SEDAXANE (259)

The first draft was prepared by Dr William Donovan, United States Environmental Protection Agency, Washington, DC, USA

EXPLANATION

Sedaxane is a novel seed treatment fungicide. It is a succinate dehydrogenase inhibitor and affords broad spectrum control of pathogens such as Ascomycetes and Oomycetes species in crops. It has been registered in France, Canada, and the USA. At the 43rd session of the CCPR (2011), it was scheduled for evaluation as a new compound by the 2012 JMPR.

The Meeting received information from the manufacturer on identity, metabolism, storage stability, residue analysis, use pattern, residues resulting from supervised trials on cereal grains (wheat, oats and barley), soya bean, rape, fate of residues during processing, and livestock feeding studies.

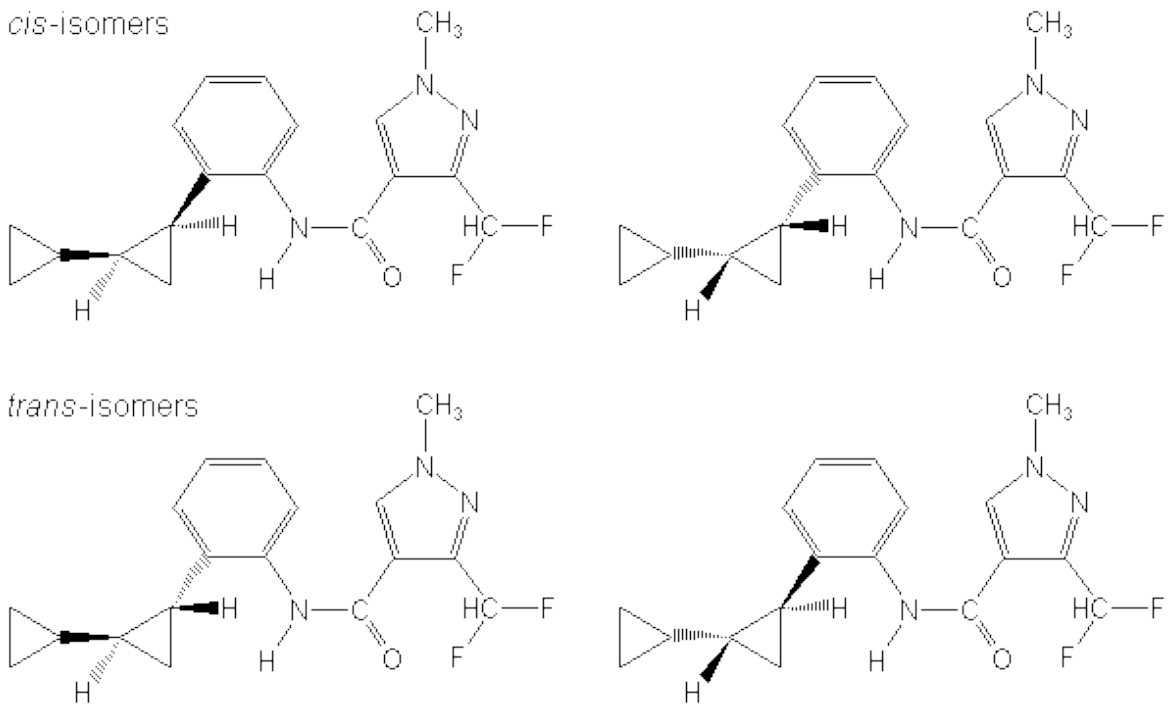
IDENTITY

Chemical Names and Numbers

ISO common name:	Sedaxane
CAS No.:	874967-67-6
IUPAC:	2'-[1,1'-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide
Chemical Abstract:	*N*-[2-[1,1′-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide
Other names:	SYN524464
CIPAC Number:	833

Structural formula

Sedaxane is a mixture of 2 *trans*- and 2 *cis*-isomers, trans-sedaxane and cis-sedaxane, in an approximate 6:1 ratio. These structures may be represented as follows:



Molecular formula: $C_{18}H_{19}F_2N_3O$

PHYSICAL AND CHEMICAL PROPERTIES

active substance (purity 99.7%):

Molecular Weight:	331.4 g/mol (001, Stulz, 2010)
Melting point:	121.4 °C (002, Geoffroy, 2008)
Decomposition:	> 270 °C (002, Geoffroy, 2008)
Vapour pressure (20 °C):	$< 1.4 \times 10^{-6}$ Pa (003, Geoffroy, 2008)
Physical state, colour (24 °C):	White powder (004, Das, 2008)
Odour:	Odourless (004, Das, 2008)
pH (technical grade):	5.9 (005, Das, 2009)
Density (26 °C):	1.23 g/cm^3 (012, Poux, 2008)

Spectra for pure active substance (006, Oggenfuss, 2009)

UV/VIS: wavelength maximum absorptions: 225, 265, and 295 nm in neutral solution (pH = 6.5).

IR: Absorbance reported at 3321, 3000, 1646, 1552, 1042, and 766 cm^{-1}.

NMR: Shifts in the carbon nmr spectrum observed at 2.8–22.2, 39.6, 76.7–77.3, 109.2–113.8, 117.5–127.5, 132.6–137.0, 143.1, and 159.5 ppm; shifts in the proton nmr spectrum observed at 0–0.3, 0.6–1.1, 1.5, 3.8, 6.8, 6.9–8, and 8.1 ppm.

MS: Molecular ion M^+ peak observed at m/z = 331, major fragment ion peaks at m/z = 302, 290, 282, 263, 172, 159, and 130.

Solubility

Water at 20 °C (mg/L) pure active ingredient (007, Khot, 2008)

Pure:	670
pH 5:	1380
pH 7:	570
pH 9:	550

Organic solvents, at 25 °C (g/L) technical grade active ingredient (97.5%) (008, Vijayakumar, 2009)

acetone:	410
dichloromethane:	500
ethyl acetate:	200
hexane:	0.41
methanol:	110
octanol:	20
toluene:	70

n-Octanol/water partition coefficient pure active ingredient at 25 °C (009 Hosmani, 2009)

pH 6.5: log $K_{o/w}$ = 3.3

Hydrolysis rate

In dilute aqueous buffer solutions, sedaxane was stable to hydrolysis at pHs of 4, 5, 7, and 9 for at least 5 days at 50 ºC; and at pHs of 5, 7, and 9 for at least 30 days at 25 ºC (022, Nicollier, 2007).

