2.5 (0.047)	-	nd	-
Total identified		102 (0.549)	89 (0.895)	83 (6.488)	91 (2.698)	87 (3.656)	81 (3.926)	38 (0.006)	22 (0.004)
Total characterised		0.7 (0.004)	7 (0.048)	0.9 (0.067)	5.4 (0.159)	4 (0.155)	10 (0.504)	37 (0.006)	20 (0.004)
		multi-component each ≤3.5% TRR (0.035 mg eq/kg)		multi-component each ≤3.3% TRR (0.099 mg eq/kg)		multi-component each ≤3% TRR (0.15 mg eq/kg)		multi-component each <4% (0.001 mg eq/kg)	
Total unextracted		1.4 (0.008)	2.1 (0.021)	0.6 (0.047)	1.2 (0.035)	1.9 (0.078)	4.0 (0.193)	34 (0.005)	37 (0.007)
Accountability [b]		104	98	85	98	93	95	109	79

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted.

[*] Not confirmed by LC-MS, peak eluting with retention time similar to the reference compound, the radioactivity was included in the total characterised.

[†] Polar compounds found in the SEP load/wash fraction.

nd: not detected

In straw, the majority of the radioactive residue remained as the parent (75.6-82.7% TRR, 3.5-3.7 mg/kg) in both labels. In the PH-labelled straw, low levels of open-ring fenpicoxamid isomer (1.7% TRR, 0.072 mg/kg) and X12314005 (2.5% TRR, 0.047 mg/kg) were present and a peak eluting with retention time similar to X12019520 (0.5% TRR, 0.006 mg/kg) was observed. No other single component accounted for more than 1.8% TRR (0.075 mg eq/kg, detected in SPE load/wash) in PH-labelled straw. For the PY-labelled straw, low levels of X642188 (1.9% TRR, 0.076 mg/kg), open-ring fenpicoxamid isomer (1.3% TRR, 0.066 mg/kg) and X12335723 (1.7% TRR, 0.049 mg/kg, detected in SPE load/wash) were present. Two peaks eluting with retention times similar to X12264475 (2.0% TRR, 0.041 mg/kg) and X696476 (1.4% TRR, 0.019 mg/kg) were observed in the PY-labelled straw SPE load/wash fraction. Radioactive residue in the SPE load/wash from the PY-labelled straw was multi-component (each ≤2.5% TRR). No other single component accounted for more than 3% TRR (0.15 mg eq/kg) in PY-labelled straw.

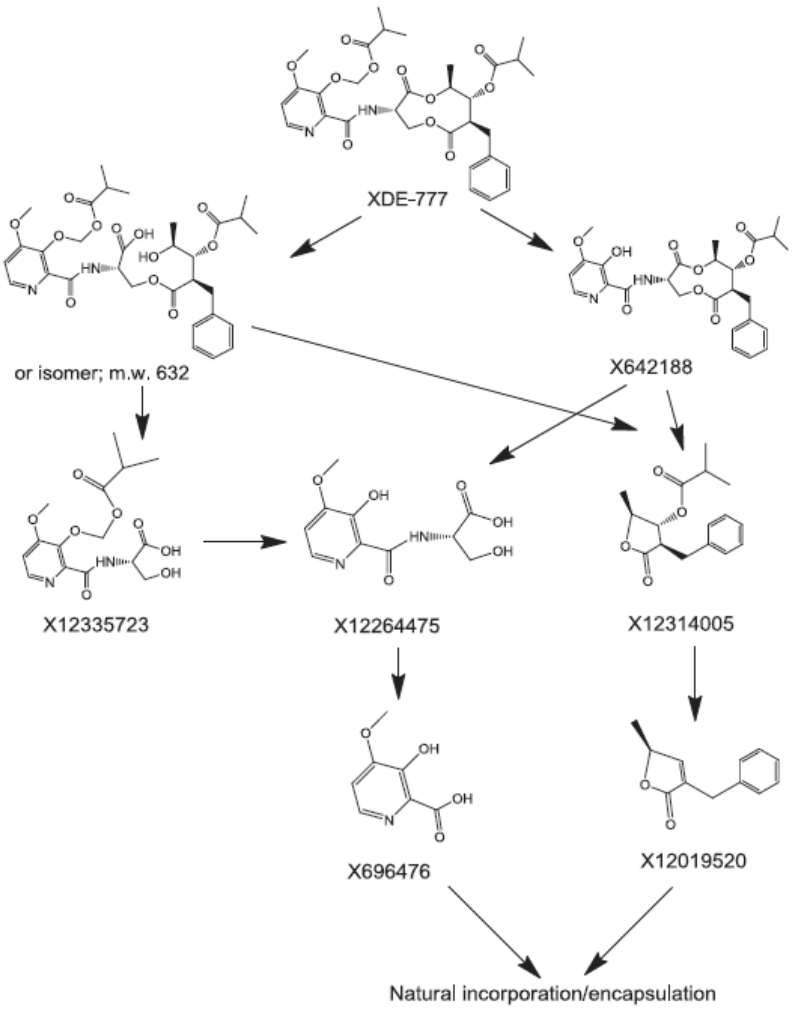


Figure 2 Proposed metabolic pathway in wheat

Unextracted residues (1.9-4.0% TRR, 0.078-0.193 mg eq/kg) in the PES of straw were incorporated into natural plant constituents and characterised as pectin (0.5-1.5% TRR, 0.021-0.071 mg eq/kg), lignin (1.3-1.7% TRR, 0.053-0.081 mg eq/kg), hemicellulose (0.5-0.6% TRR, 0.025 mg eq/kg) and cellulose (0.1-0.2% TRR, 0.005-0.008 mg eq/kg).

In grain, parent was the major compound (21.4-38.3% TRR, 0.004-0.006 mg/kg) in both labels. In the PH-labelled grain, one peak eluting with retention time similar to X12019520 (5.5% TRR, <0.001 mg/kg) was observed. Other single components were present at individually less than 4% TRR (0.001 mg eq/kg) in PH-labelled grain. For the PY-labelled grain, X642188 was present at a very low level of 0.8% TRR (<0.001 mg/kg). A peak in the SPE load/wash from the PY-labelled grain eluting with retention time similar to X12264475 (2.9% TRR, <0.001 mg/kg) was observed. No other single component account for more than 3.5% TRR (<0.001 mg eq/kg) in PY-labelled grain.

A proposed metabolic pathway in wheat is shown in Figure 2. Fenpicoxamid is not extensively metabolised in wheat. The metabolism of fenpicoxamid in wheat proceeds through loss of the oxymethylisobutyrate protecting group, ring opening, and ring cleavage. The hydrolysis of the bislactone ring causes the ring to open, and ultimately sever, forming the pyridine-label or phenol-label specific metabolites. Metabolism continues through natural incorporation of the radiolabelled carbon into natural plant constituents such as lignin.

In summary, results from three studies (tomato, cabbage and wheat) showed that fenpicoxamid is not extensively metabolised in crops following foliar applications. Parent fenpicoxamid constitutes the large majority of residues in wheat, cabbage and tomato with low levels of individual metabolites observed. A similar metabolite profile was observed across three crop groups, regardless of the application rate, growth stages at application, different PHIs or formulation types. In all crops, any metabolism

proceeds through loss of the oxymethylisobutyrate group from the pyridine ring or through opening and cleavage of the bislactone ring to ultimately produce low levels of several possible pyridine-label or phenyl-label specific metabolites.

Table 12 Profile of fenpicoxamid and metabolites in plant metabolism studies

Compound	% TRR							
	Tomato		Cabbage				Wheat	
	Fruit	Vine	Immature	Head with wrapper leaves	Head without wrapper leaves	Wrapper leaves	Grain	Forage, hay & straw
Fenpicoxamid	90 - 97	88-92	91 - 96	68 - 96	73 - 82	90-96	21 - 38	76 - 98
X642188	<10	<10	<10	<10	<10	<10	<10	<10
Open-ring fenpicoxamid isomer	<10	<10	<10	<10	<10	<10	-	<10
X12314005	<10	<10	<10	13	<10	<10	-	<10
X12335723	-	-	-	-	-	-	-	<10 (straw)

Residues in succeeding or rotational crops

Confined rotational crop study

A study was conducted to determine the amount, nature and distribution of residues in the raw agricultural commodities of three rotational crops, wheat (variety, Ultra), lettuce (variety, Butter Crunch), and radish (variety, Cherry Belle) [Ma and Aldelfinskaya, 2016, report 140050]. A single soil application of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled, SC formulation) was made on a sandy loam soil at a rate of 260 g ai/ha (1× of the current maximum seasonal rate). The crops were planted at *ca* 30, 180 and 270 days after treatment (DAT) and outdoor grown. Samples were collected at immature lettuce BBCH 44, mature lettuce BBCH 49, mature radish tops and roots BBCH 49, wheat forage BBCH 34, wheat hay BBCH 83, and wheat straw and grain BBCH 89. TRR was determined by combustion/LSC.

All samples containing TRR levels equal or greater than 0.01 mg eq/kg were subjected to accelerated solvent extraction (six extractions): twice at 50 °C with 0.1% H_3PO_4 in acetonitrile, twice each at 50 °C and 70 °C with 0.1% H_3PO_4 in acetonitrile/water (1:1). Extract pooled was subjected to analysis by LSC, SPE clean-up and characterisation by HPLC. PES (>0.010 mg eq/kg and grain) were subjected to acid and base extractions: at 70 °C for 1 hr, twice with 1 N HCl followed by twice with 1N NaOH; for grain, at 35 °C for 1hr, twice with acetonitrile/1 N HCl (1:1) and twice with acetonitrile/1 N NaOH (1:1). Metabolite identification was attempted by LC-MS: one HPLC fraction eluting at approximately 15 min was isolated from the extracts of the 30 DAT PH-label hay sample, which was subjected to LC-MS for identification. The results are shown in Table 13-14.

Residues in crops constantly declined with longer plant back interval (PBI); strongly between 30 and 180 day DAT and generally slower until 270 DAT. In food commodities (both labels), residue levels at 30 DAT were 0.006-0.020 mg eq/kg, which decreased to 0.001-0.009 mg eq/kg at 180 DAT and further to 0.001-0.004 mg eq/kg at 270 DAT. For feed commodities (both labels), residue levels were 0.008-0.13 mg eq/kg at 30 DAT, 0.001-0.032 mg eq/kg at 180 DAT and 0.001-0.009 mg eq/kg at 270 DAT.

ASE using acetonitrile (for grain, 1:1 acetonitrile/water) extracted 47-80% of the radioactivity from samples ≥0.01 mg eq/kg TRR: immature lettuce (30 DAT PH- and PY-label), radish tops (30 DAT PH-label), wheat forage (30 DAT PH-label), wheat hay (30 DAT PH- and PY-label, 180 DAT PY-label), wheat straw (30 DAT and 180 DAT, PH- and PY-label). From wheat grain (30 DAT PH- and PY-label), only 20-36% of the TRR was extracted.

Residues in PES (30 DAT PH- and PY-labelled hay, straw and grain; 180 DAT PY-labelled straw) were extracted with acid or base hydrolysis. In hay and straw samples, 1.9-10.3% TRR was released with acid and 10.5-14.8% TTR with base. From the grain PES, acid released 10.2-21.5% TRR and base 31.7-54.4% TRR. The acidic and basic extracts for hay and straw were not further analysed due to low level of radioactivity. For grain, the acidic and basic extracts were cleaned up by SPE. The majority of residue was present in SPE load/wash fraction, which was analysed by HPLC, however, the low level of residues did not allow further characterisation/identification.

ASE extracts (13 samples, except 180 DAT PH-labelled wheat) were cleaned up by SPE. In the PY-labelled samples, the majority of residue was found in SPE load/wash. For the PH-labelled samples, the majority was found in SPE eluant, except for hay (when reconstructed for HPLC: 46.9% in eluant, 11.9% TRR in SPE load/wash) and straw (16.8% TRR in SPE eluant; 23.6% TRR in SPE load/wash). See Table 14.

In immature lettuce and radish tops, residues consisted of more than 30 components with the highest 0.004 mg eq/kg. Parent was not detected. Metabolites X642188, X12264475, X696476, X763024 and X12526439 were characterised based on HPLC retention time match with the authentic standards. In grain, residue consisted of multiple polar components (SEP load/wash)

present at less than 0.01 mg eq/kg each. The SPE eluant, where parent could be present, was not subjected to HPLC analysis: in eluant, 7.4% TRR (0.001 mg eq/kg) in PH-labelled grain and 1.7% TRR (0.0004 mg eq/kg) in PY-labelled grain.

In feed commodities, residues consisted of multiple components present at individual levels up to 0.0057 mg/kg (0.017 mg eq/kg, HPLC 15 min peak of 30 DAT PH-label hay), characterised as X12526439 (glucose conjugate of X11963422). Parent (only straw) and other metabolites (X11963422, X12019520, X12314005, X642188, X12264475, X763024 and X696476) were characterised based on HPLC retention time match with the authentic standards.

LC-MS identification for the HPLC 15 min peak of 30 DAT PH-label hay was attempted but with no success. In a LC-MS trial, the 15 min peak was identified as X12019520 (eluting at 30 min) not X12526439 (considered as degradation of X12526439 during sample preparation). After 7 months, the hay sample stored at -20 °C was re-subjected to LC-MS. The initial 15 min fraction was shown to be shifted to 13 min. LC-MS trial for the 13 min fraction, partially hydrolysed with acid or base, showed X12019520 identification. X12526439 (or X11963422) and X12019520 are structurally related, providing supportive evidence on characterising the 15 min fraction as X12526439 (glucose conjugate of X11963422).

Table 13 Total radioactive residues in plant samples, 30, 180 and 270 day plant-back intervals

Sample	TRR (mg eq/kg)		
	30 DAT	180 DAT	270 DAT
Phenyl Label			
Immature lettuce	0.018	0.001	0.001
Mature lettuce	0.006	0.002	0.004
Radish tops	0.016	0.001	0.003
Radish roots	0.009	0.001	0.001
Wheat forage	0.026	0.001	0.001
Wheat hay	0.130	0.007	0.004
Wheat straw	0.057	0.010	0.004
Wheat grain	0.015	0.001	0.002
Pyridine Label			
Immature lettuce	0.010	0.003	0.001
Mature lettuce	0.007	0.003	0.001
Radish tops	0.009	0.003	0.002
Radish roots	0.008	0.002	0.001
Wheat forage	0.008	0.003	0.002
Wheat hay	0.057	0.023	0.006
Wheat straw	0.053	0.032	0.009
Wheat grain	0.020	0.009	0.003

Bold letter: thirteen samples (TRR ≥0.01 mg eq/kg), subjected to accelerated solvent extraction

Table 14 Distribution of the radioactive residue in rotated crop samples following extraction

Sample[a]	PBI	Total TRR	Extracted (ASE)[b]		Extracted (Acid)[c]		Extracted (Base)[c]		Radioactivity in PES[d]		Total recovered, %[e]		Total analysed by HPLC[f]	
		mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg
PH-label														
Imm. lettuce	30	0.018	69.6	0.013	na	na	na	na	19.4	0.004	90.7	0.017	53.2*	0.010
Radish tops	30	0.016	77.3	0.013	na	na	na	na	16.5	0.003	93.9	0.015	65.2*	0.011
Wheat forage	30	0.026	62.0	0.016	na	na	na	na	31.7	0.008	93.7	0.025	45.3*	0.012
Wheat hay	30	0.130	72.4	0.094	1.9	0.002	9.8	0.013	30.5	0.040	102.9	0.134	46.9*, 11.9†	0.077
Wheat straw	30	0.057	56.8	0.032	2.7	0.002	10.5	0.006	35.9	0.020	92.7	0.053	16.8*, 23.6†	0.023
	180	0.01	79.6	0.008	na	na	na	na	29.5	0.003	109.1	0.011	na	na
Wheat grain	30	0.015	20.2	0.003	21.5	0.003	54.4	0.008	22.6	0.003	118.7	0.019	7.0†	0.001
PY-label														
Imm. lettuce	30	0.010	46.9	0.005	na	na	na	na	22.8	0.002	69.3	0.007	26.3†	0.003
Wheat hay	30	0.057	64.4	0.037	2.9	0.002	10.3	0.06	34.6	0.020	99.0	0.057	53.4†	0.031
	180	0.023	71.0	0.016	na	na	na	na	27.6	0.006	98.7	0.022	69.6†	0.016
Wheat straw	30	0.057	64.9	0.037	4.0	0.002	11.2	0.006	31.0	0.018	95.9	0.055	58.4†	0.034
	180	0.032	64.0	0.020	10.3	0.003	14.8	0.005	30.2	0.010	119.3	0.038	54.3†	0.017
Wheat grain	30	0.020	35.9	0.007	10.2	0.002	31.7	0.006	13.6	0.003	91.4	0.019	26.1†	0.005

[a] Samples of TRR ≥0.01 mg eq/kg (13 samples)

[b] Accelerated solvent extraction

[c] After extraction, pellets were further extracted with 1 N HCl followed by 1N NaOH (for grain, using 1:1 acetonitrile:1 N HCl followed by 1:1

acetonitrile:1 N NaOH).

[d] Combusted after ASE extraction, except 30 DAT grain (PH-, PY-label) and 180 DAT straw (PY-label), which were combusted after acid and base extractions following ASE extraction.

[e] Total Recovered, % = Extracted (ASE) % + PES % + Acid/Base extraction where relevant

[f] ASE extract was cleaned up by SPE: *SPE eluant and/or †SPE load/wash (†) were analysed by HPLC.

na: not applicable.