Direct phototransformation (pH 7, 25 °C) (011, Fleming & Hand, 2008):

Sedaxane photolytic half-life in pH 7 buffered water : 52 days (40 N latitude, summer sunlight)

Sedaxane DT_{50} in natural surface water : 16.5 days

Photodegradates identified:

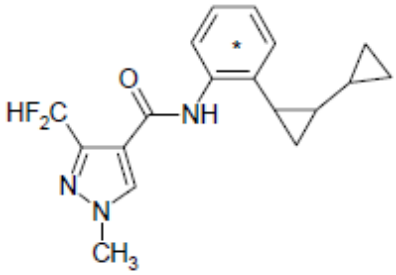
CSAA798670 reached a maximum concentration of 11.7% applied radioactivity at 30 days in pH 7 buffered water

CSAA798670 reached a maximum concentration of 25.7% applied radioactivity at 30 days in natural water

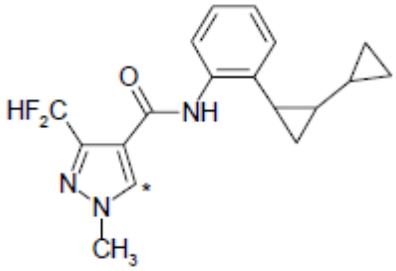
Several other minor photodegradates at ≤ 5% AR

METABOLISM AND ENVIRONMENTAL FATE

The metabolism of sedaxane in plants and animals was investigated using ^{14}C phenyl and pyrazole ring labelled sedaxane. Residues of sedaxane in succeeding crops were also investigated. A list of the main metabolites and degradates found in the studies are shown in Table 1.

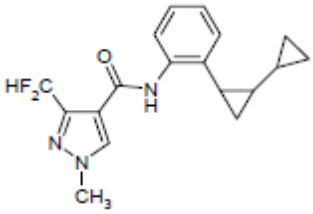
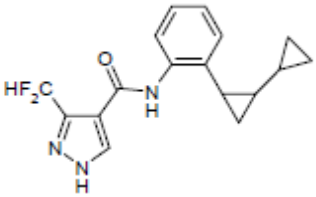
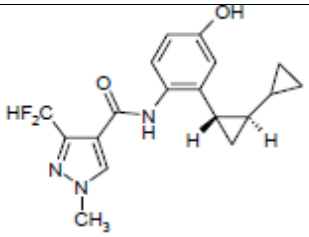
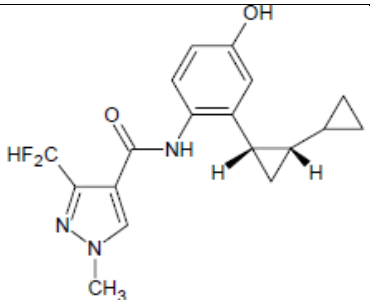


[Phenyl-U-^{14}C]sedaxane

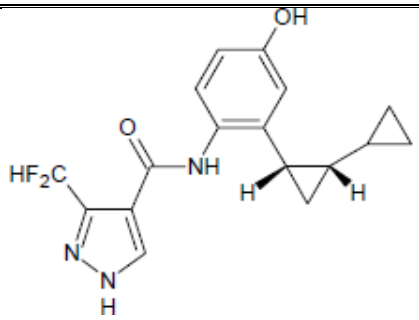
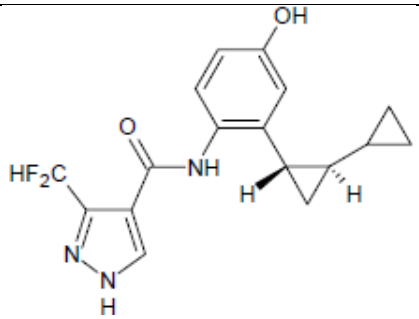
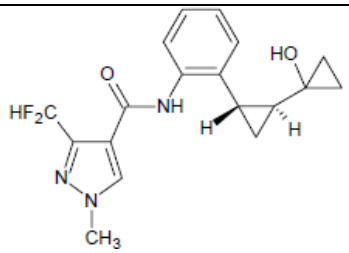
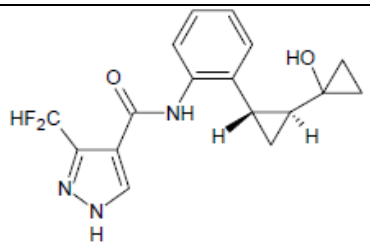


[Pyrazole-5-^{14}C]sedaxane

Table 1 Metabolites and degradates found in the metabolism studies conducted with sedaxane

Common name or code name	Chemical identification	Chemical structure	Commodities where Detected
Sedaxane SYN524464, mixture of trans-sedaxane and cis-sedaxane	Sedaxane		Primary Crops Rotated Crops Livestock
CSCD667584	N-desmethyl sedaxane		Primary Crops Rotated Crops Livestock
CSCD658906	Trans para phenol sedaxane		Primary Crops Rotated Crops Livestock
CSCD659090	cis para phenol sedaxane		Primary Crops Rotated Crops Livestock

Common name or code name	Chemical identification	Chemical structure	Commodities where Detected
CSCD668403	β-hydroxy carbonyl sedaxane		Primary Crops Rotated Crops
CSCD667555	N-glucoside (trans) sedaxane		Primary Crops
CSCD667556	N-malonyl-glucoside of sedaxane		Primary Crops
CSCC210616	pyrazole amide		Primary Crops Rotated Crops
CSCD465008	N-desmethyl pyrazole acid		Primary Crops Rotated Crops
CSAA798670	pyrazole acid		Primary Crops Rotated Crops
	Cis para phenol sedaxane		Livestock

Common name or code name	Chemical identification	Chemical structure	Commodities where Detected
CSCD668404/ CSCD659087	Trans and cis desmethyl para phenol sedaxane		Primary Crops Rotated Crops Livestock
			Primary Crops Rotated Crops Livestock
CSCD659089	Cyclopropyl alcohol sedaxane		Primary Crops Rotated Crops Livestock
CSCD659088	Desmethyl cyclopropyl alcohol sedaxane		Livestock

Metabolism in animals

The metabolism of sedaxane was investigated in the rat, lactating goat and laying hen using ^{14}C phenyl- and pyrazole-ring labelled sedaxane.

Rats

Sedaxane metabolism in rats was reviewed by the WHO panel of the JMPR in 2012. The sedaxane administered to rats was rapidly excreted, predominantly in the faeces (75–88%) and in urine (12–20%). Sedaxane was extensively metabolised in rats by demethylation, hydroxylation, oxidation and conjugation, resulting in many hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. The major metabolites have been identified as the trans para phenol sedaxane and the desmethyl trans para phenol sedaxane, which together with the equivalent cis para phenol isomers of sedaxane account for approximately half of the administered dose. There appear to be no major sex or dose related differences in the qualitative metabolite profile of sedaxane and the position of radiolabelling. There is little evidence of any cleavage between the phenyl and pyrazole

moieties of the sedaxane molecule. A small amount (< 1%) of a pyrazole amide metabolite of sedaxane also found in plants can be found in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane are subject to glucuronic acid, sulphate and glutathione conjugation.

Lactating Goats

Two studies were conducted to investigate the nature of residues in milk and tissues from lactating goats, involving dosing of [phenyl-U-^{14}C]sedaxane (P label) [Table 2] and [pyrazole-5-^{14}C]sedaxane (Py label) [Table 3] (015, Lowrie, 2009). The test substances were administered orally via gelatin capsule to two goats (one goat per radiolabel) at average dosing rates of 24.0 ppm (P label) and 22.8 ppm (Py label) in the diet for 7 consecutive days. Milk was collected twice daily throughout the study, in the morning before dose administration and in the afternoon; urine and faeces were collected daily; and tissues, including muscle (composite of forequarter, hindquarter, and tenderloin), fat (composite of perirenal, omental, and subcutaneous), liver, and kidneys, were collected at sacrifice, approximately 12 hours after the final dose.

The total radiolabelled dose recovered from both goats was greater than 85% of the administered dose with the majority excreted in the urine and faeces. Results demonstrated low accumulation of sedaxane and its metabolites in goat tissues and milk. Total radioactivity results for milk indicated that a plateau was reached after approximately 2 days. Sedaxane underwent extensive metabolism and was detected at low levels (maximum 0.034 mg/kg found in liver).

Metabolites were present mainly as conjugates except in fat and milk. The principle metabolites identified were the *trans* para phenols CSCD658906 and CSCD659087 and corresponding *cis* para phenol isomers CSCD659090 and CSCD668404. CSCD658906 was the major component in liver and kidney. CSCD659087 and CSCD668404 were the major components in milk. CSCD667584, CSCD659088 and CSCD659089 were identified as minor components in most tissues. The major component in fat was sedaxane.

Total radioactive residues in muscle were low: 0.006 and 0.004 mg/kg in the phenyl and pyrazole-labelled experiments, respectively. Attempts were made to extract and chromatograph muscle samples; however, it was not possible to quantify individual residues in the muscle samples due to the low residue levels. The extracts were described as multi-component, but no discernible peak for sedaxane was apparent.

The primary observations from the lactating goat nature of the residue study were: (i) there were no major differences in metabolic profiles obtained from the two radiolabelled experiments; (ii) there was no indication of significant cleavage between the phenyl and pyrazole moieties of sedaxane; and (iii) the primary mechanisms for the proposed biotransformation pathway of sedaxane included N-demethylation; hydroxylation of sedaxane to give the para phenols CSCD658906 and CSCD659090, and the cyclopropyl alcohol CSCD659089; hydroxylation of desmethyl sedaxane to give the para phenols CSCD659087 and CSCD668404, and the desmethyl cyclopropyl alcohol CSCD659088. Also, opening of the terminal cyclopropyl moiety of sedaxane followed by oxidation of the side chain to give a β-hydroxycarbonyl sedaxane metabolite (the *trans* isomer CSCD668403 was identified) was observed. Finally, conjugation of hydroxylated metabolites and of desmethyl sedaxane was noted.

The sedaxane trans:cis isomer ratio of the administered dose material was 6:1. The same measured ratio in goat fat and liver samples was reported as approximately 4:1 and 5:1, respectively.

Table 2 Summary of Characterization and Identification of Radioactive Residues in Goat Matrices when dosed with [^{14}C-Phenyl]Sedaxane at 24.0 mg/kg

Compound	Fat		Kidney		Liver		Milk [a]	
	TRR = 0.015 mg/kg		TRR = 0.190 mg/kg		TRR = 0.614 mg/kg		TRR = 0.045 mg/kg	
	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	%TRR	mg/kg

Compound	Fat		Kidney		Liver		Milk [a]	
	TRR = 0.015 mg/kg		TRR = 0.190 mg/kg		TRR = 0.614 mg/kg		TRR = 0.045 mg/kg	
	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	%TRR	mg/kg
Sedaxane	28.4	0.004	ND	ND	5.5	0.034	ND [b]	ND
CSCD667584	17.6	0.003	ND	ND	2.4	0.015	ND	ND
CSCD659090 [c] (as conjugates)	ND	ND	1.3 (1.3)	0.002 (0.002)	1.2 (1.2)	0.007 (0.007)	ND	ND
CSCD658906 [c] (as conjugates)	ND	ND	22.3 (22.3)	0.042 (0.042)	19.3 (17.9)	0.119 (0.110)	2.8 (0.2)	0.001 (< 0.001)
CSCD659088 [c] (as conjugates)	ND	ND	12.6 (12.6)	0.024 (0.024)	1.5 (1.5)	0.009 (0.009)	1.7 (1.7)	0.001 (0.001)
CSCD668404/ CSCD659087 [c] (as conjugates)	ND	ND	12.8 (11.3)	0.024 (0.021)	3.3 (3.3)	0.020 (0.020)	8.5 (1.3)	0.004 (0.001)
CSCD659089 [c] (as conjugates)	ND	ND	4.7 (4.7)	0.009 (0.009)	1.3 (1.3)	0.008 (0.008)	ND	ND
Baseline/Origin	0.6	< 0.001	1.4	0.003	0.9	0.006	1.4	0.001
Unassigned	10.0	0.001	NA	NA	2.7	0.016	2.1	0.002
Organo-soluble Unknowns [d]	18.6	0.003	16.6	0.032	5.7	0.035	40.4	0.017
Water-soluble Unknowns [e]	ND	ND	8.1	0.015	9.2	0.056	5.8	0.003
Post protease ACN soluble	NA	NA	NA	NA	2.1	0.013	NA	NA
Post protease ACN/water soluble	NA	NA	NA	NA	7.0	0.043	NA	NA
Post protease water soluble	NA	NA	4.1	0.008	0.2	0.001	NA	NA
Protease hydrolysate	NA	NA	NA	NA			NA	NA
MW< 3000					3.8	0.023		
MW> 3000					7.2	0.045		
Total identified	46.0	0.007	53.7	0.101	34.5	0.212	13.0	0.006
Total extractable	75.2	< 0.012	83.5	0.158	80.5	0.494	62.7	0.030
Unextractable (PES) [f]	4.1	0.001	4.4	0.008	6.3	0.038	3.5	0.002
Accountability [g]	79.3		87.9		86.8		66.2	

[a] Data from TLC conditions using acidic mobile phase.

[b] ND = Not detected.

[c] Total of unconjugated and conjugated metabolites.

[d] Comprising multiple components, the largest of which accounted for 0.009 mg/kg.

[e] Comprising multiple components, the largest of which accounted for 0.004 mg/kg.

[f] Residues remaining after exhaustive extractions.

[g] Accountability = Total extractable + Total unextractable.