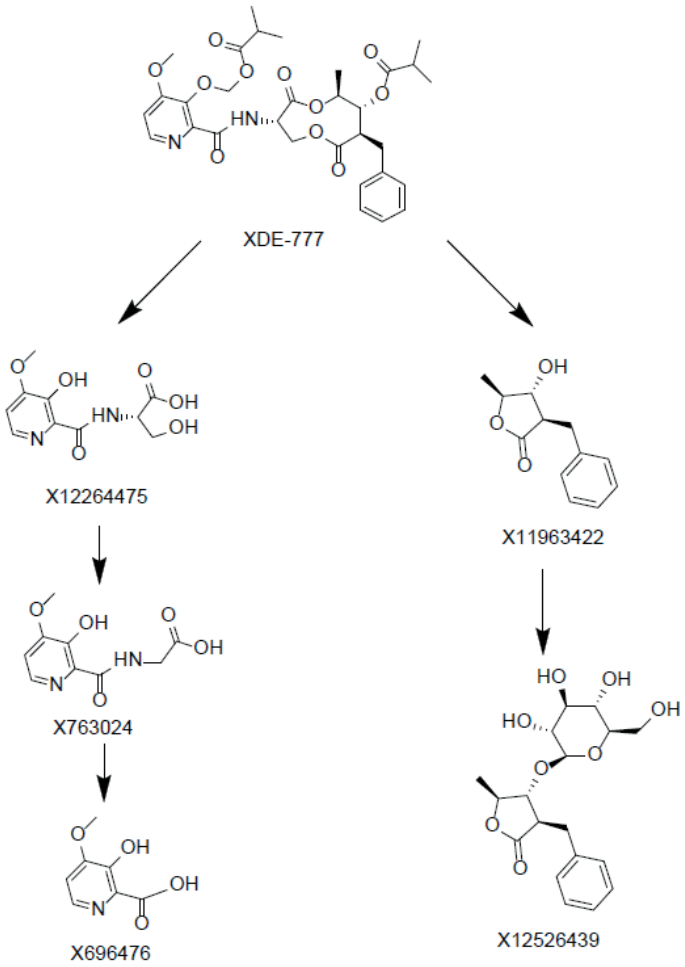


Figure 3 Proposed metabolic pathway in rotational crops

In this rotational crop study, residue levels of parent and metabolites were <0.01 mg eq/kg in food commodity and ≤0.01 mg/kg in feed commodity. Therefore, residues are not of concern for succeeding crops.

A proposed metabolism pathway in confined rotational crops is shown in Figure 3. Once fenpicoxamid is applied to aerobic soil, the compound quickly degrades. The bislactone ring is quickly cleaved and transformed to series of PH-label and PY-label metabolites. One of major PH-labelled soil metabolites that found in fenpicoxamid aerobic soil degradation study [Hastings and Jackson, 2013, report 110492] was X11963422. It was considered that X11963422 was further taken up and conjugated in crops to form X12526439.

Field rotational crop study

No information was provided.

Animal metabolism

The Meeting received information on metabolism of fenpicoxamid in goat and hens.

Rat

Metabolism studies on laboratory animals including rats were reviewed within the framework of the toxicological evaluation by the current JMPR.

Lactating goats

A metabolism study on the lactating goat (*Capra hiscus*, Saanen dairy) was performed to investigate the residue behaviour of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) [Rotondaro and Adelfinskaya, 2013, report 110766]. The test substance was orally administered in a capsule, once daily for 5 consecutive days at 21.8 ppm feed for ^{14}C-PH-fenpicoxamid and 18.7 ppm feed for ^{14}C-PY-fenpicoxamid (0.26 mg/kg bw/day and 0.30 mg/kg bw/day, respectively). Milk was collected twice daily. Urine and faeces were also collected. The animals were sacrificed 6-7 hours after the last dose and the following tissues were sampled; muscle (loin and flank), liver, kidney, fat (subcutaneous, omental and renal), GI tract and contents and blood (for mass balance only). Cage washes were collected after necropsy. TRR were determined in milk, urine and fat (melted first) samples by direct LSC. Radioactivity in tissue and faeces samples was determined by combustion/LSC. Kidney, liver and faeces (collected on days 1, 3, and 5) were extracted using organic solvents, but not for milk, muscle and fat due to the low residue levels.

Residues in kidney, liver and faeces were extracted three times with 0.1% H_3PO_4 in acetonitrile/water (75:25, v/v). Extracts were pooled, cleaned up by SPE and analysed by HPLC. Urine was analysed by HPLC, directly or after clean-up by SPE.

A replicate sample of liver (liver replicate O) was extracted three times with 0.1% formic acid in acetonitrile/water (75:25, v/v). Extracts were pooled, cleaned-up by SPE and analysed by HPLC. The PES was subjected to acid hydrolyses (at 80 °C, with 1 N HCl, again with 0.5 N HCl), and then extracted with 0.1% formic acid in acetonitrile/water (75:25, v/v). The acid extracts were pooled, cleaned up by SPE and analysed by HPLC.

Metabolites were isolated from urine and faeces and analysed by LC-MS for identification. The kidney and liver metabolites were tentatively identified by retention time match of the urine and faeces samples. The study results on lactating goat are shown in Table 15-16.

Of the administered dose, a total of 86.7-89.1% was recovered from the PH- and PY-labelled goats. In both labels, the majority (67.7-68.4%) of the dose was excreted in faces (53.5-63.4%) and in the urine (5.0-14.2%). Additionally, 18.6-20.5% of the dose was recovered in the gastrointestinal tract and contents. The majority was found in the gastrointestinal contents.

The edible tissues (muscle, fat, liver and kidney) accounted for 0.084-0.10% of the dose in both labels. Residue levels in muscle and fat were near or below the limit of quantification (≤0.005 mg eq/kg). In kidney and liver, TRR were 0.033-0.041 mg eq/kg and 0.026-0.065 mg eq/kg, respectively, in both labels. Milk accounted for totally 0.027% (PH) and 0.029% (PY) of the dose. During the dosing period the residue levels in milk reached a plateau after a maximum of approximately 0.008 mg eq/kg (day 2) in PH-label or 0.005 mg eq/kg (day 3) in PY-label. Overall, the residue levels were similar between the two radiolabels.

Table 15 Distribution of radioactivity in goats after administration of ^{14}C-fenpicoxamid

Matrix	Timing	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		mg/kg	% dose	mg/kg	% dose
Milk	Day 1 pm	0.004	0.002	(0.002)	0.001
	Day 1 am	0.005	0.004	0.004	0.003
	Day 2 pm	0.008	0.003	0.003	0.001
	Day 2 am	0.007	0.005	0.004	0.002
	Day 3 pm	0.003	0.002	0.005	0.002
	Day 3 am	(0.003)	0.002	(0.003)	0.003
	Day 4 pm	0.003	0.002	(0.002)	0.002
	Day 4 am	0.003	0.004	(0.003)	0.003
	Day 5 pm	0.004	0.002	(0.003)	0.002
Total accumulated		na	0.027	na	0.029
Urine	Day 1	2.132	3.1	0.859	1.5
	Day 2	4.442	5.2	1.584	0.8
	Day 3	1.843	2.5	1.769	0.9
	Day 4	2.193	2.4	1.017	1.4
	Day 5	2.165	1.0	1.015	0.3
Total accumulated		na	14.2	na	5.0
Faeces	Day 1	1.815	5.9	1.864	8.4
	Day 2	5.853	14.4	3.548	7.5

Matrix	Timing	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		mg/kg	% dose	mg/kg	% dose
	Day 3	5.575	9.9	5.762	14.9
	Day 4	7.856	16.7	6.688	24.6
	Day 5	4.594	6.6	3.383	8.0
Total accumulated		na	53.5	na	63.4
Cage rinse	sacrifice	0.190	0.28	0.170	0.14
Muscle-flank	sacrifice	(0.002)	0.002	0.002	0.003
Muscle-loin	sacrifice	(0.002)	0.001	0.003	0.002
Liver	sacrifice	0.026	0.034	0.065	0.064
Kidney	sacrifice	0.033	0.007	0.041	0.008
Fat-omental	sacrifice	0.005	0.008	(0.001)	0.002
Fat-subcutan.	sacrifice	nd	0.002	nd	0.001
Fat-renal	sacrifice	nd	0.002	nd	0.001
Edible tissues, total		na	0.084	na	0.100
GI Tract	sacrifice	0.119	0.56	0.387	1.8
GI contents	sacrifice	3.004	18.0	2.350	18.7
Blood	sacrifice	0.007	0.022	0.020	0.049
Grand total		na	86.7	na	89.1

Values in parentheses are below the limit of quantification but above the limit of detection

na: not applicable

nd: not detected

Residues in milk, muscle, and fat were not extracted for characterisation due to the low residue levels. Organic solvent (25% aqueous acetonitrile with 0.1% phosphoric acid) extracted 88.9-90.0% and 60.4-67.8% of the total radioactivity in kidney and liver, respectively, in both labels.

Components found in kidney and liver matrices were tentatively identified based on retention time match of urine and faeces samples.

Kidney contained multiple low-level components. The largest component was metabolite X12326349 at 32.7% TRR (0.010 mg/kg) in PY-labelled kidney and 16.8% TRR (0.004 mg/kg) in PH-labelled kidney. Metabolite 13495S-3S (isomer of X696872) was found at levels of 10.9% TRR (0.003 mg/kg) in PH-labelled kidney and 8.3% TRR (0.002 mg/kg) in PY-labelled kidney. Multiple other metabolites were found at minor levels not exceeding 10% TRR, each up to 0.001 mg/kg. Parent compound was observed only in PH-label, at a very low level of 0.2% TRR (<0.001 mg/kg). A polar peak (32.1% TRR, 0.013 mg eq/kg) was observed in PY-labelled kidney, but further characterisation and identification for the polar peak was not achieved.

Table 16 Distribution and characterisation of the parent and the metabolites in the edible tissues from a lactating goat dosed with ^{14}C-fenpicoxamid

Compound	PH-Kidney		PY-Kidney		PH-Liver		PY-Liver		PY-Liver O*	
	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]
TRR	100	0.033	100	0.041	100	0.026	100	0.065	100	0.065
Organic extract	90.0	0.029	88.9	0.036	60.4	0.016	67.8	0.044	57.5	0.038
Fenpicoxamid	0.2	<0.001	nd	nd	nd	nd	nd	nd	nr	nr
Polar	2.8	0.001	32.1	0.013	0.6	<0.001	21.4	0.014	nr	nr
X12264475	-	-	4.7	0.001	-	-	2.1	0.001	nr	nr
X12335723	-	-	0.5	<0.001	-	-	2.2	0.001	nr	nr
X129300	8.8	0.001	-	-	6.7	<0.001	-	-	nr	nr
X12326349	16.8	0.004	32.7	0.010	10.4	0.002	13.2	0.006	nr	nr
unknown @ 15.0 min	1.0	<0.001	nd	nd	nd	nd	2.4	0.002	nr	nr
X11963422	5.6	0.001	-	-	7.8	0.001	-	-	nr	nr
13495S-3S	10.9	0.003	8.3	0.002	4.5	0.001	7.8	0.004	nr	nr
X696872	nd	nd	nd	nd	0.4	<0.001	6.1	0.003	nr	nr
X737057	1.9	0.001	4.0	0.001	0.3	<0.001	2.9	0.002	nr	nr
X12019520	9.5	0.001	-	-	6.1	<0.001	-	-	nr	nr
Open-ring fenpicoxamid isomer	nd	nd	nd	nd	2.1	0.001	0.2	<0.001	nr	nr
PH-met 276	0.3	<0.001	-	-	nd	nd	-	-	nr	nr
X12314005	0.5	<0.001	-	-	0.2	<0.001	-	-	nr	nr

Compound	PH-Kidney		PY-Kidney		PH-Liver		PY-Liver		PY-Liver O*	
	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]	% TRR	mg/kg [a]
X642188	0.3	<0.001	nd	nd	nd	nd	0.3	<0.001	nr	nr
Identified	54.7	0.018	50.2	0.021	38.3	0.010	34.7	0.023	nr	nr
Characterised**	35.3	0.012	38.7	0.016	22.0	0.006	23.8	0.022	nr	nr
Post extraction solid (PES)	18.0	0.006	15.0	0.006	38.7	0.010	34.2	0.022	42.5	0.028
X12264475 (acid hydrolysate)	np	np	np	np	np	np	np	np	18.6	0.005
X12326349 (acid hydrolysate)	np	np	np	np	np	np	np	np	2.6	0.001
Unextracted (acid hydrolysate)	np	np	np	np	np	np	np	np	10.4	0.007
Total identified**	54.7	0.018	50.2	0.021	38.3	0.010	34.7	0.023	21.2	0.014
Total characterised	35.3	0.012	38.7	0.016	22.0	0.006	23.8	0.022		
Accountability [b]	108	0.035	104	0.043	99.0	0.026	92.7	0.060		

[a] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[b] Accountability is sum of identified, characterised and unextracted.

* PY-Liver O sample (replicate sample of PY-liver) was subjected to neutral extraction (57.5% TRR, 0.038 mg eq/kg: not analysed by HPLC) and then the resultant PES was subjected to acid hydrolyses (34.2% TRR, 0.022 mg eq/kg). The unextracted residue after acid hydrolyses was combusted (10.4% TRR). Of the hydrolysate (34.2% TRR), the SPE load/wash 22% TRR (0.014 mg eq/kg) was analysed by HPLC.

**Includes polar components and unknowns, each ≤0.001 mg eq/kg

nd, not detected; np, not performed; nr, not reported

Liver contained multiple low-level components. The largest component in both labels was X12326349 at 13.2% TRR(0.006 mg/kg) in PY-labelled liver and 10.4% TRR (0.002 mg/kg) in PH-labelled liver. Multiple other metabolites at minor levels did not exceed 10% TRR (up to 7.8% TRR, 0.004 mg/kg). Parent was not observed. A polar peak (21.4% TRR, 0.014 mg eq/kg) was observed in PY-labelled liver, but further characterisation and identification for the polar peak was not achieved.

In the PY-liver O sample (replicate of PY-liver sample), acid extraction for the PES remained after neutral extraction released 34.2% TRR from the liver sample. The acidic extract contained a very polar compound X12264475 (18.6% TRR, 0.005 mg/kg) and X12326349 (2.6% TRR, 0.001 mg/kg). Thus when combined with the neutral organic extract (X12264475 2.1% TRR, 0.001 mg/kg; X12326349 13.2% TRR, 0.006 mg/kg), X12264475 and X12326349 amounted to 20.7% TRR (0.006 mg/kg) and 15.8% TRR (0.007 mg/kg), respectively.

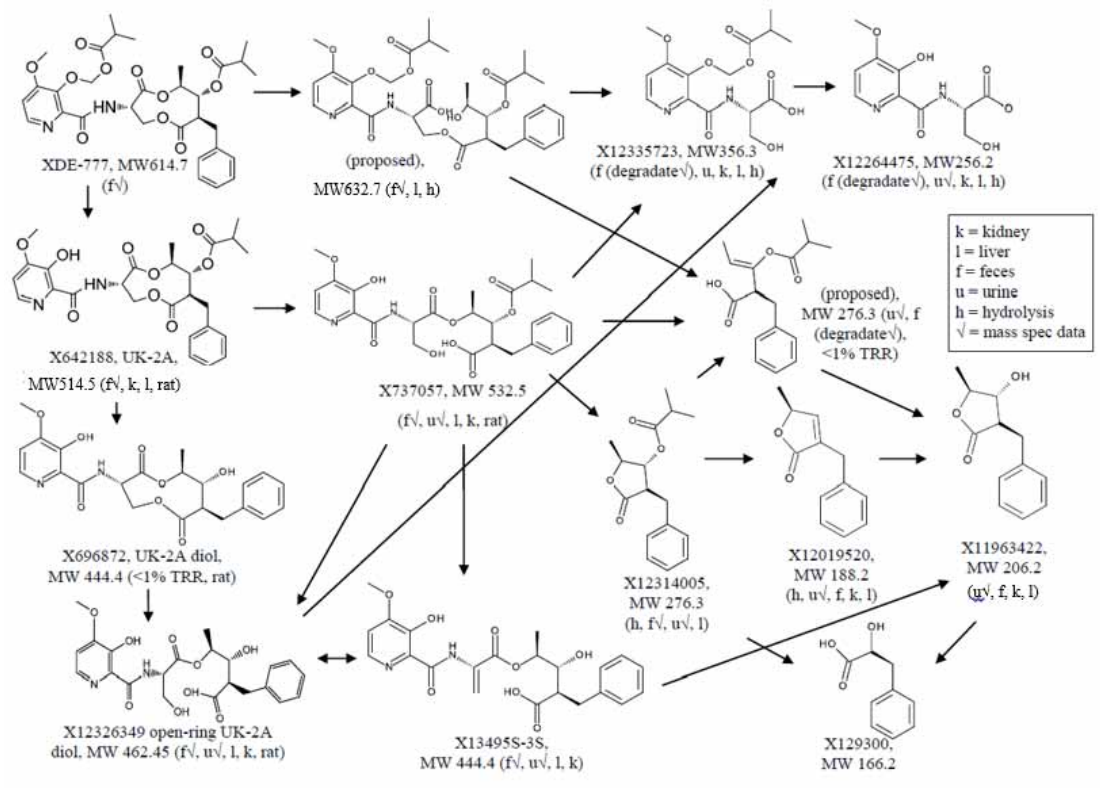


Figure 4 Proposed metabolic pathway for fenpicoxamid in goats

In either kidney or liver, or in both the following compounds were found (tentatively identified): the phenyl and pyridine ring metabolites (X12326349, 13495S-3S, X737057, open-ring fenpicoxamid, X642188 and characterized X696872), phenyl-label specific metabolites (X129300, X11963422, X12019520, PH-met 276 and X12314005) and pyridine-label specific metabolites (X12264475 and X12335723).

In faeces, the majority (86.6-130% TRR) of the radioactivity was extracted. The extract contained primarily unchanged parent (33-83% TRR) and multiple lower level metabolites found in liver and kidney.

The urine contained primarily ring cleavage products, including all nearly metabolites found in kidney, liver and faeces. Parent was not detected in most urine collected for 5 days. In some of the PY-labelled urine (PY-label days 3 and 4), parent was detected but considered as random radioactivity not associated with fenpicoxamid. The polar peak, shown at solvent-front, comprised multiple polar components and multiple other low-level components.