Table 3 Summary of Characterization and Identification of Radioactive Residues in Goat Matrices when dosed with [^{14}C-Pyrazole]Sedaxane at 22.8 mg/kg

Compound	Fat		Kidney		Liver		Milk [a]	
	TRR = 0.011 mg/kg		TRR = 0.080 mg/kg		TRR = 0.467 mg/kg		TRR = 0.033 mg/kg	
	% TRR	mg/kg	% TRR	mg/kg	% TRR	mg/kg	%TRR	mg/kg
Sedaxane	43.7	0.005	ND	ND	2.0	0.009	ND [b]	ND
CSCD667584	16.1	0.002	ND	ND	1.0	0.005	1.7	0.001
CSCD659090 [c] (as conjugates)	ND	ND	3.1 (3.1)	0.002 (0.002)	2.2 (2.2)	0.010 (0.010)	ND ND	ND ND
CSCD658906 [c] (as conjugates)	ND	ND	13.5 (12.9)	0.011 (0.011)	13.4 (11.2)	0.063 (0.053)	6.3 (6.3)	0.002 (0.002)
CSCD659088 [c] (as conjugates)	ND	ND	3.7 (3.7)	0.003 (0.003)	ND	ND	2.2 (0.7)	0.001 (0.001)
CSCD668404/ CSCD659087 [c] (as conjugates)	ND	ND	10.6 (10.0)	0.008 (0.008)	2.9 (2.3)	0.014 (0.011)	9.7 (9.7)	0.003 (0.003)
CSCD659089 [c] (as conjugates)	ND	ND	1.2 (1.2)	0.001 (0.001)	0.3 (0.3)	0.001 (0.001)	ND	ND
Origin	0.4	< 0.001	12.5	0.010	7.3	0.034	0.1	< 0.001
Unassigned	2.4	< 0.001	1.3	0.002	0.6	0.002	1.7	< 0.001
Organo-soluble Unknowns [d]	16.9	0.002	19.8	0.016	4.0	0.019	46.0	0.016
Water-soluble Unknowns [e]	ND	ND	7.4	0.006	9.0	0.042	11.3	0.004
Post protease ACN soluble	NA	NA	NA	NA	3.5	0.016	NA	NA
Post protease ACN/water soluble	NA	NA	NA	NA	8.7	0.041	NA	NA
Post protease water soluble	NA	NA	4.5	0.004	1.1	0.005	NA	NA
Protease hydrolysate (MW< 3000)	NA	NA	NA	NA	10.4	0.049	NA	NA
Protease hydrolysate (MW> 3000)	NA	NA	NA	NA	3.9	0.018	NA	NA
Total identified	NA	NA	32.1	0.025	21.8	0.102	19.9	0.007
Total extractable	79.5	< 0.011	84.7	0.069	70.3	0.328	79.0	< 0.029
Unextractable (PES) [f]	3.9	< 0.001	6.8	0.005	7.6	0.035	3.1	0.001
Accountability [g]	83.4		91.5		77.9		82.1	

[a] Data from TLC conditions using acidic mobile phase.

[b] ND = Not detected; NA = Not applicable.

[c] Total of unconjugated and conjugated metabolites.

[d] Comprising multiple components, the largest of which accounted for 0.008 mg/kg.

[e] Comprising multiple components, the largest of which accounted for 0.006 mg/kg.

[f] Residues remaining after exhaustive extractions.

[g] Accountability = Total extractable + Total unextractable.

Poultry

Five laying hens each were dosed orally by gelatin capsule with either [pyrazole-5-^{14}C]-sedaxane [Table 4] or with [phenyl-U-^{14}C]-sedaxane [Table 5], each with trans/cis ratios of approximately 6:1 (016 Green 2010). However, one hen dosed with the phenyl labelled sedaxane was sacrificed early due to poor health and was not included in the study. The daily dose rate was 20 ppm (calculated based on feed dry matter) and dosing continued for 14 consecutive days. Eggs were collected twice daily throughout the study (yolk and white were separated); excreta and cage wash were collected once daily. The birds were sacrificed approximately 12 hours after the final dose, and liver, peritoneal fat, subcutaneous fat with skin, and muscle tissues were taken for quantification and analysis.

The mean radioactive balances were 94.4% and 98.2% of the administered dose for hens dosed with phenyl and pyrazole-labelled forms, respectively. There were no major differences between the metabolic profiles of the two radiolabelled experiments and there was no indication of significant cleavage between the phenyl and pyrazole moieties. The majority of the radioactivity was recovered in excreta (mean of 89.0% and 93.8% for birds dosed with phenyl and pyrazole-labelled forms, respectively).

The primary observations from the laying hen nature of the residue study were: (i) the principal metabolites identified were the *trans* para phenol CSCD658906, the N-desmethyl *trans* para phenol CSCD659087 and the corresponding *cis* para phenol isomers CSCD659090 and CSCD668404; (ii) CSCD658906 was the major metabolite in liver and egg yolk; (iii) sedaxane and CSCD667584 were identified in all tissues except liver; and (iv) sedaxane was the major component present in fat.

The primary mechanisms for the proposed biotransformation pathway of sedaxane in laying hen were: (i) N-demethylation to give CSCD667584; (ii) hydroxylation of the phenyl ring of sedaxane to give the para phenols CSCD658906 and CSCD659090 and the cyclopropyl alcohol CSCD659089; and (iii) O-glucuronidation of the hydroxylated metabolites of sedaxane and N-desmethyl sedaxane.

The sedaxane trans:cis isomer ratio of the administered dose material was 6:1. The same measured ratio in hen egg and fat samples was reported as approximately 7:1 and 15:1, respectively.

Table 4 Summary of Characterization and Identification of Radioactive Residues in Hen Matrices when dosed with [^{14}C-Phenyl]Sedaxane at 18.7–21.6 mg/kg [a]

Metabolite Fraction	Egg Yolk		Egg White		Muscle		Liver		Abdominal Fat		Skin and Fat	
	TRR= 0.078 mg/kg [b]		TRR= 0.007 mg/kg [b]		TRR= 0.005 mg/kg [b]		TRR= 0.264 mg/kg [b]		TRR = 0.016 mg/kg [b]		TRR = 0.024 mg/kg [b]	
	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg
Sedaxane	2.1	0.002	12.1	0.001	12.9	0.001	ND	ND	46	0.007	24.6	0.006
CSCD667584	1.9	0.001	13.7	0.001	8.9	< 0.001	ND	ND	9.3	0.001	6.0	0.001
CSCD659090 (as conjugates)	0.7 (0.7)	0.001 (0.001)	ND	ND	ND	ND	1.1 (1.1)	0.003 (0.003)	ND	ND	ND	ND
CSCD658906 (as conjugates)	16.3 (16.3)	0.013 (0.013)	ND	ND	ND	ND	13.5 (12.5)	0.036 (0.033)	ND	ND	ND	ND
CSCD668404/ CSCD659087 (as conjugates)	ND	ND	ND	ND	ND	ND	2.3 (2.3)	0.006 (0.006)	ND	ND	ND	ND

Metabolite Fraction	Egg Yolk		Egg White		Muscle		Liver		Abdominal Fat		Skin and Fat	
	TRR= 0.078 mg/kg [b]		TRR= 0.007 mg/kg [b]		TRR= 0.005 mg/kg [b]		TRR= 0.264 mg/kg [b]		TRR = 0.016 mg/kg [b]		TRR = 0.024 mg/kg [b]	
	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg
Origin	2.6	0.002	1.6	< 0.001	0.7	< 0.001	5.7	0.015	0.1	< 0.001	0.8	< 0.001
Unassigned	< 0.1	< 0.001	5.3	< 0.001	7.3	< 0.001	–3.0	< 0.001	7.1	0.001	3.0	< 0.001
Organo-soluble Unknowns [d]	20.9	0.016	61.1	0.004	47.7	0.003	14.8	0.039	14.8	0.003	36.2	0.008
Water-soluble Unknowns [e]	5.5	0.004	ND	ND	ND	ND	7.5	0.020	ND	ND	ND	ND
Water extractable (not included in combined extract for chromatographic profiling) [c]	2.3	0.002	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Precipitate	7.5	0.006	NA	NA	NA	NA	5.8	0.015	NA	NA	NA	NA
Post β-Glucuronidase Water Soluble	5.5	0.004	NA	NA	NA	NA	7.5	0.020	NA	NA	NA	NA
Post protease aqueous soluble (mw> 3000) (mw< 3000)	9.3	0.007	NA	NA	NA	NA	 2.7 9.3	 0.006 0.025	NA	NA	NA	NA
Post protease ACN soluble	3.3	0.002	NA	NA	NA	NA	2.7	0.008	NA	NA	NA	NA
Post protease ACN:water soluble	NA	NA	NA	NA	NA	NA	3.6	0.009	NA	NA	NA	NA
Total identified	21.0	0.017	25.8	0.002	21.8	0.001	16.9	0.045	55.3	0.008	30.6	0.007
Total extractable	72.4	0.056	93.8	0.006	77.5	0.004	66.0	0.182	77.3	0.012	70.6	0.015
Unextractable (PES) [f]	9.0	0.007	5.9	< 0.001	27.1	0.001	10.8	0.029	6.5	0.001	30.4	0.007
Accountability [g]	81.4		99.7		104.6		76.8		83.8		101.0	

[a] Values represent the sum of both the free and conjugated forms. If both free and conjugated forms were found, the proportion of the residue that was found in the conjugated form is shown in parentheses. Conjugates calculated with reference to TLC analysis of the pre-enzyme hydrolysis extract.

[b] TRR based on summation of extracts and PES.

[c] Water extract was considered to contain large proportions of endogenous material which would interfere with chromatography and was not included in the combined extract.

[d] Comprising multiple components, the largest of which accounted for 0.021 mg/kg.

[e] Comprising multiple components, the largest of which accounted for 0.006 mg/kg.

[f] Residues remaining after exhaustive extractions.

[g] Accountability = Total extractable + Total unextractable.

Table 5 Summary of Characterization and Identification of Radioactive Residues in Hen Matrices when dosed with [^{14}C-Pyrazole]Sedaxane at 18.1–23.5 mg/kg [a]

Metabolite Fraction	Egg Yolk		Egg White		Muscle		Liver		Abdominal Fat		Skin and Fat	
	TRR= 0.070 mg/kg [b]		TRR= 0.009 mg/kg [b]		TRR= 0.005 mg/kg [b]		TRR= 0.193 mg/kg [b]		TRR = 0.008 mg/kg [b]		TRR = 0.012 mg/kg [b]	
	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg
Sedaxane	1.5	0.001	4.7	< 0.001	5.8	< 0.001	ND	ND	53.1	0.004	26.9	0.003
CSCD667584	1.6	0.001	7.6	0.001	3.6	< 0.001	ND	ND	7.5	0.001	7.9	0.001
CSCD659090 (as conjugates)	0.9 (0.9)	0.001 (0.001)	ND	ND	ND	ND	0.9 (0.9)	0.002 (0.002)	ND	ND	ND	ND
CSCD658906 (as conjugates)	13.3 (9.1)	0.009 (0.006)	ND	ND	ND	ND	16.2 (14.7)	0.031 (0.028)	ND	ND	ND	ND
CSCD668404/ CSCD659087 (as conjugates)	1.3 (1.3)	0.001 (0.001)	ND	ND	ND	ND	1.2 (1.2)	0.002 (0.002)	ND	ND	ND	ND
CSCD659089 (as conjugates)	0.4 (0.4)	< 0.001 (< 0.001)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Origin	2.6	0.002	1.1	< 0.001	4.9	< 0.001	0.6	0.001	0.5	< 0.001	0.5	< 0.001
Unassigned	< 0.1	< 0.001	2.4	< 0.001	4.2	< 0.001	–1.9	< 0.001	5.2	< 0.001	0.3	< 0.001
Organo-soluble Unknowns [d]	19.0	0.013	81.6	0.008	61.1	0.002	8.7	0.018	17.7	0.001	47.3	0.006
Water-soluble Unknowns [e]	3.3	0.002	ND	ND	ND	ND	6.7	0.013	ND	ND	ND	ND
Water extractable (not included in combined extract for chromatographic profiling) [c]	2.6	0.002	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Precipitate	11.8	0.008	NA	NA	NA	NA	6.3	0.012	NA	NA	NA	NA
Post β-Glucuronidase Water Soluble	3.3	0.002	NA	NA	NA	NA	6.7	0.013	NA	NA	NA	NA
Post protease aqueous soluble (mw> 3000) (mw< 3000)	11.0	0.008	NA	NA	NA	NA	3.2 7.8	0.006 0.015	NA	NA	NA	NA
Post protease ACN soluble	2.9	0.002	NA	NA	NA	NA	5.1	0.010	NA	NA	NA	NA
Post protease ACN:water	NA	NA	NA	NA	NA	NA	4.6	0.009	NA	NA	NA	NA

Metabolite Fraction	Egg Yolk		Egg White		Muscle		Liver		Abdominal Fat		Skin and Fat	
	TRR= 0.070 mg/kg [b]		TRR= 0.009 mg/kg [b]		TRR= 0.005 mg/kg [b]		TRR= 0.193 mg/kg [b]		TRR = 0.008 mg/kg [b]		TRR = 0.012 mg/kg [b]	
	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg	%TRR	mg/kg
soluble												
Total identified	19.0	0.013	12.3	0.001	9.4	< 0.001	18.3	0.035	60.6	0.005	34.8	0.004
Total extractable	72.2	0.050	97.4	0.009	79.6	0.002	59.4	0.119	84.0	0.006	82.9	0.010
Unextractable (PES) [f]	8.1	0.006	3.2	< 0.001	16.9	0.001	8.3	0.016	8.1	0.001	22.2	0.003
Accountability [g]	80.3		100.6		96.5		67.7		92.1		105.1	

[a] Values represent the sum of both the free and conjugated forms. If both free and conjugated forms were found, the proportion of the residue that was found in the conjugated form is shown in parentheses. Conjugates calculated with reference to TLC analysis of the pre-enzyme hydrolysis extract.

[b] TRR based on summation of extracts and PES.

[c] Water extract was considered to contain large proportions of endogenous material which would interfere with chromatography and was not included in the combined extract.