The metabolic profile was similar between kidneys and liver. Residues in liver and kidney comprised multiple components including X12326349, 13495S-3S and X12264475 with the highest, X12326349, 0.010 mg/kg. No parent was observed.

A proposed pathway in goats is shown in Figure 4. Metabolism proceeds through loss of either or both of the oxymethylisobutyrate side chains (O-dealkylation of the ester side chains) and opening of the bislactone ring at one of two possible positions. Further metabolism resulted in complete cleavage of the bislactone ring to give a variety of phenyl-ring and pyridine-ring specific metabolites.

Laying hens

A metabolism study on the laying hen was performed to investigate the residue behaviour of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in poultry (*Gallus domesticus*, variety HY-Line Browns) [Ma *et al*., 2013, report 110421]. Separate groups of animals were treated for 7 days with ^{14}C-PH-label or ^{14}C-PY-label test material, delivered in gelatin capsules, at the rate of 10.3 - 10.7 ppm feed per day in the diet. Eggs were collected twice daily. The animals were sacrificed 6 - 8 hours after the last dose and the following tissues were sampled; muscle (leg and breast), liver, kidney, fat (all available), skin with subcutaneous fat and GI tract and contents. Excreta and cage washes were also collected.

Total radioactive residues were determined in cage wash and fat (melted first) samples by direct LSC. TRR in tissue and excreta samples were determined by combustion/LSC. Extraction using organic solvents were made for the samples of liver (PH- and PY-label), fat (PH-label) and skin/fat (PH-label), eggs (day 5, 6, and 7 for PH- and PY labels), and excreta (day 1, 5, 7 for PH- and PY-labels).

Liver was extracted three times with 0.1% formic acid in acetonitrile/water (75:25, v/v) and then twice with 0.1% formic acid in acetonitrile/water (25:75, v/v). Extract pooled was cleaned up by SPE and analysed by HPLC. The resultant PES was subjected to acid and base extraction. Acid extraction was made with 1 N HCl (70 °C, 1 hr) and then with 0.1% formic acid in acetonitrile/water (75:25, v/v). The acid extracts were pooled, cleaned up by SPE and analysed by HPLC. After acid extraction, base extraction (only PH-label) was made with 1 N NaOH at room temperature and then separated into three fractions by acid precipitation, pellet re-extraction and dissolving the pellet. The three fractions were separately cleaned up by SPE, and selective fractions (eluant and load/wash) were analysed by HPLC.

Fat dissolved in hexane was extracted three times with 0.1% formic acid in acetonitrile/water (80:20, v/v) and then three times with 0.1% formic acid in acetonitrile/water (75:25, v/v). Extract pooled was cleaned up by SPE and analysed by HPLC. Skin with fat dissolved in hexane was separated to dissolved fat and connective tissue. The dissolved fat was extracted three times with 0.1% formic acid in acetonitrile/water (80:20, v/v). The extract was pooled, cleaned up by SPE and analysed by HPLC. The connective tissue was extracted three times with 0.1% formic acid in acetonitrile/water (75:25, v/v) and the extract was pooled, cleaned up by SPE and analysed by HPLC.

Eggs were extracted with four times (last two extraction, heated for 30 min at 40 °C before shaking) with 0.1% formic acid in acetonitrile/water (80:20, v/v). Extract pooled was cleaned up by SPE and analysed by HPLC. Excreta were extracted three times with 0.1% formic acid in acetonitrile/water (75:25, v/v). Extract pooled was cleaned up by SPE and analysed by HPLC.

SPE clean-up procedure used in this study was the same in all samples. SPE load/wash fraction was obtained by applying sample extract and consecutively sample vial rinse (0.1% formic acid in water) to SPE cartridge. SPE eluant fraction was obtained by eluting with consecutively three solutions of acetonitrile/water (80:20, v/v), 0.1% formic acid in acetonitrile/water (80:20, v/v) and 0.1% formic acid in acetonitrile.

Metabolites isolated from PH-labelled excreta and liver samples were analysed by LC-MS for identification. The lower level liver, egg, fat and skin/fat samples metabolites were tentatively identified by retention time match of the liver and excreta samples. Two compounds X763024 and X12313581 were tentatively assigned by HPLC retention time match with the reference standards, not confirmed by LC-MS of excreta and liver samples. The study results are shown in Tables 17-21.

Table 17 Total radioactive residue levels in the tissues, eggs and excreta from laying hens dosed with ^{14}C-fenpicoxamid for seven consecutive days at a level equivalent to 10 ppm diet

Matrix	Timing	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		mg/kg	% dose	mg/kg	% dose
Eggs	Day 1	0.001	0.001	0.001	0.001
	Day 2	0.003	0.002	0.003	0.001
	Day 3	0.003	0.003	0.004	0.002
	Day 4	0.004	0.003	0.004	0.003
	Day 5	0.005	0.004	0.007	0.005
	Day 6	0.006	0.004	0.006	0.004
	Day 7	0.007	0.002	0.006	0.002
Total accumulated		n/a	0.019	n/a	0.018
Excreta	Day 1	9.933	13.0	10.97	13.8
	Day 2	11.56	14.8	8.792	12.4
	Day 3	8.879	12.9	8.160	12.0
	Day 4	10.52	13.3	8.694	12.7
	Day 5	9.438	11.9	9.524	13.37
	Day 6	11.36	14.3	8.572	12.6
	Day 7	13.14	8.8	13.35	10.9
Total accumulated		n/a	88.7	n/a	87.8
Cage rinse	sacrifice	0.087	0.007	0.233	0.027
Leg muscle	sacrifice	0.009	0.020	0.006	0.013
Breast muscle	sacrifice	0.008	0.019	0.006	0.015
Liver	sacrifice	0.153	0.080	0.039	0.020
Fat	sacrifice	0.010	0.005	0.005	0.003
Skin with fat	sacrifice	0.016	0.023	0.008	0.010
Tissues, total		n/a	0.15	n/a	0.061
Total (All)		n/a	88.9	n/a	87.9%

n/a: not applicable

Table 18 Distribution of the radioactive residue in hen excreta, tissue and eggs following extraction

Sample	Fraction	^{14}C-PH-fenpicoxamid		^{14}C-PY-fenpicoxamid	
		% TRR	mg eq/kg	% TRR	mg eq/kg
Liver	Initial residue	100	0.153	100	0.039
	Acetonitrile/water	44.7	0.068	46.1	0.018
	PES	55.3	0.085	53.9	0.021
	Acid extract	16.6	0.025	37.3	0.015
	Base extract	27.5	0.042	na	na
	Analysis by HPLC[a]	88.8	0.135	83.4	0.033
	Unextracted	12.0	0.018	13.6	0.005
Fat	Initial residue	100	0.010	100	0.005
	Acetonitrile/water	83.7	0.009	na	na
	Unextracted in hexane	4.3	<0.001	na	na
	Analysis by HPLC[a]	83.7	0.009	na	na
Skin with fat	Initial residue	100	0.016	100	0.005
	Acetonitrile/water	95.3	0.016	na	na
	Unextracted in hexane	1.4	<0.001	na	na
	Analysis by HPLC[a]	95.3	0.016	na	na
Eggs (day 5)	Initial residue	100	0.005	100	0.006
	Acetonitrile/water	64.3	0.003	61.1	0.004
	PES	35.3	0.002	34.6	0.002
	Analysis by HPLC[a]	64.3	0.003	61.1	0.004
Excreta (day 5)	Initial residue	100	9.438	100	9.524
	Acetonitrile/water	93.5	8.824	75.8	7.217
	PES	10.0	0.942	20.5	1.948
	Analysis by HPLC[a]	93.5	8.824	75.8	7.217

[a] Sum of organic extracts and acid/base extracts when conducted

na: not analysed

Table 19 Distribution of residues in liver from hens dosed with [^{14}C]-fenpicoxamid and its metabolites as determined by HPLC

Residue component	RT (min)	MW	PH-Liver				PY-Liver	
			% TRR, Org. ext.[+]	% TRR, Acid ext.	% TRR, total[a]	mg/kg, total[b]	% TRR total[a]	mg/kg, total[b]
Initial residue					100	0.153	100	0.039
Total extracted			44.7	16.6	61.3	0.094	83.4	0.033
Fenpicoxamid	25.2	614.2	nd	nd	nd	nd	nd	nd
Polar	2-4	167.0	1.8	0.9	2.7	0.004	2.9	0.001
X12313581	4.0	167.0	-	-	-	-	0.7	<0.001
X12264475	5.8	256.1	-	-	-	-	0.9	<0.001
X696476	6.3	169.0	-	-	-	-	3.5	<0.001
X763024	7.5	532.2	-	-	-	-	3.0	0.001
X12399889	13.2	224.1	1.2	0.0	1.2	0.001	-	-
X12335723	13.5	356.1	-	-	-	-	1.1	<0.001
X129300	13.8-14.2	166.1	5.0	0.8	5.9	0.002	-	-
X12326349	14.5	462.2	2.4	1.1	3.5	0.004	2.9	0.001
X11963422/MW208 [*]	16.8-17.3	206/208	7.9	3.7	11.6	0.006	-	-
X696872	18.3	444.2	2.8	nd	2.8	0.003	1.4	0.002
X737057	18.7	532.2	0.7	nd	0.7	0.001	1.4	0.001
X12019520	19.7	188.1	0.7	0.6	1.2	0.001	-	-
X642188	23.8	514.2	nd	nd	nd	nd	nd	nd
Total identified					26.9	0.041	14.9	0.006
Total characterised					34.4	0.053	68.4	0.027
Total unextracted					39.5	0.060	13.6	0.005
Accountability[c]					101	0.154	97.0	0.038

a % TRR, total = organic extraction + acid extraction (PH- and PY-label liver were further extracted with 1N HCl and then 1N NaOH (only PH-label) following organic extraction)

+ For organic extract, both SPE load/wash and SPE eluant were analysed by HPLC. For acid extract, the SPE eluant (PH label) and SPE load/wash (PY-label) were analysed by HPLC. In PY-label acid extract (37.3% TRR, 0.015 mg eq/kg), no peak was shown in HPLC. For PH-label base extract (27.5% TRR, 0.042 mg eq/kg), selective fractions of SPE load/wash and SPE eluant were analysed by HPLC, where multiple components were shown at each ≤0.003 mg eq/kg.

b If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

c Accountability is sum of identified, characterised and unextracted

* Co-eluting metabolites

nd: not detected

X12313581 and X763024: tentatively assigned by HPLC retention time match, not confirmed by LC-MS

Of the total administered dose, 87.8–88.7% (both labels) was eliminated in the excreta. The PH- and PY-labelled eggs and edible tissues (muscle, fat, skin with fat and liver) accounted for about 0.018–0.019% and 0.061–0.15% of the administered dose, respectively.

Total residue levels (both labels) were 0.006–0.009 mg eq/kg in muscle, 0.005–0.010 mg eq/kg in fat, 0.008-0.016 mg eq/kg in skin with fat and 0.039-0.15 mg eq/kg in liver.

In eggs, total residue levels were in the range of 0.001-0.007 mg eq/kg in both labels. Residue levels in eggs from the PY-labelled hens were plateaued by day 5, while were not plateaued by day 7 for the PH-labelled hens.

Organic solvent (aqueous acetonitrile) extracted 61-64% TRR in eggs, 45-46% TRR in liver, 84% TRR in fat, 95% TRR in skin with fat and 76-94% TRR in excreta. In liver, acid and base extraction after organic extraction further released 17-37% TRR (both labels) and 28% TRR (PH-label only), respectively, remaining 12% TRR (0.018 mg eq/kg, PH-label) and 14% TRR (0.005 mg eq/kg, PY-label) in the PES.

Table 20 Distribution of residues in fat and skin with fat from hens dosed with [^{14}C]-fenpicoxamid and its metabolites as determined by HPLC

Residue component	RT (min)	MW	PH-Fat		PH-Skin with fat	
			% TRR[a]	mg/kg[b]	% TRR[a]	mg/kg[b]
Initial residue			100	0.010	100	0.016
Total extracted			83.7	0.009	95.3	0.016
Fenpicoxamid	25.2	614.2	nd	nd	5.2	<0.001
Polar	2-4	167.0	nd	nd	0.4	<0.001
X12313581	4.0	167.0	-	-	-	-
X12264475	5.8	256.1	-	-	-	-
X696476	6.3	169.0	-	-	-	-
X763024	7.5	532.2	-	-	-	-
X12399889	13.2	224.1	nd	nd	2.0	<0.001
X12335723	13.5	356.1	-	-	-	-
X129300	13.8-14.2	166.1	3.6	<0.001	14.1	<0.001
X12326349	14.5	462.2	nd	nd	2.9	<0.001
X11963422/MW208*	16.8-17.3	206/208	14.0	0.001	28.4	0.002
X696872	18.3	444.2	17.0	0.001	14.7	0.002
X737057	18.7	532.2	nd	nd	nd	nd
X12019520	19.7	188.1	0.5	<0.001	nd	0.000
X642188	23.8	514.2	0.7	<0.001	3.5	<0.001
Total identified			35.8	0.004	70.6	0.012
Total characterised			47.9	0.005	24.7	0.004
Total unextracted			4.3	<0.001	1.4	<0.001
Accountability[c]			88.1	0.009	96.7	0.016

[a] % TRR = organic extraction. The SPE eluant fraction (majority, found) was analysed by HPLC.

[b] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[c] Accountability is sum of identified, characterised and unextracted.

* Co-eluting metabolites

nd: not detected

Lower level liver, egg, fat and skin/fat samples metabolites were tentatively identified by HPLC retention time match of the liver and extra samples, except X12313581 and X763024 (characterised only by HPLC retention time match with the reference standards).

In liver (both labels), residue consisted of multiple low-level components with the largest component, X11963422/MW208 (11.6% TRR, 0.006 mg/kg in the PH-label). The MW208 (PH-met 208) with a proposed structure (Table 1) was a co-eluting component with X1196342. No other single component exceeded 5.9% TRR or 0.004 mg/kg. Parent was not observed.

Residue in fat (PH-label) consisted of multiple low-level components. The largest components X696872 and X11963422/MW208 accounted for 17.0% TRR (0.001 mg/kg) and 14.0% TRR (0.001 mg/kg), respectively. Other metabolites found at minor levels did not exceed 3.6% TRR (<0.001 mg/kg). Parent was not observed in fat.

Residue in skin with fat (PH-label) consisted of multiple low-level components. The largest components were X696872 and X11963422/MW208 accounting for 14.7% TRR (0.002 mg/kg) and 28.4% TRR (0.002 mg/kg), respectively. X129300 was found at a level of 14.1% TRR (<0.001 mg/kg). Other metabolites found at minor levels did not exceed 3.5% TRR (<0.001 mg/kg). Parent was detected but at a very low level (5.2% TRR, <0.001 mg/kg).

Eggs (PH-label) contained primarily 11963422/MW208 (32.2% TRR, <0.001 mg/kg) and other lower level metabolites (up to 6.4% TRR, at less than 0.001 mg/kg). PY-labelled eggs contained the largest polar components (26.7% TRR, 0.002 mg eq/kg) and X12264475 (13.9% TRR, <0.001 mg/kg) and a lower level metabolite (1.6% TRR, <0.001 mg/kg). No parent was found in eggs.

Table 21 Distribution of residues in day 5 eggs from hens dosed with [^{14}C]-fenpicoxamid and its metabolites as determined by HPLC

Residue component	RT (min)	MW	PH-Egg		PY-Egg	
			% TRR[a]	mg/kg [b]	% TRR[a]	mg/kg [b]
Initial residue			100	0.005	100	0.007
Total extracted			64.3	0.003	61.1	0.004
Fenpicoxamid	25.2	614.2	nd	nd	nd	nd
Polar	2-4	167.0	0.7	<0.001	26.7	0.002
X12313581	4.0	167.0	-	-	nd	nd
X12264475	5.8	256.1	-	-	13.9	<0.001
X696476	6.3	169.0	-	-	nd	nd
X763024	7.5	532.2	-	-	nd	nd
X12399889	13.2	224.1	nd	nd	-	-
X12335723	13.5	356.1	-	-	nd	nd
X129300	13.8-14.2	166.1	6.4	<0.001	-	-
X12326349	14.5	462.2	nd	nd	nd	nd
X11963422/MW208*	16.8-17.3	206/208	32.2	<0.001	-	
X696872	18.3	444.2	4.2	<0.001	1.6	<0.001
X737057	18.7	532.2	nd	nd	nd	nd
X12019520	19.7	188.1	nd	nd	-	-
X642188	23.8	514.2	nd	nd	nd	nd
Total identified			42.8	0.002	15.5	0.001
Total characterised			21.6	0.001	45.7	0.003
Total unextracted			35.3	0.002	34.6	0.002
Accountability[c]			99.7	0.005	95.7	0.006

[a] % TRR = organic extraction. The SPE eluant fraction (majority, found) was analysed by HPLC.

[b] If adjustment with molecular weight is possible, it means mg metabolite/kg and if not, fenpicoxamid equivalent/kg.

[c] Accountability is sum of identified, characterised and unextracted

* Co-eluting metabolites

nd: not detected

In edible tissues of hen (liver, fat, skin with fat, and eggs), metabolites found in at least one tissue were as follows: the phenyl and pyridine ring metabolites (X12326349, X696872, X737057 and X642188), phenyl-label metabolites (X11963422, PH-met 208, X12399889, X129300 and X12019520) and pyridine-label metabolites (X12313581, X12264475, X696476, X763024 and X12335723).

In excreta, parent accounted for 48-49% TRR in both labels. Most metabolites found in edible tissues were observed in excreta.

A proposed metabolic pathway is shown in Figure 5. In hens, residue comprised multiple low-level components at a level of less than 0.01 mg/kg. No conjugate compound was observed. The metabolic pathway on fenpicoxamid in hens was similar to that in lactating goat.