[d] Comprising multiple components, the largest of which accounted for 0.007 mg/kg.

[e] Comprising multiple components, the largest of which accounted for 0.005 mg/kg.

[f] Residues remaining after exhaustive extractions.

[g] Accountability = Total extractable + Total unextractable.

Animal metabolism summary

The metabolism and distribution of sedaxane have been investigated in poultry and ruminant species (hen and goat). The metabolic routes determined for sedaxane were found to be similar in the goat, hen and rat.

In all studies, the majority of the dosed radioactivity was excreted (mainly in the faeces of the goat) and residues in tissues, milk and eggs were low.

In both species, the highest tissue residues were observed in liver (0.26 mg/kg in hen and 0.61 mg/kg in goat). Residues in muscle were < 0.006 mg/kg and in fat were < 0.016 mg/kg in both hen and goat. In the goat kidney, TRR levels were < 0.19 mg/kg.

Unchanged sedaxane was detected mainly in the fat and, although it represented high TRR values (up to 53% TRR in the hen abdominal fat), the concentrations were low, < 0.007 mg/kg. No sedaxane was observed in the milk and concentrations in the egg yolk and white and muscle were < 0.002 mg/kg. Sedaxane was not found in the liver of the hen but was observed in goat liver, < 5.5% TRR, 0.034 mg/kg.

The major identified metabolites in the tissues, eggs and milk were the *trans* para phenol CSCD658906, the N-desmethyl *trans* para phenol CSCD659087 and the corresponding *cis*-para phenol isomers (CSCD659090 and CSCD668404).

The proposed biotransformation pathway in livestock is shown in Figure 1.

The remaining residues, not identified, were characterized as multiple unknowns in several organosoluble and water soluble fractions generated in the fractionation schemes. The higher levels of unextractable residues in the livers, kidney and egg yolk were demonstrated to be associated with endogenous proteins.

There was very little transfer of residues into tissues, milk or eggs following the dosing of sedaxane. Metabolic profiles observed in livestock commodities and excreta arise from just a few types of biotransformation.

The principal routes of metabolism are oxidation resulting in hydroxylation of the phenyl ring or at the cyclopropane moiety. Additionally the same oxidations are observed following demethylation of sedaxane. Overall results showed that the biotransformation pathway of sedaxane in ruminants and poultry is similar to that observed in the rat.

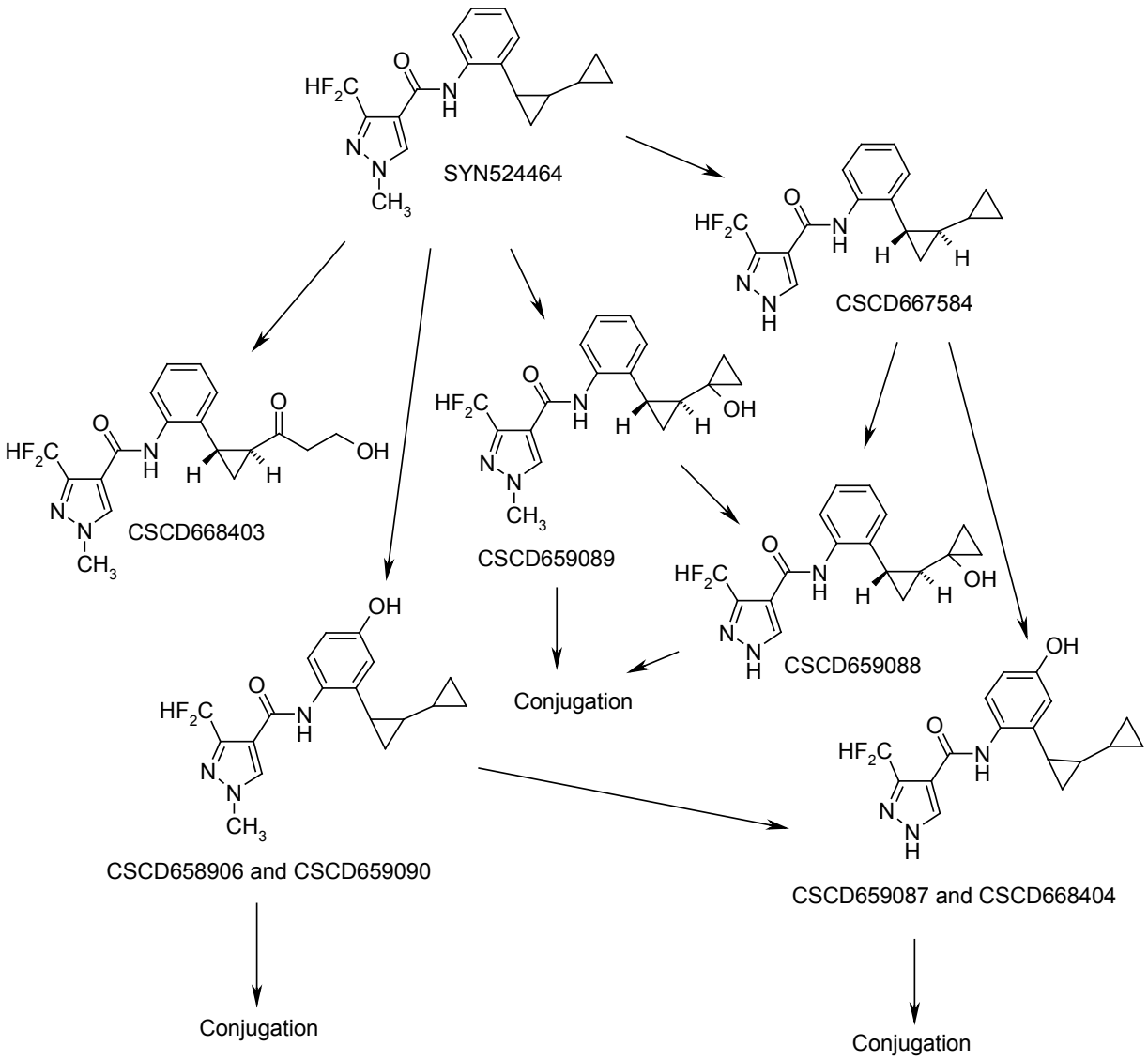


Figure 1 Proposed metabolic pathway of sedaxane in livestock

Plants

The metabolism of sedaxane following seed treatment applications was investigated in three representative crops—wheat (cereal grain), Swiss chard (leafy green), and soya bean (oilseed). In addition, an uptake study into canola (rape) was conducted.

Radioactive residues in the crop commodities were quantified using sample combustion and radioassay by Liquid Scintillation Counting (LSC). In addition, radioactive residues were quantified following extraction by radioassay of the extracts and combustion of the remaining solids.