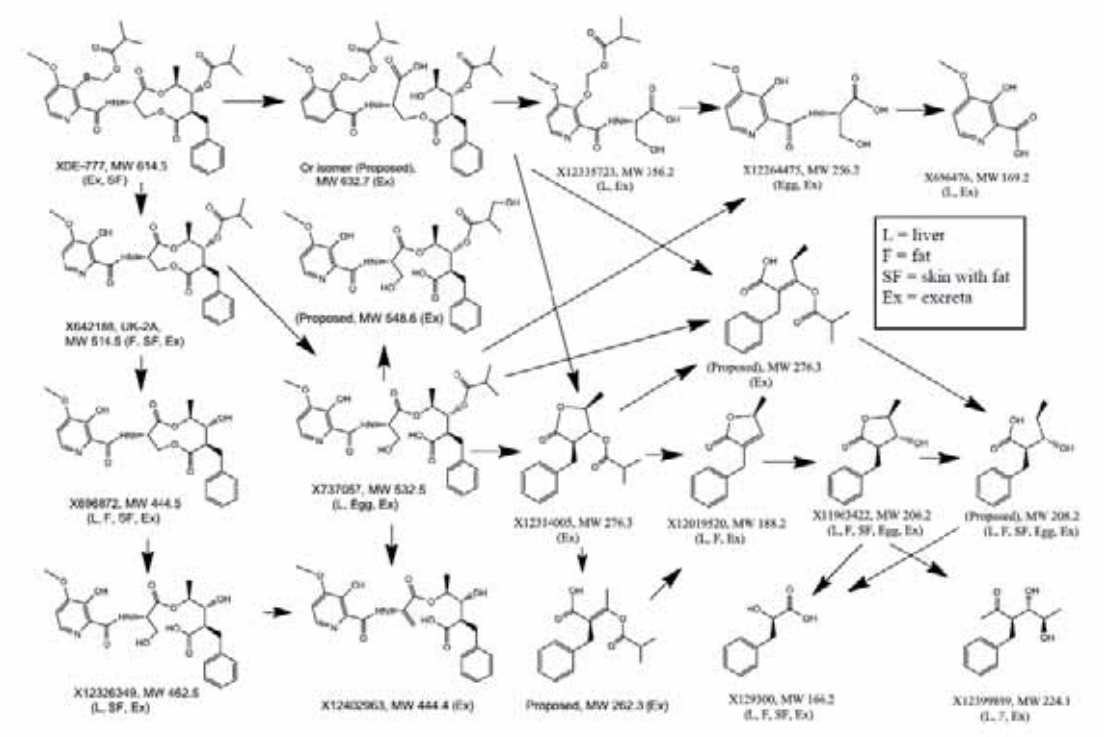


Figure 5 Proposed metabolic pathway in poultry

Environmental fate

The Meeting received information on hydrolysis, aqueous photolysis, aerobic degradation in soil and soil photolysis. Only hydrolysis is relevant for this evaluation. Additionally information on aerobic soil degradation and soil photolysis were included below.

Hydrolysis

The hydrolysis of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in the dark at 10, 25 and 35 °C in sterile aqueous buffered solutions at pH 4, 7 and 9 for up to 32 days at an initial concentration of 0.1 mg/L with 1% acetonitrile co-solvent [Yoder and Jackson, 2013, report 120538]. Duplicate samples of each radiolabel were analysed after 0, 1, 3 (4), 7, 14, 21 and 30 (31 or 32) days of incubation. Due to the rapid degradation of fenpicoxamid at higher pH values, additional early time points of less than 1 day were taken for pH 7 and pH 9 samples. Analysis was done using aqueous acetonitrile containing formic acid, LSC, HPLC, LC-MS and LC-MS/MS.

Material balance ranged from 89 to 108% of applied, with all ^{14}C residues detected in solution. Hydrolytic degradation of fenpicoxamid was rapid and extensive and was observed under all test conditions. Degradation rate increased with increased pH and temperature. DT_{50} values for fenpicoxamid (simple first-order degradation rates) were calculated: at pH 4, 34 days at 10 °C, 7.1 days at 25 °C and 3.2 days at 35 °C; at pH 7, 4.1 days at 10 °C, 0.92 days at 25 °C and 0.38 days at 35 °C; at pH 9, 0.35 days at 10 °C, 0.024 days at 25 °C and 0.016 days at 35 °C.

Hydrolysis products were formed primarily by the opening and cleavage of the bislactone ring. X12314005, X12019520, X12264475, X12335723, X12386481, X12433979, isomer of X11963422 (MW 206, pH 9), MW 632 (open-ring fenpicoxamid isomer, pH 4) were observed at levels of >10% AR at two consecutive time points. In addition, X12393285 and an unknown component (eluting at 29 minutes) were observed at levels of greater than 5% AR but less than 10% AR.

In a separate study, the hydrolysis of X642188 was tested in the dark at 10, 25, and 35 °C in sterile aqueous buffered solutions at pH 4, 7 and 9 until 90% had degraded, or for up to 30 days after dosing. The initial sample concentration was 0.4 mg/L. Analysis was done using aqueous acetonitrile containing formic acid and LC-MS/MS.

Hydrolytic degradation of X642188 was extensive and was observed under all test conditions. DT_{50} values of X642188 (simple first-order degradation rates) were calculated: at pH 4, 14.9 days at 10 °C, 4.5 days at 25 °C and 2.4 days at 35 °C; at pH 7, 1.3 days at 10 °C, 0.22 days at 25 °C and 0.075 days at 35 °C; at pH 9, 0.039 days at 10 °C, 0.0098 days at 25 °C and 0.0036 days at 35 °C.

Aqueous photolysis

A photolysis study was conducted for ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in sterile buffer at pH 7 (initial concentration, 0.10 mg/L) using xenon light [Blakeslee and Jackson, 2014, report 110422]. Samples were continuously irradiated at 25 °C for up to 33 days of summer sunlight at 40°N latitude. Aqueous acetonitrile was used for extraction of photolysis products from the acidified samples with formic acid. LSC, HPLC, LC-MS and LC-MS/MS were used for the determination of radioactivity, characterization and identification.

Material balance ranged from 92 to 105% of applied, with all ^{14}C-residues detected in solution. The expected DT_{50} and DT_{90} values for fenpicoxamid photolysis were 3.1 and 10.2 days, respectively (DT_{50} of fenpicoxamid in the dark controls, 1.3 days).

In both the irradiated samples and the dark control samples, degradation products found at concentrations greater than 10% AR at two or more consecutive time points, were X12314005, X12019520, X12433979, X12335723 and X12386481 (only in dark control). In the irradiated samples, a unique photolytic product, X12446477 (10-14% AR at 12 and 19 DAT), and multi-component polar photodegradates were observed.

Aerobic degradation in soil

The biotransformation of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in four soils [Hastings and Jackson, 2013, report 110492]. Soils treated at the rate of 25 µg ai/50 g soil (133 g ai/ha) were incubated for 120 days under aerobic conditions in the dark at 20 °C, and 50% moisture holding capacity. The four soils tested were RefSol 03-G clay loam (Germany), Site E-Farditch Farm clay loam (UK), Site K-Woodside Farm light clay (UK) and Site J3-Hareby House heavy clay (UK). Duplicate samples from each time point were collected and analysed.

In the kinetic study, soil samples treated with each radiolabel were taken after 0, 1, 2, 3, 7, 14, 30, 60, 90 and 120 days of incubation.

In addition to the kinetic study, a 1:1 mixture of both radiolabels was applied to four soils to measure the overall mineralisation via CO_2 collection in the caustic traps. Degradation parameters other than CO_2 produced were not measured. Samples were taken at 0, 7, 14, 30, 60 and 106 days of incubation.

The degradation of fenpicoxamid in sterile soils was investigated in PY-labelled loam soil, in order to differentiate between microbial and abiotic degradation. Samples were taken at 0, 3, 10, 30, 60, 90 and 120 days of incubation.

Soil samples were combusted and generated CO_2 was assayed by LSC. Extraction of residue from soil was done twice with 0.1% H_3PO_4 in acetonitrile/water (1:1, v/v) at room temperature. Where the total radioactivity (caustic trap plus organic solvent extract) was <95%, ASE using mildly acidic solutions was additionally conducted: twice, at 50 °C and 70 °C using acetonitrile/water (1:1, v/v) containing 0.1% phosphoric acid. Extracts were analysed by LSC, cleaned up by SPE and analysed by HPLC. LC-MS was used for identification of metabolite. Unextracted residue (kinetic study) was partitioned into fulvic acid, humic acid and humin.

In all studies, no decline in material balance was observed, representing *ca*. 100% of the applied radioactivity over time.

In the kinetic study (four soils), extracted residues decreased from 95-97% (day 0) to 25-71% (day 120) of the AR in PY-label and 94-98% (day 0) to 8-14% (day 120) of the AR in PH-label. Unextracted residue increased from 1-10% (day 0) to 20-69% (day 120) of the AR in PY-label and 1-7% (day 0) to 19-24% (day 120) of the AR in PH-label. The majority of the unextracted radioactivity was associated with the humin fraction indicating complete incorporation of the radioactivity into the soil structure. By end of study end, CO_2 was generated 5-23% AR in PY-label and 56-66% AR in PH-label.

In the mineralisation study (1:1 mixture of both labels), 31-40% AR (4 soils) was observed as CO_2 by day 106.

Parent decreased from 87-95% AR at day 0 to 2-6% AR at day 120 (day 2, <50% AR) in all tested soils (4 soils, both labels). A geometric mean DT_{50} and DT_{90} values of fenpicoxamid were 1.2 days (0.76-1.9 days) and 15.6 days (8.3-33.1 days), respectively.

Major metabolites were observed: six in the PY-label and three in the PH-label. Metabolites less than 5% AR were not analysed for identification.

In the PY-label (at two consecutive time points in at least one type of soil), X642188, X696872, X12264475 and X696476 were observed at >10% AR and X12313581 and X763024 at >5% AR. The maximum levels were: X642188 39.2% AR, X696872 17.2%AR, X12264475 37.1% AR, X763024 5.7% AR, X696476 45.1% AR and X12313581 11.1% AR.

In the PH-label (at two consecutive time points in least one type of soil), X642188, X696872 and X11963422 (at one time point) were observed at >10% AR. The maximum levels were: X642188 37.9% AR, X696872 17.2% AR and X11963422 11.1% AR.

Best fit DT_{50} and DT_{90} values of parent and its metabolites are shown in Table 22-23.

Table 22 Best fit DT_{50} and DT_{90} values of fenpicoxamid on four soils at 50% MHC moisture and 20 °C

Soil	DT_{50} (days)	DT_{90} (days)	r^2	Model
RefSol 03-G: loam (pH 5.6, 3.9% organic carbon)	1.4	24.9	0.997	DFOP
Site E-Farditch Farm: clay loam (pH 5.7, 3.1% organic carbon)	1.9	33.1	0.993	DFOP
Site K-Woodside Farm: light clay (pH 7.2, 4.4% organic carbon)	0.76	8.6	0.997	DFOP
Site J3-Hareby House: heavy clay (pH 7.7, 1.8% organic carbon)	1.2	8.3	0.997	DFOP
Range	0.76-1.9	8.3-33.1		
Arithmetic mean	1.3	18.7		
Geometric mean	1.2	15.6		

International texture class, loam, clay loam, light clay and heavy clay correspond to sandy loam, silt loam, clay loam and clay of USDA, respectively.

DFOP: double first-order in parallel

Table 23 Best fit DT_{50} and DT_{90} values of fenpicoxamid metabolites on four soils at 50% MHC moisture and 20 °C

Metabolites	DT_{50} (days)			DT_{90} (days)			r^2	Model
	Range	Arithmetic mean	Geometric mean	Range	Arithmetic mean	Geometric mean		
X642188	1.1-2.3	1.6	1.5	3.7-7.8	5.4	5.2	0.906-0.967	DFOP/SFO
X696872	1.3-3.0	2.5	2.3	4.3-10.1	8.2	7.8	0.611-0.759	DFOP/SFO
X12264475	2.4-47.5	15.6	7.8	8.1-157	51.6	25.8	0.529-0.924	DFOP/SFO
X12313581	23.1-71.2	42.2	38.2	76.8-236	140.1	126.7	0.800-0.930	DFOP/SFO
X119632	11.2			37.2				SFO top down

DFOP: double first-order in parallel

SFO: simple first-order

In moist sterile loam soil, fenpicoxamid (PY-label) decreased rapidly, however, at a slower rate when compared to microbially active soils. The aerobic soil best fit DT_{50} of fenpicoxamid in the sterile soil tested was 8.5 days. Mineralisation of parent was low ($^{14}CO_2$, 1% AR), compared to that ($^{14}CO_2$, 6% AR) in viable soil (PY-label). Levels of extracted (a total of room temp. and ASE extractions) and unextracted radioactivity were similar in the sterile and viable soils, with higher extraction in sterile soil by room temperature extraction during the course of study.

Metabolites found in viable soil (PY-label) were also found in sterile loam soil except X763024 (maximum 5.7% AR in viable soil). Metabolites X12313581, X12264475 and X642188 were at levels of >10% AR at two consecutive time points. X696476 and X696872 were found at up to 2.8% AR and 8.7% AR, respectively. A total of unidentified metabolites in each time point was observed up to 6.6% AR, none exceeded 5% AR at two consecutive time points.

A proposed metabolic pathway for fenpicoxamid in soil under aerobic conditions is shown in Figure 6.

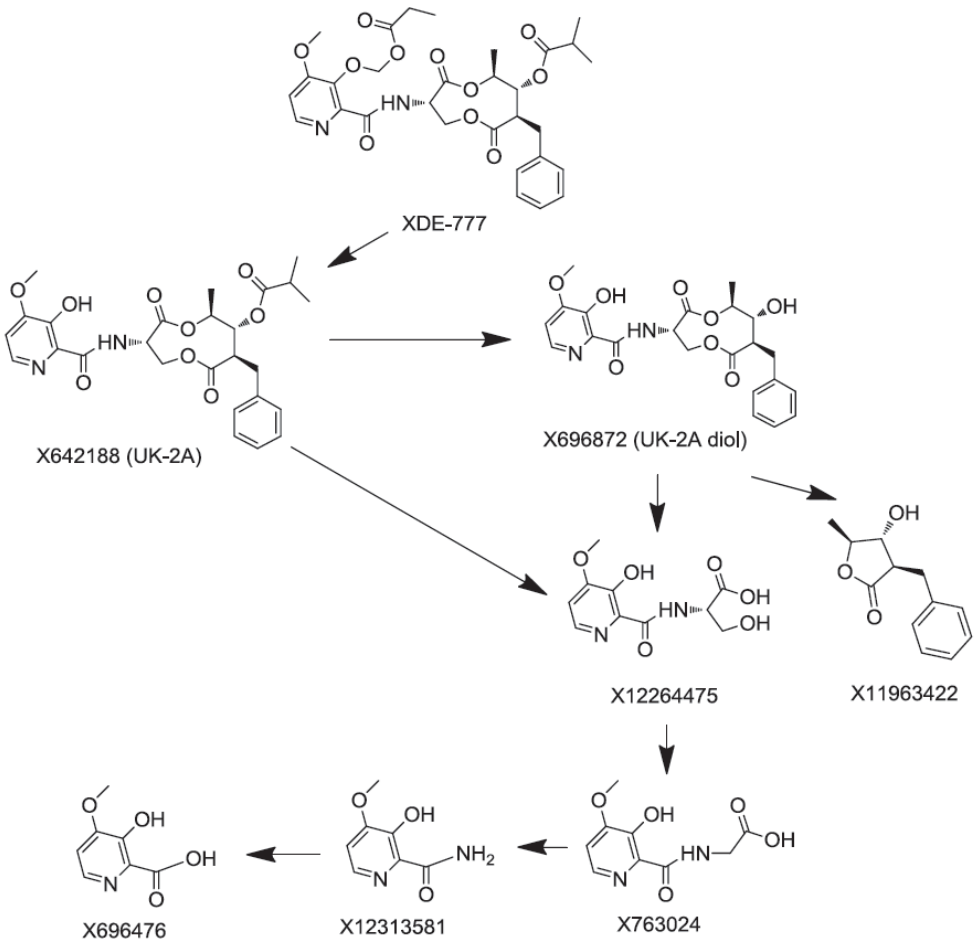


Figure 6 Proposed metabolic pathway for fenpicoxamid in soil under aerobic conditions

Soil photolysis

The phototransformation of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in a loam soil (International textural class), series M885 Refsol 03-G, (pH 6.3, organic carbon 4.9%) from Ebbinghof, Germany with continuous irradiation using a xenon lamp [Cooke, 2013, report 130655]. Samples applied with [^{14}C]-fenpicoxamid at the rate of 260 g ai/ha were incubated (20±2°C) for up to the equivalent of 30 days of summer sunlight at 40° N latitude (approximately 12 days of continuous irradiation). Treated dark control samples were maintained in the dark and at 50% of 0 bar. One set of irradiated soil samples was maintained moist (50% of 0 bar) as were the dark control samples. Another set of irradiated soil samples was kept under dry conditions. Samples were taken at 0, 1, 3, 7, 10 and 14 days after treatment. Radioactivity was determined by combustion/LSC.

Extraction for soil sample was done using acetonitrile/water (1:1, v/v) containing 0.1% H_3PO_4. The PH-label samples were extracted twice using the solvent at room temperature. For the PY-label samples, extraction was done using the same solvent, twice at room temperature and/or twice by accelerated solvent extraction procedure. Extracts were subjected to SPE clean-up and fenpicoxamid residues were analysed by HPLC. Confirmation of the transformation products was performed by LC-MS.