Wheat

A study was submitted investigating the uptake, distribution and degradation of sedaxane in spring wheat after treatment of seeds with a suspension concentrate containing either [phenyl-U-^{14}C] sedaxane or [pyrazole-5-^{14}C]sedaxane (017, Graham, Gilbert, 2010). Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to spring wheat seeds at a nominal concentration of 40 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The wheat was grown under greenhouse conditions. Spring wheat treated with [^{14}C]sedaxane was harvested from 27 days (forage) to 111 days (mature grain and straw) after the seeds were treated.

The harvested samples were homogenized and the total radioactive residues (TRR) were determined for each raw agricultural commodity by sample oxidation of aliquots followed by liquid scintillation counting (LSC). The spring wheat commodities were further investigated to provide initial storage stability profiles and preliminary characterization of the nature of the residue. Comparison of the initial and final radiocomponent profiles obtained showed no significant change in the profiles had occurred.

The radioactive residues in wheat grain RAC samples from both radiolabels were < 0.01 mg/kg and were not further analysed. The TRR of the remaining wheat commodities ranged from 0.451 mg/kg for wheat forage (phenyl label) to 1.13 mg/kg for wheat straw (phenyl label) [Table 6]. The residue profiles for wheat forage, hay, and straw were all similar. Each of the wheat commodities was extracted with various solvents and extracted residues were further fractionated and characterized by aqueous/organic partitioning, Driselase hydrolysis, mineral acid hydrolysis or base hydrolysis procedures. Specifically, the extractions steps were as follows:

Wheat forage: ACN (100%) (1×), then ACN:water (4:1; v:v) (1–3×).

Wheat hay, wheat straw: ACN:water (4:1; v:v) (5×).

Wheat grain: ACN (100%) (1×), then ACN:water (4:1; v:v) (3–4×), then ACN:water (3:7; v:v) (1×).

Residues in the principal fractions were subjected to thin layer chromatography/bioimage analysis for quantification and identification /characterization by comparison with reference standards of sedaxane and its metabolites. Post extraction solids for both radiolabels were extracted with 0.05M phosphate buffer and refluxed with dioxane:2M hydrochloric acid (9:1).

The highest residue levels of parent compound sedaxane were in wheat forage (16% TRR, 0.163 mg/kg). Parent sedaxane was found in all commodities at 10.9 to 18.3% TRR (0.066 to 0.163 mg/kg). The N-demethylated parent CSCD667584 was also found in all commodities at 2.9 to 5.1% TRR (0.019 to 0.036 mg/kg). The *trans* para phenol metabolite CSCD658906, in both free and conjugated forms, was a major residue in all commodities with residues between 9.5 to 17.1% (0.069 to 0.178 mg/kg). Other significant metabolites in forage, hay and straw were the cyclopropyl alcohol CSCD659089 (4.3 to 12% TRR, 0.042 to 0.068 mg/kg), the β-hydroxyl carbonyl compound CSCD668403 (4.9 to 11.2% TRR, 0.036 to 0.083 mg/kg), and the N-desmethyl *trans* para phenol metabolite CSCD659087 (5.0 to 7.2% TRR, 0.032 to 0.062 mg/kg). These metabolites were found in the free and conjugated forms. Trace levels of the N-desmethyl pyrazole acid CSCD465008, the pyrazole acid CSAA798670 and the pyrazole amide CSCC210616 were also observed.

The principal metabolism transformation involved hydroxylation of the phenyl ring, hydroxylation of the cyclopropyl ring and ring opening of the cyclopropyl ring. A more minor metabolic transformation involved N-demethylation of the pyrazole ring. Cleavage of the amide bond between the two aromatic rings is not a significant metabolic transformation of sedaxane in wheat commodities.

The sedaxane trans:cis isomer ratio of the administered dose material was 6:1. The same measured ratio in wheat forage and hay samples was reported as approximately 10:1.

Table 6 Summary of Characterization and Identification of Radioactive Residues in Wheat Matrices when dosed with Labelled Sedaxane

	Wheat Forage (BBCH 22)		Wheat Hay (BBCH 41-57)		Wheat Straw (BBCH 89)	
	Phenyl-U-^{14}C	Pyrazole-5-^{14}C	Phenyl-U-^{14}C	Pyrazole-5-^{14}C	Phenyl-U-^{14}C	Pyrazole-5-^{14}C
TRR, mg/kg	0.451	0.606	0.730	1.04	1.13	0.884
Component	%TRR	%TRR	%TRR	%TRR	%TRR	%TRR
Sedaxane (as conjugates)	18.3 (0.0)	10.9 (0.0)	15.1 (0.0)	15.7 (0.0)	13.4 (0.0)	11.8 (0.0)
CSCD667584 (as conjugates)	5.1 (0.6)	3.2 (0.5)	3.5 (0.4)	3.5 (0.6)	2.9 (0.0)	3.9 (0.4)
CSCD658906 (as conjugates)	15.8 (9.7)	16.4 (11.1)	9.5 (8.1)	17.1 (15.5)	13.2 (10.4)	12.6 (10.8)
CSCD659089 (as conjugates)	12.0 (12.0)	9.4 (9.4)	5.9 (5.9)	6.5 (6.5)	4.3 (4.3)	4.7 (4.7)
CSCD668403 (as conjugates)	11.2 (5.6)	8.8 (4.0)	4.9 (3.5)	8.0 (6.0)	5.6 (4.2)	4.7 (3.1)
CSCD659087 (as conjugates)	7.2 (1.8)	5.8 (1.9)	5.2 (3.5)	6.0 (4.2)	5.0 (3.5)	5.2 (4.0)
CSCC210616 (as conjugates)	ND	0.3 (0.0)	ND	0.3 (0.0)	ND	0.2 (0.0)
CSCD465008/ CSAA798670 (as conjugates)	ND	0.2 (0.0)	ND	ND	ND	0.5 (0.0)
Unassigned [a]	6.3 (3.4)	4.7 (2.2)	2.6 (1.5)	3.5 (2.0)	1.0 (0.0)	1.8 (0.4)
Baseline [b]	0.9 (0.0)	0.9 (0.0)	0.6 (0.0)	1.5 (0.7)	0.1 (0.0)	0.1 (0.0)
Remainder [c]	1.3 (0.5)	0.4 (0.2)	0.3 (0.2)	0.5 (0.4)	0.7 (0.3)	0.7 (0.3)
Organo soluble extract [d]	3.7	4.7	3.8	3.5	2.7	3.8
Organo soluble extract [e]	ND	0.9	ND	1.2	1.3	1.5
Aqueous extract [f]	ND	ND0	ND	ND	ND	ND
Aqueous hydrolysate [g]	5.9	8.0	7.9	14.5	8.7	10.9
Unextracted [h]	11.9	10.4	21.8	16.0	37.3	30.5
Total	99.6	85.0	81.1	97.8	96.2	92.9

Note: Values without brackets are the sum of both the free and conjugated forms. The values within brackets indicate the proportion of the TRR that is conjugated.