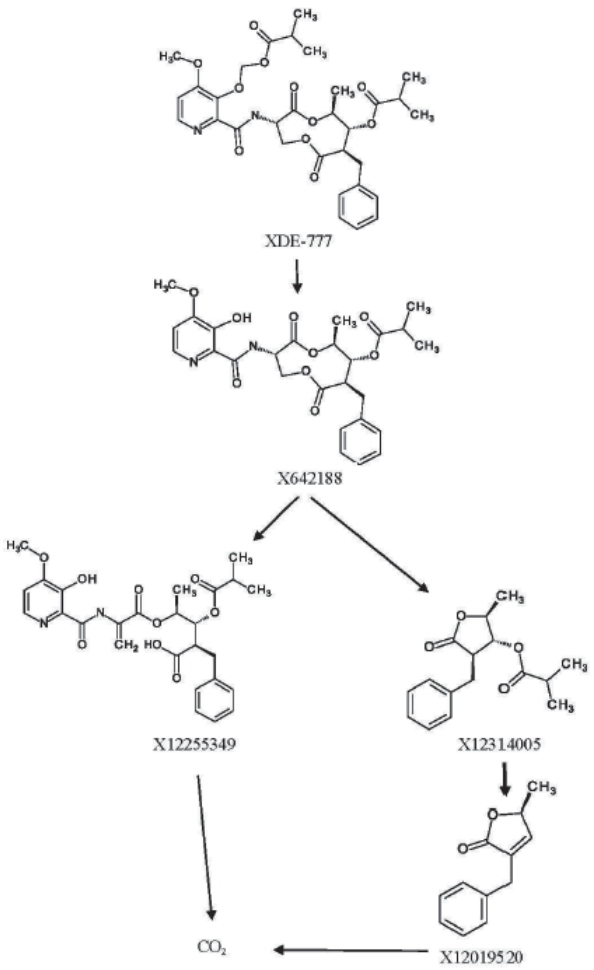


Figure 7 Proposed photolysis degradation pathway of fenpicoxamid in soil

In all samples, extracted radioactivity was 83-99% of the applied radioactivity and in volatile in caustic trap, 0.5-6.8% AR.

At test termination (both labels), parent was detected in levels of 13-17% AR in dark control soil (moist), 26-32% AR in irradiated moist soil and 64-76% AR in irradiated dry soil. DT_{50} and DT_{90} values of fenpicoxamid (days observed under continuous exposure to xenon light) were: 1.9 days and 20 days in dark control (moist), 7.0 days and 23 days in irradiated moist soil and 25 days and 84 days in irradiated dry soil (1 day = 2.5 days summer sunlight at 40° N latitude).

In both dark moist control and irradiated moist soils (both labels), X12399889, X11963422, X12019520, X12255349, X12314005, X642188, X12264475, and X696476 (only dark moist control) were observed. In irradiated dry soils, the all compounds (except X12399889 and X11963422) were observed, but at much lower levels. Only X12019520 was present at a higher level in irradiated soils (moist and dry) than dark moist control (maximum 1.5% AR), representing 8.6% AR in irradiated moist soil and 5.3% AR in irradiated dry soil.

In this study, phototransformation was not a major pathway of degradation of fenpicoxamid and X12019520 (known as hydrolysis product) was formed primarily by phototransformation. A proposed pathway of fenpicoxamid photodegradation is shown in Figure 7.

RESIDUE ANALYSIS

Analytical methods

Analytical methods have been developed for the determination of residues of fenpicoxamid and metabolites in plant and animal commodities. The provided information are summarised in Table 24.

Table 24 Summary of analytical methods developed for plant and animal commodities

Matrix	Analyte	Detection system	LOQ	Study No.
Plant	Fenpicoxamid, X642188	MS/MS	Wheat (grain, straw, bran, flour and bread), cabbage, lettuce, grapefruit, orange, oilseed and olives: 0.01 mg/kg	120615 (2012): method in the study 120615 (monitoring)
	Fenpicoxamid, X642188	MS/MS	Wheat grain and lettuce: 0.01 mg/kg	120951 (2013): ILV of method in the study 120615
	Fenpicoxamid, X642188	MS/MS	Banana: 0.01 mg/kg	131080 (2015): validation of method in the study 120615, included in residue trial study
Animal	Fenpicoxamid, X642188	MS/MS	Bovine (meat, fat and milk) and poultry eggs: 0.01 mg/kg	120998 (2013): method in the study 120988 (multi-residue method)
	Fenpicoxamid, X642188	MS/MS	Bovine (muscle, fat and milk) and poultry eggs: 0.01 mg/kg	130114 (2013): ILV of method in the study 120998
	Fenpicoxamid, X12326349	MS/MS	Bovine (muscle, fat, liver and milk) and poultry eggs: 0.01 mg/kg	131027 (2014): method in the study 131027
	Fenpicoxamid, X12326349	MS/MS	Bovine (fat, liver and milk) and poultry eggs: 0.01 mg/kg	130712 (2014): ILV of method in the study 131027

Plant commodities

Method in the study 120615 (monitoring)

Residues of fenpicoxamid and its metabolite X642188 were extracted with an acetonitrile/water (90:10, v/v) solution from plant samples: high starch (wheat grain, straw, bran, flour and bread), high water (lettuce and cabbage), high acid (orange and grapefruit) and high oil (oil seed and olive oil) crops. After extraction, extract was diluted with an acetonitrile/water (90:10, v/v) solution containing 0.1% formic acid. Determination of residues was performed by LC/MS/MS, monitoring two MS/MS transitions characteristic of each analyte: m/z 615→239 (quantitation) and m/z 615→515 (confirmation) for fenpicoxamid, and m/z 515→239 (quantitation) and m/z 515→142 (confirmation) for X642188 [Watson, 2012, report 120615].

The method was highly selective for both the quantitation and confirmation of fenpicoxamid and X642188. Matrix effects for each analyte were less than 20%. The linearity of the detector response covered a working range of 0.0075-1 ng/mL (n = 7, r = ≥0.99 for each analyte). The mean recoveries for each matrix were 87-110% and 95-108% at fortification levels of at 0.01 mg/kg and 1.0 mg/kg, respectively, with the RSDs of all below 15%. The LOQ was 0.01 mg/kg for each analyte and matrix. (Table 25).

Independent laboratory validation (ILV) of method in the study 120615 (monitoring)

Independent laboratory validation on the method in the study 120615 was conducted applying the same analytical procedure [Chambers and Jarett, 2013, report 120951]. Fenpicoxamid and X642188 each was fortified at levels of 0.01 and 1.0 mg/kg in wheat grain and lettuce. Specificity, linearity, recovery and repeatability were all acceptable. The LOQ was 0.01 mg/kg for each analyte and matrix (Table 26).

Table 25 Validation of method in the study 120615: analysis of fenpicoxamid and X642188 in plant commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Cabbage	Fenpicoxamid 615→239	0.01	6	92 – 111	99	7.1
		1.0	6	98 – 104	101	2.3
	Fenpicoxamid 615→515	0.01	6	95 – 111	104	5.4
		1.0	6	93 – 108	101	6.3
	X642188 515→239	0.01	6	91 – 109	99	6.9
		1.0	6	100 – 109	104	3.4
	X642188 515→124	0.01	6	87 – 107	98	8.3
		1.0	6	95 – 107	103	4.5
Lettuce	Fenpicoxamid 615→239	0.01	6	98 – 113	105	5.2
		1.0	6	90 - 100	96	3.6
	Fenpicoxamid 615→515	0.01	6	99 - 112	104	5.3
		1.0	6	96 - 103	98	2.5
	X642188 515→239	0.01	6	85 - 113	102	11.2
		1.0	6	86 - 106	97	9.4
	X642188 515→124	0.01	6	80 - 114	98	14.0
		1.0	6	87 - 104	96	7.9
Wheat grain	Fenpicoxamid	0.01	6	97 - 108	101	4.6

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
	615→239	1.0	6	94 - 105	100	3.6
	Fenpicoxamid	0.01	6	97 - 110	103	4.4
	615→515	1.0	6	98 - 103	101	1.8
	X642188	0.01	6	93 - 105	101	4.6
	515→239	1.0	6	104 - 112	108	3.3
	X642188	0.01	6	97 - 103	101	2.8
	515→124	1.0	6	104 - 112	108	3.0
Wheat straw	Fenpicoxamid	0.01	6	97 - 112	104	6.5
	615→239	1.0	6	101 - 108	104	2.6
	Fenpicoxamid	0.01	6	96 - 108	104	4.9
	615→515	1.0	6	99 - 104	103	1.8
	X642188	0.01	6	102 - 106	104	1.6
	515→239	1.0	6	99 - 113	108	5.2
	X642188	0.01	6	99 - 106	102	2.5
	515→124	1.0	6	98 - 113	107	5.8
Oilseed	Fenpicoxamid	0.01	6	100 - 110	105	3.7
	615→239	1.0	6	94 - 107	100	4.4
	Fenpicoxamid	0.01	6	100 - 112	106	4.4
	615→515	1.0	6	100 - 104	102	1.2
	X642188	0.01	6	98 - 110	106	4.2
	515→239	1.0	6	100 - 109	106	3.3
	X642188	0.01	6	99 - 113	104	5.4
	515→124	1.0	6	102 - 111	107	3.6
Olives	Fenpicoxamid	0.01	6	95 - 106	100	4.1
	615→239	1.0	6	96 - 105	101	2.9
	Fenpicoxamid	0.01	6	95 - 106	100	4.3
	615→515	1.0	6	96 - 103	102	2.7
	X642188	0.01	6	92 - 102	97	3.5
	515→239	1.0	6	97 - 108	103	5.5
	X642188	0.01	6	93 - 105	98	4.5
	515→124	1.0	6	94 - 109	103	5.9
Grapefruit	Fenpicoxamid	0.01	6	97 - 103	99	2.4
	615→239	1.0	6	94 - 100	98	2.3
	Fenpicoxamid	0.01	6	91 - 104	97	4.9
	615→515	1.0	6	91 - 102	98	4.1
	X642188	0.01	6	101 - 109	105	3.1
	515→239	1.0	6	106 - 110	109	1.4
	X642188	0.01	6	100 - 107	103	2.5
	515→124	1.0	6	106 - 109	108	1.4
Orange	Fenpicoxamid	0.01	6	100 - 107	104	2.3
	615→239	1.0	6	91 - 100	95	3.8
	Fenpicoxamid	0.01	6	84 - 108	100	8.4
	615→515	1.0	6	92 - 101	97	3.1
	X642188	0.01	6	96 - 107	100	4.0
	515→239	1.0	6	104 - 112	108	2.9
	X642188	0.01	6	91 - 118	102	10.0
	515→124	1.0	6	100 - 112	107	4.0
Bran	Fenpicoxamid	0.01	6	102 - 114	110	4.3
	615→239	1.0	6	101 - 107	105	2.7
	Fenpicoxamid	0.01	6	103 - 112	109	2.9
	615→515	1.0	6	100 - 105	103	1.8
	X642188	0.01	6	92 - 110	102	8.4
	515→239	1.0	6	96 - 109	104	4.6
	X642188	0.01	6	90 - 114	102	7.6
	515→124	1.0	6	96 - 110	103	5.6
Flour	Fenpicoxamid	0.01	6	98 - 109	104	4.4
	615→239	1.0	6	100 - 111	105	3.6
	Fenpicoxamid	0.01	6	99 - 115	107	5.6
	615→515	1.0	6	99 - 110	104	4.1
	X642188	0.01	6	82 - 113	97	13.8
	515→239	1.0	6	85 - 111	98	13.5

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
	X642188 515→124	0.01	6	83 - 114	100	14.1
		1.0	6	82 - 113	97	14.5
Bread	Fenpicoxamid 615→239	0.01	6	94 - 106	100	5.5
		1.0	6	97 - 108	102	3.6
	Fenpicoxamid 615→515	0.01	6	93 - 103	99	4.1
		1.0	6	97 - 108	103	3.6
	X642188 515→239	0.01	6	79 - 95	87	7.8
		1.0	6	85 - 109	98	12.5
	X642188 515→124	0.01	6	80 - 100	89	9.2
		1.0	6	83 - 108	97	12.6

Table 26 ILV of method in the study 120615: analysis of fenpicoxamid and X642188 in plant commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Wheat grain	Fenpicoxamid 615→239	0.01	5	82-100	91	7.8
		1.0	5	89-94	91	2.2
	Fenpicoxamid 615→515	0.01	5	94-114	104	7.0
		1.0	5	89-93	91	1.9
	X642188 515→239	0.01	5	90-107	97	6.6
		1.0	5	95-100	97	1.9
	X642188 515→124	0.01	5	79-111	100	12.5
		1.0	5	88-93	91	2.0
Lettuce	Fenpicoxamid 615→239	0.01	5	79-110	92	14.3
		1.0	5	86-92	90	2.7
	Fenpicoxamid 615→515	0.01	5	94-110	103	5.7
		1.0	5	86-91	89	2.1
	X642188 515→239	0.01	5	91-104	96	5.1
		1.0	5	90-92	91	1.3
	X642188 515→124	0.01	5	101-107	103	2.3
		1.0	5	81-87	84	2.7

Table 27 Validation of method in the study 120615 on banana: analysis of fenpicoxamid and X642188

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Banana whole fruit	Fenpicoxamid	0.01	5	89 – 96	93	3.3
		0.1	5	95 – 99	97	1.6
		1	3	95 – 96	95	0.6
		10	3	91 – 94	93	1.6
	X642188	0.01	5	81 – 92	87	6.6
		0.1	5	91 – 95	92	1.8
		1	3	93 – 94	93	0.7
		10	3	91 – 92	92	0.4
Banana pulp	Fenpicoxamid	0.01	5	94 – 98	96	1.9
		0.1	5	103 – 105	104	0.8
		1	3	95 – 99	97	2.2
		10	3	95 – 100	97	3.0
	X642188	0.01	5	80 – 88	85	3.8
		0.1	5	96 – 98	97	0.9
		1	3	92 – 93	93	0.6
		10	3	92 – 96	94	2.2
Banana peel	Fenpicoxamid	0.01	5	93 – 100	96	3.4
		0.1	5	104 – 107	106	1.2
		1	3	97 – 100	98	1.6
		10	3	96 – 98	97	1.2
	X642188	0.01	5	80 – 89	85	4.1
		0.1	5	96 – 99	98	1.2
		1	3	94 – 96	95	1.1
		10	3	93 – 97	95	2.2

Validation of method in the study 120615 in a residue trial study on banana

Analytical method in the study 120615 was validated in a residue trial study on banana [Hampton, 2015, report 131080]. Extraction procedure was the same with minor modifications. In the determination of residues, one transition per analyte was monitored: m/z 615→239 for fenpicoxamid and m/z 515→239 for X642188. Recovery was tested at fortification levels of 0.01, 0.1, 1, and 10 mg/kg in whole banana, peel and pulp. Recoveries were in the range of 80-107% (RSD, ≤6.6%) in all tests. The LOQ value was 0.01 mg/kg for each analyte and matrix (Table 27).

Animal commodities

Method in the study 120998 (multi-residue method)

Residues of fenpicoxamid and its metabolite X642188 were extracted with acetonitrile from the matrices of animal origin (bovine meat, liver, fat, milk and poultry eggs). Samples of bovine fat were melted completely with the acetonitrile at 60 °C. QuEChERS was used for sample preparation, and diluted with an acetonitrile/water (50:50, v/v) solution containing 0.1% formic acid for determination by LC-MS/MS, monitoring two MS/MS transitions the same with the study 120615 [Lindner and Giesau, 2013, report 120998].

The method was highly selective for both the quantitation and confirmation of fenpicoxamid and X642188. Matrix effects for each analyte were less than 19%. The linearity of the detector response covered a working range of 0.075-5 ng/mL (n = 7, r = ≥0.99 for each analyte). The mean recoveries for each matrix (except fenpicoxamid in liver) were 89-107% and 83-103% at fortification levels of 0.01 and 0.1 mg/kg, respectively with the RSDs of all below 12%. The LOQ was 0.01 mg/kg for each analyte and matrix, except for fenpicoxamid in liver. The mean recovery of fenpicoxamid in bovine liver was 0%. The reason was due to spiking both analytes jointly, a quantitative decomposition of fenpicoxamid into its metabolite X642188 (Table 28).

Table 28 Validation of method in the study 120998: analysis of fenpicoxamid and X642188 in animal commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Bovine milk	Fenpicoxamid 615→239	0.01	5	98 – 106	102	3.3
		0.1	5	94 - 101	97	2.6
	Fenpicoxamid 615→515	0.01	5	98 - 104	102	2.8
		0.1	5	93 - 100	96	2.6
	X642188 515→239	0.01	5	88 - 95	91	3.4
		0.1	5	67 - 93	83	12
	X642188 515→142	0.01	5	85 - 93	89	4.0
		0.1	5	67 - 96	83	13
Poultry eggs	Fenpicoxamid 615→239	0.01	5	95 - 99	98	1.7
		0.1	5	98 - 101	99	1.1
	Fenpicoxamid 615→515	0.01	5	96 - 100	98	1.7
		0.1	5	97 - 102	99	1.9
	X642188 515→239	0.01	5	93 - 105	100	4.6
		0.1	5	90 - 95	93	2.2
	X642188 515→142	0.01	5	94 - 104	99	4.6
		0.1	5	91 - 94	92	1.5
Bovine meat	Fenpicoxamid 615→239	0.01	5	87 - 90	89	1.5
		0.1	5	91 - 95	93	1.6
	Fenpicoxamid 615→515	0.01	5	89 -90	90	0.6
		0.1	5	92 - 96	94	1.6
	X642188 515→239	0.01	5	89 - 97	94	3.6
		0.1	5	77 - 89	84	5.3
	X642188 515→142	0.01	5	91 - 98	96	3.5
		0.1	5	75 - 88	83	5.9
Bovine fat	Fenpicoxamid 615→239	0.01	5	99 - 102	100	1.1
		0.1	5	102 - 104	103	0.7
	Fenpicoxamid 615→515	0.01	5	100 - 104	102	1.8
		0.1	5	102 - 104	103	0.7
	X642188 515→239	0.01	5	87 - 91	89	2.0
		0.1	5	90 - 94	92	2.0
	X642188 515→142	0.01	5	85 - 96	92	4.4
		0.1	5	89 - 94	91	2.3
Bovine liver	Fenpicoxamid [a] 615→239	0.01	5	0	0	na
		0.1	5	0 - 1	0	0.4
	Fenpicoxamid [a] 615→515	0.01	5	0	0	na
		0.1	5	0 - 1	0	0.5

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
	X642188[b]	0.01	5	95 - 109	105	2.0
	515→239	0.1	5	83 - 89	85	2.6
	X642188[b]	0.01	5	100 - 110	107	1.6
	515→142	0.1	5	82 - 88	84	2.9

[a] Both analytes were spiked jointly, a quantitative decomposition of fenpicoxamid into its metabolite X642188 was considered to be the probable explanation. In the same fortification experiments the recoveries of X642188 were about 200% (data not shown).

[b] X642188 was spiked separately from fenpicoxamid.

na: not applicable

ILV of method in the study 120998 (multi-residue method)

Independent Laboratory Validation on the method in the study 120998 was conducted applying the same analytical procedure [Amic, 2013, report 130114]. Fenpicoxamid and X642188 each was spiked in bovine samples (milk, muscle, fat and liver) and poultry eggs at fortification levels of 0.01 and 0.1 mg/kg. Specificity, linearity, recovery and repeatability were all acceptable. The LOQ was 0.01 mg/kg for each analyte and matrix, except fenpicoxamid in bovine liver due to the same reason as the study 120998 (Table 29).

Table 29 ILV of method in the study 120998 (multi-residue method): analysis of fenpicoxamid and X642188 in animal commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Bovine milk	Fenpicoxamid	0.01	5	73-79	77	3
	615→239	0.1	5	63, 66, 73-78	71	9
	Fenpicoxamid	0.01	5	73-79	76	3
	615→515	0.1	5	64, 66, 72-78	72	9
	X642188	0.01	5	81-89	84	4
	515→239	0.1	5	65, 78-92	83	14
	X642188	0.01	5	73-102	87	12
	515→142	0.1	5	68, 81-97	87	14
Poultry egg	Fenpicoxamid	0.01	5	96-99	98	1
	615→239	0.1	5	97-100	98	1
	Fenpicoxamid	0.01	5	95-104	100	4
	615→515	0.1	5	96-102	100	2
	X642188	0.01	5	97-101	99	2
	515→239	0.1	5	99-102	100	1
	X642188	0.01	5	90-102	94	6
	515→142	0.1	5	96-99	98	2
Bovine muscle	Fenpicoxamid	0.01	5	87-97	92	4
	615→239	0.1	5	88-94	90	3
	Fenpicoxamid	0.01	5	89-101	95	5
	615→515	0.1	5	89-97	91	4
	X642188	0.01	5	101-105	103	2
	515→239	0.1	5	99-106	102	3
	X642188	0.01	5	101-107	104	2
	515→142	0.1	5	87-98	94	5
Bovine fat	Fenpicoxamid	0.01	5	55, 73-91	76	18
	615→239	0.1	5	97-108	105	6
	Fenpicoxamid	0.01	5	55, 72-92	78	19
	615→515	0.1	5	99-114	106	6
	X642188	0.01	5	70-90	82	10
	515→239	0.1	5	110-116	111	4
	X642188	0.01	5	75-94	83	9
	515→142	0.1	5	104-114	110	3
Bovine liver	Fenpicoxamid [a]	0.01	5	2-8	na	na
	615→239	0.1	5	2-29	na	na
	Fenpicoxamid [a]	0.01	5	1-6	na	na
	615→515	0.1	5	2-29	na	na
	X642188[b]	0.01	5	103-107	104	1
	515→239	0.1	5	99-107	103	3
	X642188[b]	0.01	5	102-113	108	5
	515→142	0.1	5	99-108	103	4

[a] Both analytes were spiked jointly, a quantitative decomposition of fenpicoxamid into its metabolite X642188 was considered to be the probable explanation.

[b]X642188 was spiked separately from fenpicoxamid.

na: not applicable

Method in the study 131027

Fenpicoxamid and its metabolite X12326349 were extracted with a mixture solution of acetonitrile/water/phosphoric acid (75:25:0.1, v/v/v) from animal matrices [Garcia-Alix, 2014, report 131027]. Extract from bovine samples (milk, muscle, fat and liver) and poultry eggs was dissolved in acetonitrile/water/formic acid (50:50:0.1, v/v/v) for determination by LC-MS/MS, monitoring two MS/MS transitions characteristic of each analyte: m/z 615→239 (quantitation) and m/z 615→515 (confirmation) for fenpicoxamid, and m/z 463→257 (quantitation) and m/z 463→152 (confirmation) for X12326349. Residues were quantified against matrix-matched standard. The method was highly selective for both the quantitation and confirmation of fenpicoxamid and X12326349. The linearity of the detector response covered a working range of 0.0375-2.5 ng/mL (n = 8, r = ≥0.99). The mean recoveries for each matrix (bovine milk, muscle, fat and liver) were 60-120% and 70-120% at fortification levels of 0.01 mg/kg and 0.5 mg/kg, respectively, with the RSDs of all below 20%. The LOQs was 0.01 mg/kg for each analyte and matrix (Table 30).

Table 30 Validation of method in the study 131027: analysis of fenpicoxamid and X12326349 in animal commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Bovine milk	Fenpicoxamid 615→239	0.01	5	93-108	99	5.8
		0.5	5	95-102	99	3.0
	Fenpicoxamid 615→515	0.01	5	95-108	102	5.0
		0.5	5	90-100	96	3.8
	X12326349 463→257	0.01	5	75-85	80	5.7
		0.5	5	78-90	84	6.4
	X12326349 463→152	0.01	5	73-93	82	9.9
		0.5	5	76-88	82	7.0
Poultry eggs	Fenpicoxamid 615→239	0.01	5	85-96	92	6.9
		0.5	5	84-92	87	3.5
	Fenpicoxamid 615→515	0.01	5	84-106	92	9.5
		0.5	5	78-90	85	5.8
	X12326349 463→257	0.01	5	81-94	88	6.6
		0.5	5	76-88	83	6.5
	X12326349 463→152	0.01	5	79-93	86	7.3
		0.5	5	77-91	83	7.6
Bovine muscle	Fenpicoxamid 615→239	0.01	5	82-94	87	6.0
		0.5	5	83-90	86	3.5
	Fenpicoxamid 615→515	0.01	5	89-100	93	5.5
		0.5	5	73-90	82	7.6
	X12326349 463→257	0.01	5	72-79	76	3.5
		0.5	5	76-87	82	4.9
	X12326349 463→152	0.01	5	73-81	79	4.1
		0.5	5	80-86	83	2.8
Bovine fat	Fenpicoxamid 615→239	0.01	5	81-97	88	7.4
		0.5	5	81-96	88	6.5
	Fenpicoxamid 615→515	0.01	5	83-98	90	6.4
		0.5	5	81-90	84	4.0
	X12326349 463→257	0.01	5	74-82	79	4.2
		0.5	5	75-84	80	4.5
	X12326349 463→152	0.01	5	77-88	82	5.4
		0.5	5	79-86	82	3.4
Bovine liver	Fenpicoxamid 615→239	0.01	5	71-84	80	6.8
		0.5	5	82-95	89	5.5
	Fenpicoxamid 615→515	0.01	5	70-78	74	3.1
		0.5	5	76-88	85	5.9
	X12326349 463→257	0.01	5	74-84	76	5.7
		0.5	5	76-79	77	1.7
	X12326349 463→152	0.01	5	77-86	80	4.2
		0.5	5	71-81	75	5.0

ILV of method in the study 131027

Independent laboratory validation on the method in the study 131027 was conducted applying the same analytical procedure [Lindner and Grewe, 2014, report 130712]. Fenpicoxamid and X12326349 each was fortified in bovine samples (milk, fat and liver) and poultry eggs at fortification levels of 0.01 and 0.1 mg/kg. Specificity, linearity, recovery and repeatability were all acceptable. The LOQ was 0.01 mg/kg for each analyte and matrix (Table 31).

Table 31 ILV of method in the study 131027: analysis of fenpicoxamid and X12326349 in animal commodities

Commodity	Analyte	Fortification level (mg/kg)	n	Range of recovery (%)	Mean recovery (%)	RSD (%)
Bovine milk	Fenpicoxamid 615→239	0.01	5	88-98	91	4.2
		0.1	5	73-96	81	12
	Fenpicoxamid 615→515	0.01	5	91-94	92	1.4
		0.1	5	75-94	83	9.3
	X12326349 463→257	0.01	5	72-87	78	7.8
		0.1	5	76-83	79	3.5
	X12326349 463→152	0.01	5	73-88	80	8.7
		0.1	5	74-83	80	4.2
Poultry eggs	Fenpicoxamid 615→239	0.01	5	81-97	88	6.6
		0.1	5	75-84	80	5.0
	Fenpicoxamid 615→515	0.01	5	82-87	84	2.5
		0.1	5	82-87	84	2.5
	X12326349 463→257	0.01	5	60-87	75	13
		0.1	5	67-74	70	3.9
	X12326349 463→152	0.01	5	72-90	78	9.2
		0.1	5	66-74	70	4.1
Bovine liver	Fenpicoxamid 615→239	0.01	5	65-71	70	6.0
		0.1	5	69-71	70	1.9
	Fenpicoxamid 615→515	0.01	5	68-72	70	2.4
		0.1	5	70-73	72	1.7
	X12326349 463→257	0.01	5	81-126	97	19
		0.1	5	93-109	102	5.8
	X12326349 463→152	0.01	5	80-95	85	7.5
		0.1	5	86-106	100	8.6
Bovine fat	Fenpicoxamid 615→239	0.01	5	87-111	96	9.6
		0.1	5	91-98	93	3.0
	Fenpicoxamid 615→515	0.01	5	89-104	94	6.1
		0.1	5	87-97	90	4.7
	X12326349 463→257	0.01	5	66-86	74	10
		0.1	5	69-86	80	8.4
	X12326349 463→152	0.01	5	61-85	73	13
		0.1	5	82-87	84	2.8

Stability of pesticide residues in stored analytical samples

A storage stability study was conducted with fenpicoxamid and its metabolite X642188 in banana (whole fruit) and banana (pulp) [Lindner, 2016, report 131079]. Banana samples were separately fortified with aliquots of fenpicoxamid and X642188 at the level of 0.1 mg/kg, and then stored frozen at -18 °C for 1, 3, 6, 12 and 24 months. Residue analysis was performed according to the method in study 120615, validated with banana matrices with LOQ of 0.01 mg/kg for each analyte, as shown in Table 27.

Fresh recoveries were within the acceptable range of 70-110%. No significant degradation was observed on subsequent storage periods when considering corresponding fresh recoveries. Therefore, the residues of fenpicoxamid and X642188 were shown to be stable for at least 24 months in banana whole fruit and pulp when stored at -18°C.

Table 32 Stability of fenpicoxamid residues in crops following storage at -18 °C± 2 °C

Commodity	Level (mg/kg)	Storage interval (months)	% Procedural recovery (mean, n = 2[a])	Residues after storage (mg/kg)		Recovery	
				Individual values	Mean	% Spiking level	% Day 0
Banana whole fruit	0.1	0 day	100	0.099, 0.101, 0.099	0.100	100	-
		1	74	0.067, 0.069, 0.068	0.068	68	68
		3	89	0.088, 0.081, 0.081	0.083	83	83

Commodity	Level (mg/kg)	Storage interval (months)	% Procedural recovery (mean, n = 2[a])	Residues after storage (mg/kg)		Recovery	
				Individual values	Mean	% Spiking level	% Day 0
		6	79	0.080, 0.077, 0.079	0.079	79	79
		12	95	0.100, 0.094, 0.097	0.097	97	97
		24	76	0.072, 0.085, 0.083	0.080	80	80
Banana pulp	0.1	0 day	98	0.100, 0.098, 0.096	0.098	98	-
		1	90	0.071, 0.080, 0.077	0.076	76	78
		3	95	0.099, 0.088, 0.096	0.094	94	96
		6	93	0.086, 0.081, 0.086	0.084	84	86
		12	92	0.086, 0.087, 0.092	0.088	88	90
		24	77	0.079, 0.073, 0.074	0.075	75	77

[a] except 0 day (n = 3)

Table 33 Stability of X642188 residues in crops following storage at -18 °C± 2 °C

Commodity	Level (mg/kg)	Storage interval (months)	% Procedural recovery (mean, n = 2[a])	Residues after storage (mg/kg)		Recovery	
				Individual values	Mean	% Spiking level	% Day 0
Banana whole fruit	0.1	0 day	88	0.089, 0.087, 0.088	0.088	88	-
		1	80	0.077, 0.089, 0.091	0.086	86	98
		3	94	0.088, 0.084, 0.087	0.086	86	98
		6	73	0.064, 0.073, 0.072	0.070	70	80
		12	92	0.092, 0.093, 0.094	0.093	93	106
		24	96	0.075, 0.080, 0.082	0.079	79	90
Banana pulp	0.1	0 day	82	0.086, 0.081, 0.080	0.082	82	-
		1	88	0.086, 0.088, 0.087	0.087	87	106
		3	110	0.110, 0.108, 0.105	0.108	108	132
		6	74	0.070, 0.067, 0.070	0.069	69	84
		12	97	0.092, 0.093, 0.081	0.089	89	109
		24	93	0.078, 0.084, 0.083	0.082	82	100

[a] n = 3 at 0 day

USE PATTERN

Fenpicoxamid is a contact fungicide, translaminar and residual, used in agriculture for foliar diseases in crops. The Meeting received information on registered use on banana, as shown in Table 34.

Table 34 Registered use of fenpicoxamid on banana

Region	Formation	Appl. method	Max No. of appl.	App. Interval (days)	Application		PHI (days)
					kg ai/ha	g ai/hL	
Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panama	Suspension concentrate (GF-2925 13 SC)	Aerial only [a] (plane or helicopter)	3	8	0.050	143- 417[b]	No restriction

GF-2925 13 SC (131 g ai/L) is used in emulsion only, adding oil and emulsifier.

[a] Terrestrial equipment is not recommended.

[b] Calculated based on the typical water volume for use in bananas, 12-35 L/ha.

RESIDUES RESULTING FROM SUPERVISED TRIALS ON CROPS

Supervised residue trial data on banana was provided.

CODEX Group	Commodity	Table No.
006 Assorted tropical and sub-tropical fruits - inedible peel	FI 0327 Bananas	35

Twelve residue trials on banana were conducted in Central and South America during the 2014 and 2015 growing seasons: Guatemala (four trials), Ecuador (three trials), Costa Rica (three trials), Colombia (1 trial) and Honduras (1 trial). In each trial fenpicoxamid was applied as three foliar broadcast applications of GF-2925 (130 g/L, SC) at a rate of 0.046-0.051 kg ai/ha using ground equipment (motor driven backpack sprayer). The applications (BBCH 72-80) were made nominally at 16, 8 and 0 days before harvest. To simulate aerial application, the spray volumes ranged from 20 to 35 L/ha (2.1 to 3.7 gal/A). A paraffinic mineral oil and an emulsifier, labelled for agricultural use, were added to the spray mixtures.

Bagged and un-bagged bunches (racemes) were harvested at normal commercial maturity, zero days after the last application (DALA). In three trials (131080-03, -05 and -09), the banana bunches were harvested additionally at 7 or 8 DALA. The decline trials were conducted in six trials (131080-06, -07, -08, -10, -11 and -12). Samples were generated by collecting four fingers from a raceme from six plants to achieve 24 fruit per sample. Fresh whole bananas were separated for pulp and peel samples. All samples were placed in frozen storage within 1.7 to 12.5 hours of collection in the field. Samples were shipped frozen with dry ice from the field facilities to analysis laboratory. The banana samples were stored frozen (below freezing at the field sites and -25 to -11ºC at the analytical laboratory) for 17 to 151 days between sample collection and extraction for analysis.

Residues of fenpicoxamid and its metabolite X642188 were quantitated using the validated method described in the section of residue analysis (Table 27). LOQ was 0.01 mg/kg in whole banana, pulp and peel. Procedural mean recoveries at fortification levels of 0.01 and 0.1 mg/kg were 79-120% (RSD, ≤6.5%) for fenpicoxamid and 67-104% (RSD, ≤9.5%) for X642188.

Residues in treated samples were not corrected for procedural recovery results. No detectable residues or parent metabolite were found in any untreated control samples. If a higher residue level was observed at a longer PHI than the GAP, the higher value was selected for an estimation of a maximum residue level. Selected residue values for estimation of a maximum residue level are underlined in Table 35.

For bagged banana (whole fruit, peel and pulp), fenpicoxamid was at <0.01 mg/kg) in all trials except trial 04 (0.027 mg/kg in whole and 0.026 mg/kg in peel), trial 5 (0.010 mg/kg in whole fruit) and trial 12 (0.013 mg/kg in whole fruit). In un-bagged banana, fenpicoxamid was detected at a maximum of 0.066 mg/kg in whole fruit, 0.23 mg/kg in peel and <0.01 mg/kg in pulp. X642188 was not detected in any bagged and un-bagged banana samples (whole, peel and pulp samples).

Table 35 Residues of fenpicoxamid and its metabolite X642188 in banana following foliar application with 130 g/L SC formulation

Country, Year (Variety) Trial ID	Application		PHI (days)	Commodity	Residues (mg/kg)	
	kg ai/ha	No.			Fenpicoxamid	X642188
GAP: Central and South America	0.050	3	0			
La Troncal, Cañar, Ecuador	0.051	3		Bagged		
2014			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01; < 0.01 (< 0.01)
(Cavendish/ Williams)			0	Pulp	< 0.01	< 0.01
131080-01			0	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.012, 0.015 (<u>0.014</u>)	< 0.01; < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	< 0.01	< 0.01
Milagro, Guayas, Ecuador	0.051	3		Bagged		
2014			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01; < 0.01 (< 0.01)
(Cavendish/ Williams)			0	Pulp	< 0.01	< 0.01
131080-02[a]			0	Peel	< 0.01	< 0.01

Country, Year (Variety) Trial ID	Application kg ai/ha	Application No.	PHI (days)	Commodity	Residues (mg/kg) Fenpicoxamid	Residues (mg/kg) X642188
				Un-bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01; < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	< 0.01	< 0.01
Lorenzo de Garaicoa, Guayas, Ecuador 2014 (Cavendish/ Williams) Trial: 131080-03[a]	0.051	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01; < 0.01 (< 0.01)
			7	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01; < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	< 0.01,< 0.01 (< 0.01)	<0.01 (< 0.01)
			7	Whole fruit	0.014, .013 (0.014)	< 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	0.032	< 0.01
El Semillero, Tiquisate, Guatemala 2014 (Cavendish/Grand Naine) 131080-04	0.046-0.050	3		Bagged		
			0	Whole fruit	0.029, 0.025 (0.027)	< 0.01; < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	0.029, 0.022 (0.026)	< 0.01
				Un-bagged		
			0	Whole fruit	0.048; 0.043 (0.046)	< 0.01; < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	0.23	< 0.01
El Semillero, Tiquisate, Guatemala 2015 (Cavendish/Grand Naine) 131080-05	0.050	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	0.010, < 0.01 (0.010)	< 0.01, < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.046, 0.030 (0.038)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	0.025, 0.045 (0.035)	< 0.01, < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	0.021	< 0.01
El Arisco, Tiquisate, Guatemala 2015 (Cavendish/Grand Naine) 131080-06	0.050	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			15	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			22	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			15	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	< 0.01	< 0.01
			15	Peel	< 0.01	< 0.01
			29	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.038, 0.030 (0.034)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	0.026, 0.031 (0.029)	< 0.01, < 0.01 (< 0.01)
			15	Whole fruit	0.012, 0.033 (0.022)	< 0.01, < 0.01 (< 0.01)
			22	Whole fruit	0.010, 0.012 (0.011)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	0.030, 0.010 (0.020)	< 0.01, < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			15	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Un-bagged		
			0	Peel	0.023	< 0.01
			15	Peel	0.037	< 0.01
			29	Peel	0.023	< 0.01

Country, Year (Variety) Trial ID	Application kg ai/ha	Application No.	PHI (days)	Commodity	Residues (mg/kg) Fenpicoxamid	Residues (mg/kg) X642188
Tiquisate, Guatemala	0.050	3		Bagged		
2015			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
(Cavendish/Grand Naine)			6	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
131080-07			11	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			20	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			11	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	< 0.01	< 0.01
			11	Peel	< 0.01	< 0.01
			29	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.025, 0.043 (0.034)	< 0.01, < 0.01 (< 0.01)
			6	Whole fruit	0.025, 0.016 (0.021)	< 0.01, < 0.01 (< 0.01)
			11	Whole fruit	< 0.01, 0.018 (0.014)	< 0.01, < 0.01 (< 0.01)
			20	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	< 0.01, 0.012 (0.011)	< 0.01, < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			11	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Un-bagged		
			0	Peel	0.067	< 0.01
			11	Peel	0.039	< 0.01
			29	Peel	0.014	< 0.01
La Lima, Cortés, Honduras	0.050	3		Bagged		
2014			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
(Cavendish/Grand Naine)			7	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
131080-08			14	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			21	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			28	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	< 0.01	< 0.01
			14	Peel	< 0.01	< 0.01
			28	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.012,0.011 (0.012)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			14	Whole fruit	< 0.01, 0.012 (0.011)	< 0.01, < 0.01 (< 0.01)
			21	Whole fruit	0.010, 0.013 (0.012)	< 0.01, < 0.01 (< 0.01)
			28	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01
				Un-bagged		
			0	Peel	0.020	< 0.01
			14	Peel	0.022	< 0.01
			28	Peel	< 0.01	< 0.01

Country, Year (Variety) Trial ID	Application kg ai/ha	Application No.	PHI (days)	Commodity	Residues (mg/kg) Fenpicoxamid	Residues (mg/kg) X642188
Siquirres, Limón, Costa Rica 2014 (Cavendish/Williams) 131080-09	0.049-0.051	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.017, 0.014 (0.016)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	0.024, 0.023 (0.024)	< 0.01, < 0.01 (< 0.01)
			0	Pulp	< 0.01	< 0.01
			0	Peel	0.032	< 0.01
Cariari, Limón, Costa Rica 2014 (Cavendish/Valery) 131080-10	0.050	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			15	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			22	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			15	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	< 0.01	< 0.01
			15	Peel	< 0.01	< 0.01
			29	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.048, 0.083 (0.066)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	0.050, 0.047 (0.049)	< 0.01, < 0.01 (< 0.01)
			15	Whole fruit	0.015, 0.015 (0.015)	< 0.01, < 0.01 (< 0.01)
			22	Whole fruit	0.016, 0.015 (0.016)	< 0.01, < 0.01 (< 0.01)
			29	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			15	Pulp	< 0.01	< 0.01
			29	Pulp	< 0.01	< 0.01
				Un-bagged		
			0	Peel	0.14	< 0.01
			15	Peel	0.023	<0.01
			29	Peel	<0.01	<0.01
La Virgen de Sarapiquí, Heredia, Costa Rica 2014 (Cavendish/Grand Naine) Trial: 131080-11	0.050	3		Bagged		
			0	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			7	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			14	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			21	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			28	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	0.014	< 0.01
			14	Peel	< 0.01	< 0.01
			28	Peel	0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.052, 0.064 (0.058)	< 0.01; < 0.01 (< 0.01)
			7	Whole fruit	0.027, 0.026 (0.027)	< 0.01; < 0.01 (< 0.01)
			14	Whole fruit	0.016, 0.014 (0.015)	< 0.01; < 0.01 (< 0.01)
			21	Whole fruit	0.024, 0.014 (0.019)	< 0.01; < 0.01 (< 0.01)
			28	Whole fruit	0.016, 0.016 (0.016)	< 0.01; < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01

Country, Year (Variety) Trial ID	Application kg ai/ha	Application No.	PHI (days)	Commodity	Residues (mg/kg) Fenpicoxamid	Residues (mg/kg) X642188
				Un-bagged		
			0	Peel	0.075	< 0.01
			14	Peel	0.020	< 0.01
			28	Peel	0.044	< 0.01
Trial: 131080-12 Santa Marta, Riofrio, Colombia 2014 (Cavendish/ Grand Williams)	0.050	3		Bagged		
			0	Whole fruit	< 0.01, 0.022 (0.013)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			14	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			21	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
			28	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01
				Bagged		
			0	Peel	< 0.01	< 0.01
			14	Peel	< 0.01	< 0.01
			28	Peel	< 0.01	< 0.01
				Un-bagged		
			0	Whole fruit	0.025, 0.020 (0.023)	< 0.01, < 0.01 (< 0.01)
			8	Whole fruit	0.017, 0.017 (0.017)	< 0.01, < 0.01 (< 0.01)
			14	Whole fruit	0.016, 0.012 (0.014)	< 0.01, < 0.01 (< 0.01)
			21	Whole fruit	0.013, 0.010 (0.012)	< 0.01, < 0.01 (< 0.01)
			28	Whole fruit	< 0.01, < 0.01 (< 0.01)	< 0.01, < 0.01 (< 0.01)
				Un-bagged		
			0	Pulp	< 0.01	< 0.01
			14	Pulp	< 0.01	< 0.01
			28	Pulp	< 0.01	< 0.01
				Un-bagged		
			0	Peel	0.057	< 0.01
			14	Peel	0.029	< 0.01
			28	Peel	0.013	< 0.01

Mean values in parentheses

[a] Not independent : two trial were conducted on the same application dates at closely located sites.

FATE OF RESIDUES IN STORAGE AND PROCESSING

Nature of the residue during processing

A processing hydrolysis study was conducted on ^{14}C- fenpicoxamid in buffered water using three sets of processing conditions representative of processing of raw agricultural commodities [Ma *et al.,* 2013, report 121153] Triplicate buffered water samples, dosed at approximately 0.03 µg/mL with either phenyl- or pyridine-radiolabelled fenpicoxamid, were heated at 90 °C for 20 minutes (pH 4), boiled at 100 °C for 60 minutes (pH 5), and steamed at 120 °C for 20 minutes (pH 6), to simulate industrial or household preparation. Analysis was made by LSC and HPLC. Chromatographic results of authentic reference standards were compared to chromatograms of hydrolysed samples. Major degradates at greater than 10% of the applied radioactivity were identified by LC-MS.

Table 36 Distribution of residues in processing hydrolysis

Hydrolysis condition	% of applied radioactivity (residue formed at greater than 10% of applied radioactivity) Fenpicoxamid (PH-, PY-label)	X12019520 (PH-label)	X12314005 (PH-label)	X12264475 (PY-label)	X12335723 (PY-label)
pH 4, 90 °C, 20 min	86.9, 80.3	2.9	10.2	nd	15.4
pH 5, 100 °C, 60 min	28.0, 18.9	12.3	47.5	nd	76.5
pH 6, 120 °C, 20 min	nd, nd	87.4	nd	17.5	64.9

nd: not detected

Average mass balance for the nine replicates of phenyl- and pyridine-radiolabelled fenpicoxamid was 96.4% and 97.8%, respectively. ^{14}C-fenpicoxamid (both labels) was degraded more significantly with increased pH and temperature, representing 80.3-86.9%, 18.9-28.0% of the applied radioactivity and non-detection at pH 4, 5 and 6 conditions, respectively.

Metabolites X12314005 and X12019520 for PH-label and X12335723 and X12264475 for PY-label were found at greater than 10% of the applied radioactivity. X12314005 accounted for 10.2% and 47.5% of the applied radioactivity at pH 4 and 5 conditions, respectively and was not detected at pH 6 conditions. At pH 4, 5 and 6 conditions, X12019520 accounted for 2.9%, 12.3% and 87.4% of the applied radioactivity at pH 4, 5 and 6 conditions, respectively. X12335723 accounted for 15.4%, 76.5% and 64.9% of the applied radioactivity at pH 4, 5 and 6 conditions, respectively. X12264475 accounted for 17.5% of applied radioactivity at pH 6 conditions and was not detected at pH 4 and 5 conditions. Several minor metabolites (<10% of applied radioactivity) were also observed. Based on the results, it is proposed that fenpicoxamid at processing conditions is degraded to X12019520 or X12264475 via X12314005 or X12335723, respectively.

Residues after processing

No information was provided.

RESIDUES IN ANIMAL COMMODITIES

Farm animal feeding studies

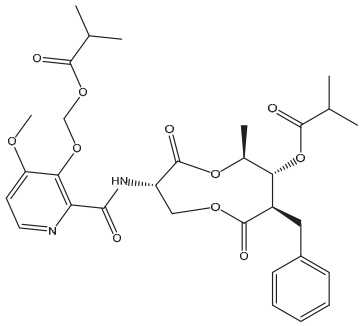
No information was provided.

APPRAISAL

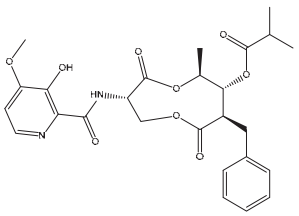
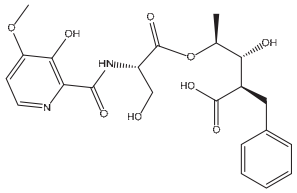
Fenpicoxamid is a picolinamide fungicide for the control of foliar diseases. It acts as a contact and residual protectant with limited systemic activity but some translaminar activity. The representative uses in Europe were for cereals for control of Septoria leaf blotch (Zymoseptoria tritici. syn: Septoria tritici). Fenpicoxamid is also registered for use on banana for the control of Black sigatoka (Mycosphaerella fijiensis).

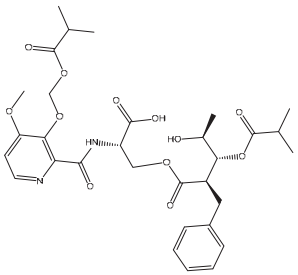
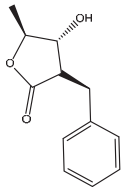
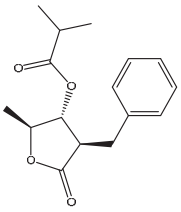
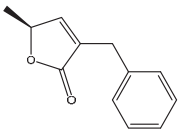
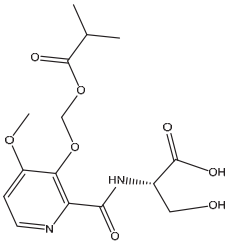
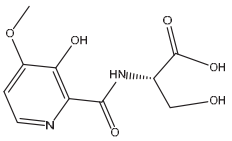
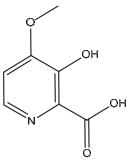
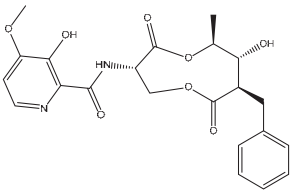
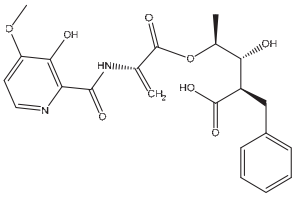
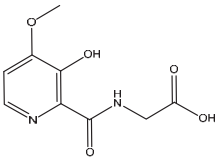
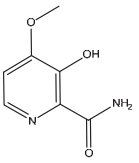
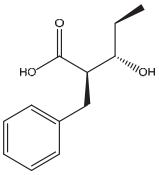
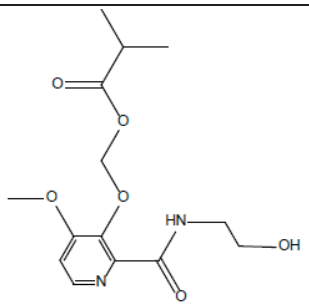
Fenpicoxamid was scheduled at the Forty-ninth Session of the CCPR for the evaluation of toxicology and residues for the first time by the 2018 JMPR. The Meeting received information on plant and animal metabolism, a confined rotational crop study, methods of residue analysis, storage stability, environmental fate, and supervised trials and GAP information on banana.

The IUPAC name of fenpicoxamid is (3S,6S,7R,8R)-8-benzyl-3-{3-[(isobutyryloxy)methoxy]-4-methoxypyridine-2-carboxamido}-6-methyl-4,9-dioxo-1,5-dioxonan-7-yl isobutyrate. The structural formula is:



Some metabolites referred to in the appraisal are addressed by their company codes:

Code	Structure	Code	Structure
X642188 (MW: 514.5)		X12326349 (MW: 462.5)	

Code	Structure	Code	Structure
Open-ring fenpicoxamid isomer (MW: 632.7)		X11963422 (MW: 206.2)	
X12314005 (MW: 276.3)		X12019520 (MW: 188.2)	
X12335723 (MW: 356.3)		X12264475 (MW: 256.1)	
X696476 (MW: 169.1)		X696872 (MW: 444.4)	
13495S-3S (MW: 444.4)		X763024 (MW: 226.2)	
X12313581 (MW: 168.2)		PH-met 208 (MW: 208.3)	
X12446477 (MW: 312.32)			

Fenpicoxamid is not volatile. The log KOW value (4.2 at pH 5) indicates that the compound may be partitioned into fat. Hydrolysis is likely to be a significant route of degradation. Aqueous photolysis is also likely to be a significant route of degradation, but at a less extent than hydrolysis.

Plant metabolism

The Meeting received information on the fate of fenpicoxamid following foliar application on fruits (tomato), leafy vegetables (cabbage) and cereals (wheat).

Tomato

The metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in greenhouse grown tomatoes following two foliar applications at a rate equivalent to 300 g ai/ha at a 30-day re-treatment interval. Mature fruits were collected 1, 7 and 14 days after the last application (DALA).

TRR levels in mature fruits (1, 7 and 14 DALA) were in the range of 0.057–0.13 mg eq/kg and greater than 99% of the radioactivity was extracted with acetonitrile and aqueous acetonitrile, with the majority of residues recovered in the surface rinse (80–90%). No significant differences in TRR levels of fruits were observed for either 14C-label at all harvest intervals.

Parent was the major component in tomato fruit, accounting for 90–97% (0.051–0.12 mg/kg) of the total radioactivity. Minor metabolites X642188, an open-ring fenpicoxamid isomer, and phenyl-label specific X12314005 were found at very low levels up to 0.7% TRR and present at 0.001 mg/kg each. There were 2 to 5 unidentified metabolites, but no single component was present at concentrations greater than 0.001 mg eq/kg. A similar trend was observed in the vines.

Cabbage

The metabolism of ^{14}C- fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in outdoor grown cabbage following two foliar applications at a rate of 300 g ai/ha with a 30-day re-treatment interval. Immature cabbage samples were collected 14 days after the first application and mature cabbage samples were collected 7 DALA.

For both labels, TRR levels in immature cabbage were in the range of 0.93–1.3 mg eq/kg. In mature cabbage heads with wrapper leaves, TRRs for both labels were 0.42–0.51 mg eq/kg, while those in mature cabbage heads without wrapper leaves were approximately one-fifth of the residue in intact cabbage. Greater than 98% of the total residue in cabbage samples could be extracted with acetonitrile and aqueous acetonitrile, containing 0.1% phosphoric acid.

In all cabbage samples (immature cabbage, cabbage head with or without wrapper leaves, and wrapper leaves), parent was a major component accounting for 68–96% of the TRR and present at levels of 0.054–1.5 mg/kg. In cabbage heads with wrapper leaves, X12314005 (13% TRR, 0.030 mg/kg) was also present in amounts approximately 10-fold less than the parent compound and showed much lower levels in the edible portion of the commodity (cabbage head without wrapper leaves: 3.4% TRR, 0.002 mg/kg). Two metabolites, X642188 and an open-ring fenpicoxamid isomer, were found at low levels, up to 5.4% and 5.0% TRR, respectively and present at up to 0.013 and 0.058 mg/kg, respectively. Additionally, 3 to10 unidentified metabolites were present, none of which were greater than 4.8% TRR and 0.028 mg eq/kg.

Wheat

Metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was studied in outdoor grown wheat following two foliar applications at a rate of 133 g ai/ha. Immature wheat forage samples were collected at 28 days after the first application. Immature wheat hay samples were collected at 24 DALA and dried. Mature grain and straw were collected at 78 DALA.

TRR levels in wheat samples (both labels) were 0.54–0.99 mg eq/kg in forage, 3.0–7.8 mg eq/kg in hay, 4.2–4.9 mg eq/kg in straw and 0.016–0.019 mg eq/kg in grain. 90–110% of the TRR in forage, hay, and straw were extracted using acetonitrile/H_3PO_4 solvent system at elevated temperatures. In grain, 50–97% of the TRR was extracted, with 34–37% TRR (0.005–0.007 mg eq/kg) remaining in the PES.

For grain (both labels), parent represented 21–38% of the TRR (0.004–0.006 mg/kg). Metabolite X642188 was found at 0.8% TRR (< 0.001 mg/kg). Two other minor metabolites were present at 2.9–5.5% TRR (< 0.001 mg/kg). No unidentified single component accounted for more than 4% TRR (0.001 mg eq/kg).

In forage, hay and straw (both labels), the majority of the residue remained as the parent, representing 76–98% TRR. Seven minor metabolites were found at 0.5–3.4% TRR each (up to 0.12 mg/kg). No unidentified single component accounted for more than 3.5% TRR (0.15 mg eq/kg). Unextracted residues in straw (1.9–4.0% TRR, 0.078–0.19 mg eq/kg) were incorporated into natural plant constituents characterised as pectin, lignin, hemicellulose and cellulose.

In summary, fenpicoxamid is not extensively metabolised in tomato, cabbage and wheat following foliar application. Parent fenpicoxamid constitutes the large majority of residues in wheat, cabbage and tomato, with low levels of several metabolites

observed. A similar metabolite profile was observed across the three crop groups investigated. The metabolism proceeds through loss of the oxymethylisobutyrate group from the pyridine ring or through opening and cleavage of the bislactone ring to ultimately produce low levels of several postulated pyridine-label or phenyl-label specific metabolites.

Plant metabolite X642188 was identified as a metabolite in rats.

Confined rotational crops

A confined study was conducted to investigate the metabolism of fenpicoxamid in the representative crops wheat, lettuce, and radish. ^{14}C- fenpicoxamid (phenyl- and pyridine-radiolabelled) was applied to sandy loam soil at 260 g ai/ha. The crops were planted at 30, 180 and 270 days plant-back intervals (PBI) and harvested. Residues in lettuce (immature and mature), radish (tops and roots), wheat (forage, hay, straw and grain) were analysed.

Residues in crops consistently declined with longer PBIs. In food commodities TRR levels (both labels) were 0.006–0.020 mg eq/kg and 0.001–0.009 mg eq/kg at 30 and 180 days PBI, respectively. For feed (both labels), residues were 0.008–0.13 mg eq/kg and 0.001–0.032 mg eq/kg at 30 and 180 days PBI, respectively.

In immature lettuce and radish tops (TRR, ≥ 0.01 mg eq/kg only at 30 day PBI), residues consisted of more than 30 individual components at concentrations of up to 0.004 mg eq/kg. Parent was not detected. In wheat grain, the recovered residue consisted of multiple polar components present at less than 0.01 mg eq/kg each. Parent was considered present at less than a quantifiable level, 0.01 mg/kg.

In feed commodities, residues consisted of multiple components up to 0.01 mg/kg observed in PH-labelled hay (30 days PBI). Parent was detected only in straw present at less than 0.01 mg eq/kg.

The Meeting concluded that significant transfer of residues into rotated crops is not expected following an application of up to 260 g ai/ha.

Animal metabolism

The Meeting received information on metabolism of fenpicoxamid in rats, goat and hens.

Rat

Metabolism studies on laboratory animals including rats were reviewed in the framework of toxicological evaluation by the current JMPR.

Lactating goats

Metabolism of ^{14}C- fenpicoxamid (phenyl- and pyridine-radiolabelled) was investigated in lactating goats. Goats were dosed orally once daily for five consecutive days at *ca.* 20 ppm in the diet. Milk was collected twice daily. Animals were sacrificed 6–7 hours after the last dose.

The majority of the administered dose was excreted in faeces (54–63%) and in urine (5–14%) for both labels. The total radioactivity (both labels) was near or below 0.005 mg eq/kg in muscle and fat, 0.026–0.065 mg eq/kg in liver and 0.033–0.041 mg eq/kg in kidney. During the dosing period the residue levels in milk reached a plateau quickly with a maximum of 0.008 mg eq/kg (day 2, PH-label) or 0.005 mg eq/kg (day 3, PY-label). Milk, muscle, and fat were not characterised further due to the low residue levels.

Organic solvent (25% aqueous acetonitrile) extracted 89% and 64% of the total radioactivity in kidney and liver, respectively, in both labels. For liver (PY-label), acid extraction after organic extraction released an additional 34% of the total radioactivity.

In kidney (both labels), the largest components were X12326349 and 13495S-3S, accounting for 17–33% TRR (0.004–0.01 mg/kg) and 8.3–11% TRR (0.002–0.003 mg/kg), respectively. Nine other metabolites found did not exceed each 10% TRR (up to 0.001 mg/kg). A polar peak with 32% TRR (0.013 mg eq/kg) was found in the PY-labelled kidney, but further characterisation and identification for the polar peak was not achieved. Parent compound was observed in only PH-label at a very low level, 0.2% TRR (< 0.001 mg/kg).

In liver (both labels), the largest components were metabolites X12326349 and X12264475. X12326349 was found at up to 16% TRR (0.007 mg/kg): 10–13% TRR (0.002–0.006 mg/kg) from neutral extraction and 2.6% TRR (0.001 mg/kg) by additional acid hydrolysis. X12264475 was found at up to 21% TRR (0.006 mg/kg): 2.1% TRR (0.001 mg/kg) from neutral extraction and 19% TRR (0.005 mg/kg) by additional acid hydrolysis. A polar peak with 21% TRR (0.014 mg eq/kg) was found in the PY-labelled liver, but further characterisation and identification was not achieved. Parent was not observed in liver.

In goats (liver and kidney), metabolites X12326349, 13495S-3S and X12264475 were the main components. Parent and any metabolites were not present at levels greater than 0.01 mg/kg.

Laying hens

Metabolism of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) was investigated in laying hens. Separate groups of animals were orally dosed for 7 days at *ca*. 10 ppm in the diet. Eggs were collected twice daily. The animals were sacrificed 6–8 hours after the last dose.

The majority (*ca*. 88% in both labels) of the total administered dose was eliminated in the excreta. Total residue levels (both labels) were 0.006–0.009 mg eq/kg in muscle, 0.005–0.010 mg eq/kg in fat, 0.008–0.016 mg eq/kg in skin with fat, 0.039–0.15 mg eq/kg in liver and 0.001–0.007 mg eq/kg in eggs. Residue levels in PY-labelled eggs plateaued by day 5, while no plateau was reached by day 7 in PH-labelled eggs.

Aqueous acetonitrile solvent extracted 61–64% TRR in eggs, 45–46% TRR in liver, 84% TRR in fat and 95% TRR in skin with fat, in both labels. In liver, acid extraction after organic extraction further released 17–37% TRR in both labels, leaving unextracted residues of 12% TRR (0.018 mg eq/kg) in PH-label and 14% TRR (0.005 mg eq/kg) in PY-label.

In liver (both labels), fat (PH-label) and skin with fat (PH-label) the residue consisted of multiple low-level components. The largest component co-elute X11963422/MW208 accounted for 12–28% TRR (or 0.001–0.006 mg/kg) in the all tissues. X696872 was found at 17% TRR (0.001 mg/kg) in fat and 15% TRR (0.002 mg/kg) in skin with fat. X129300 was found at 14% TRR (< 0.001 mg/kg). Parent was not detected in liver and fat, but at a very low level (5.2% TRR, < 0.001 mg/kg) in skin with fat. No other single component exceeded 5.9% TRR and 0.004 mg/kg.

In eggs (both labels), the largest components were the co-elute 11963422/MW208 and X12264475, accounting for 32% TRR (< 0.001 mg/kg) and 14% TRR (< 0.001 mg/kg), respectively. Other metabolites were present at up to 6.4% TRR (< 0.001 mg/kg) except a polar component at up to 27% TRR (0.002 mg eq/kg). No parent was found in eggs.

In summary for animal metabolism (goats and hens), metabolism of fenpicoxamid was extensive, proceeding through loss of either or both of the oxymethylisobutyrate side chains (O-dealkylation of the ester side chains) and opening of the bislactone ring at one of two possible positions. Further metabolism resulted in complete cleavage of the bislactone ring to give a variety of phenyl-ring and pyridine-ring specific metabolites.

Goat metabolite X12326349 was identified as a metabolite in rats.

Environmental fate

The Meeting received information on hydrolysis, aqueous photolysis, aerobic degradation in soil and soil photolysis.

Hydrolysis

Hydrolytic degradation of ^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in the dark sterile aqueous buffered solution was rapid and extensive. The degradation rate increased with increasing pH and temperature. The DT_{50} values of fenpicoxamid at pH 7 were 4.1 days at 10 °C, 0.92 days at 25 °C and 0.38 days at 35 °C. Hydrolysis products X12314005, X12019520, X12264475, X12335723, X12386481, X12433979, isomer of X11963422, open-ring fenpicoxamid isomer and X12393285 were observed.

In a separate study, the hydrolysis of X642188 in the dark sterile aqueous buffered solutions was rapid and extensive. Degradation rate increased with increasing pH and temperature. The DT_{50} values of X642188 at pH 7 were 1.3 days at 10 °C, 0.22 days at 25 °C and 0.075 days at 35 °C.

Hydrolysis is likely to be a significant route of degradation.

Aqueous photolysis

^{14}C-fenpicoxamid (phenyl- and pyridine-radiolabelled) in the sterile aqueous buffered solution under irradiation conditions at 25 °C of summer sunlight at 40 °N latitude was degraded with the photolytic DT_{50} value of 3.1 days. The degradate X12446477 and a multi-component peak were observed only in the irradiated sample; otherwise, identical degradation products were found under both the irradiation and non-irradiation conditions. Given that the DT_{50} of fenpicoxamid in the dark control sample was 1.3 days, the Meeting concluded that hydrolysis is likely to be a more prominent dissipation pathway than photolysis.

Aerobic degradation in soil

Soils were treated with ^{14}C- fenpicoxamid (phenyl- and pyridine-radiolabelled) at 133 g ai/ha and incubated under aerobic conditions in the dark at 20 °C, with 50% maximum water holding capacity.

In both labels, parent degraded rapidly and extensively in all four tested soils. The geometric mean DT_{50} and DT_{90} values of parent were 1.2 days and 15.6 days, respectively. Major metabolites X642188, X696872, X12264475, X763024, X696476, X12313581 and X11963422 were observed.

Fenpicoxamid was not considered to be persistent in soil.

Soil photolysis

In a soil photolysis study, fenpicoxamid was significantly degraded in dark (13–17% applied radioactivity (AR) remaining) and irradiated (26–32% AR remaining) moist soils and less degradation occurred in irradiated dry soil (64–76% AR remaining). Phototransformation was not a major pathway of degradation of fenpicoxamid.

Methods of analysis

Three methods involving aqueous acetonitrile extraction and determination by LC-MS/MS were fully validated for analysis of fenpicoxamid and its metabolites in plant (X642188) and animal (X642188 and X12326349) commodities. In one method for plant commodities, LOQs of fenpicoxamid and X642188 were 0.01 mg/kg in matrices of high water, high acid, high oil and high starch content. In two methods for animal commodities, LOQs for parent, X642188 and X12326349, where measured, were 0.01 mg/kg.

Stability of residues in stored analytical samples

In a storage stability study on fenpicoxamid and X642188, the compounds were stable for at least 24 months in banana whole fruit and pulp when stored frozen at -18 °C.

No storage stability data were available for animal commodities.

Definition of the residue

The fate of fenpicoxamid was investigated after foliar application to tomato, cabbage and wheat plants. In plant metabolism studies, the parent compound was a major component of radioactive residues, accounting for 90–97% TRR in tomato, 68–96% TRR in cabbage, 21–38% TRR in wheat grain and 76–98% TRR in wheat feed commodities. All metabolites identified were present at less than 10% TRR.

The confined rotational crop study indicated very limited transfer of radioactivity into food or feed commodities. The Meeting concluded that it is unlikely to find parent and the metabolites in succeeding crops.

A validated analytical method for parent compound in plant matrices is available.

The Meeting therefore considered that fenpicoxamid is a suitable marker for enforcement of maximum residue levels and for dietary risk assessment for plant commodities.

In establishing the residue definition for assessing dietary exposure from plants, the Meeting considered that metabolite levels in plants were much lower than residue levels of parent compound and would be unlikely to contribute significantly to dietary exposure. While significant levels of the degradates X12314005, X12016520, X12335723, and X12264475 were observed in the simulated processing study, the Meeting noted that there were no quantifiable residues of fenpicoxamid in banana pulp. Therefore, based on the uses considered by the Meeting, there are no concerns regarding the formation of these metabolites. Should the Meeting evaluate future uses involving commodities subject to high-temperature conditions, these compounds may need to be considered for assessing dietary risk.

For all animal species investigated, no quantified residues of the parent compound were found.

In goat liver and kidney matrices, X12326349 was the predominant residue with TRR levels of 16–33%.The kidney and liver samples also showed residues of 13495S-3S at 8.3–11% TRR and X12264475 at up to 21% TRR. However, the concentrations of all metabolites found were < 0.01 mg/kg, except for X12326349 in kidney (0.01 mg/kg).

In hens, the co-elute X11963422/MW208 was the predominant residue in all matrices (12–32% TRR). Further metabolites exceeding 10% TRR were X696872 (fat: 17% TRR, skin with fat: 15% TRR), X12264475 (eggs: 14% TRR) and X129300 (skin with fat: 14% TRR). However, the concentrations of all metabolites found were very low, not exceeding 0.01 mg/kg.

Metabolism studies with lactating goat and laying hen demonstrated that residues above 0.01 mg/kg are not expected in animal commodities at feeding levels up to 20 ppm and 10 ppm, respectively. Provided dietary burdens do not exceed these feeding levels, the Meeting decided that residues definitions for enforcement and dietary risk assessment for animal commodities are not necessary.

Based on the above, the Meeting recommended the following residue definitions.

Definition of the residue for compliance with the MRL and dietary risk assessment for plant commodities: *fenpicoxamid*.

The Meeting did not recommend residue definitions for animal commodities (compliance with the MRL and dietary risk assessment) as they are not necessary for the uses considered by the current Meeting.

Results of supervised residue trials on crops

The Meeting received supervised trial data for banana.

Banana

Fenpicoxamid is registered for foliar use on banana in Central and South America (Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua and Panama). A total of eleven independent trials were conducted in Colombia, Costa Rica, Ecuador, Guatemala and Honduras during 2014 and 2015, approximating the GAP (three foliar applications at 0.050 kg ai/ha with 8 day re-treatment intervals and no restriction on PHI; aerial application only).

Fenpicoxamid residues in un-bagged banana (whole fruit) were (n = 11): 0.012, 0.014, 0.014, 0.023, 0.024, 0.034, 0.034, 0.038, 0.046, 0.058, and 0.066 mg/kg.

Fenpicoxamid residues in un-bagged banana (pulp) were (n = 11): < 0.01 mg/kg (11).

The Meeting estimated a maximum residue level of 0.15 mg/kg and a STMR of 0.01 mg/kg for banana.

Fate of residue during processing,

High temperature hydrolysis

Buffered water samples, dosed at approximately 0.03 µg/mL with either phenyl- or pyridine-radiolabelled fenpicoxamid, were heated at 90 °C for 20 minutes (pH 4), boiled at 100 °C for 60 minutes (pH 5), and steamed at 120 °C for 20 minutes (pH 6), to simulate industrial or household preparation.

At pH 4, 5 and 6 respectively, the following hydrolysis products were found:

- Fenpicoxamid (PH- and PY-label): 80–87% (pH 4), 19–28% (pH 5) and not detected (pH 6);
- X12314005 (PH-label): 10%, 48% and not detected;
- X12019520 (PH-label): 2.9%, 12% and 87%;
- X12335723 (PY-label): 15%, 77% and 65% ;
- X12264475 (PY-label): not detected, not detected and 18%.

Should the Meeting evaluate future uses involving commodities subject to high-temperature conditions, these compounds may need to be considered for assessing dietary risk.

Fate of residues during processing

No information was provided.

Farm animal feeding studies

No information was provided.

Farm animal dietary burden

There are no relevant feed items from the use on banana.

RECOMMENDATIONS

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

The Meeting recommended the following residue definitions for fenpicoxamid.

Definition of the residue for compliance with the MRL and dietary risk assessment for plant commodities: *fenpicoxamid*

The Meeting concluded that if future uses of fenpicoxamid result in an increase of the exposure for the goat metabolite X12326349 and the hydrolysis products X12314005, X12019520, X12335723 and X12264475, reconsideration of the residue definitions may become necessary.

Commodity		Recommended maximum residue level (mg/kg)		STMR or STMR-P (mg/kg)	HR, HR-P, highest residue (mg/kg)
CCN	Name	New	Previous		
FI 0327	Banana	0.15	-	0.01	

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for fenpicoxamid is 0–0.05 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for fenpicoxamid were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the JMPR. The results are shown in Annex 3 of the 2018 JMPR Report. The IEDIs were 0% of the maximum ADI.

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

Acute dietary exposure

The 2018 JMPR decided that an ARfD for fenpicoxamid was unnecessary. The Meeting therefore concluded that the acute dietary exposure to residues of fenpicoxamid from the use considered is unlikely to present a public health concern.

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