[a] Phenyl label: no discrete components greater than 0.6% TRR (0.004 mg/kg), 0.6% TRR (0.004 mg/kg) or 0.3% TRR (0.004 mg/kg) in wheat forage, hay and straw respectively

Pyrazole label: no discrete components greater than 1.6%TRR (0.010 mg/kg), 0.7% TRR (0.007 mg/kg) or 0.4% TRR (0.003 mg/kg) in wheat forage, hay and straw respectively

[b] Baseline material on TLC plate

[c] The remainder consists of areas of the chromatogram which cannot be assigned to discrete radioactive components / streaks

[d] Post-enzyme hydrolysis organic fraction

[e] Post-acid hydrolysis organic fraction

[f] Post-basic hydrolysis organic fraction

[g] Post-basic hydrolysis aqueous fraction

[h] Radioactivity remaining in the debris after the initial extractions

Soya bean

Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to soya bean seeds at a nominal concentration of 110 g ai/100 kg seeds (018 Graham, Gilbert, 2010). Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The soya bean plants were grown under greenhouse conditions. Soya bean treated with [phenyl-U-^{14}C]sedaxane was harvested 28 days (forage), 42 days (hay), and 103 days (soya bean seed) after the seeds were treated. Soya bean treated with [pyrazole-5-^{14}C]sedaxane was harvested 28 days (forage), 35 days (hay), and 96 days (soya bean seed) after the seeds were treated.

Subsamples of processed forage, hay and beans were homogenized in the presence of solvents (e.g., acetonitrile, hexane (beans only) acetonitrile:water (4:1 v/v) and acetonitrile:water (3:7 v/v)). During homogenization, samples were cooled in an ice bath. Solid and liquid phases were separated by centrifugation allowing radioassay of the solid and liquid phases to be carried out by combustion and LSC, respectively. Representative aliquots of appropriate extracts were combined for further analysis.

The highest residue levels of parent compound sedaxane were in soya hay (23.2% TRR, 0.082 mg/kg) and soya forage (16.5% TRR, 0.020 mg/kg). The N-glucoside metabolite CSCD667555 and N-malonyl glucoside metabolite CSCD667556 were the major metabolites in forage and hay, resulting from N-demethylation of sedaxane and subsequent conjugation with glucose and then malonic acid. CSCC210616 and CSCD465008, resulting from the cleavage of the amide bridge, were also observed in pyrazole label forage and hay samples.

TRR levels in soya bean seeds were: 0.0093 and 0.0553 mg/kg in the phenyl and pyrazole labelled experiments, respectively (Table 8). No single compound identified in the pyrazole experiment exceeded 0.007 mg/kg. In the soya bean seeds, the major metabolites resulted from N-demethylation and cleavage of the amide bridge generating the N-desmethyl pyrazole acid CSCD465008, which subsequently conjugated with aspartic acid and sugar. The parent compound was not detected in the soya bean seeds. Soya bean seed extracts were the only extracts subjected to enzyme hydrolysis; however, the Driselase enzymes were ineffective in hydrolysing conjugated metabolites present in the soya bean seeds.

The sedaxane trans:cis isomer ratio of the administered dose material was 6:1. The same measured ratio in soya bean forage and hay samples was reported as approximately 4:3 and 3:1, respectively. However, it was noted that considerable uncertainty was associated with these ratios because of the low levels of the cis isomer.

Table 7 Summary of identification of radioactive residues in [^{14}C] Sedaxane treated soya forage and hay (in %TRR and mg of sedaxane eq/kg)

	Soya forage (BBCH 16)		Soya hay (BBCH 61)	
	Phenyl-U-^{14}C	Pyrazole-5-^{14}C	Phenyl-U-^{14}C	Pyrazole-5-^{14}C
TRR, mg/kg	0.138	0.123	0.354	0.438
Component	%TRR	%TRR	%TRR	%TRR

Sedaxane	12.0	16.5	23.2	16.6
CSCD667584	3.1	3.4	5.3	5.1
CSCD658906	0.5	0.4	0.9	0.6
CSCD659089	0.2	0.3	0.2	ND
CSCD465008	ND	4.2	ND	3.3
CSCC210616	ND	2.7	ND	1.0
CSCD667555	28.1	23.9	26.9	22.3
CSCD667556	13.0	16.5	12.6	22.1
Unassigned [a]	NA	0.7	NA	NA
Baseline [b]	28.4	18.8	17.5	26.1
Remainder [c]	1.2	1.6	2.5	0.7
Unextracted [d]	18.1	12.1	18.3	14.7
Total	104.6	101.1	107.4	112.5

[a] Pyrazole label: no discrete components greater than 0.4% TRR (< 0.001 mg/kg) for soya forage

[b] Baseline material on TLC plate

[c] The remainder consists of areas of the chromatogram which cannot be assigned to discrete radioactive components/ streaks

[d] Radioactivity remaining in the debris after the initial extractions

Table 8 Summary of Characterization and Identification of Radioactive Residues in Soya bean Seed Following One Application of Either [Phenyl-U-^{14}C]Sedaxane or [Pyrazole-5-^{14}C]Sedaxane at an Application Rate of 110 g ai/100 kg seeds, 96-103 DAP, BBCH 89

	Phenyl-U-^{14}C		Pyrazole-5-^{14}C	
	TRR = 0.0093 mg/kg [a, b]		TRR = 0.0553 mg/kg [a, b]	
Metabolite Fraction	% TRR	mg/kg	% TRR	mg/kg
Sedaxane	NA	NA	ND	ND
CSCD465008	NA	NA	9.30	0.005
CSCD465008 aspartic acid conjugate	NA	NA	9.70	0.005
CSCD465008 sugar conjugate	NA	NA	12.4	0.007
Unassigned [c]	NA	NA	39.5	0.022
Baseline [d]	NA	NA	9.10	0.005
Remainder [e]	NA	NA	3.70	0.002
0.05 M phosphate buffer	4.95	0.0005	3.83	0.002
Dioxane:2M HCl (9:1)	15.4	0.0014	3.99	0.002
Total identified	NA	NA	31.4	0.017
Total extractable	NA	NA	91.5	0.050
Post Extraction Solid (PES)	7.0	0.0006	1.5	0.001
Accountability [f]	NA		93	

[a] TRR determined by the sum of the residue in extraction of the tissue followed by combustion of the PES.

[b] Expressed as mg/kg Sedaxane equivalents.

[c] Unassigned = no discreet components greater than 17% TRR (0.010 mg/kg) for the pyrazole label.

[d] Baseline = baseline material on TLC plate.

[e] Remainder = the areas of the chromatogram which cannot be assigned to discrete radioactive components/streaks.

[f] Accountability = Total extractable + Total unextractable (PES).

Swiss chard

The metabolism of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane was investigated in Swiss chard after treatment of seeds with a suspension concentrate containing either [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane [Table 9] (019, Brice & Gilbert, 2009). Swiss chard seeds were treated at a nominal application rate of 40 g ai/100 kg seeds and sown into containers of soil on the same day as treatment. Swiss chard plants were grown under greenhouse conditions and harvested 49 days after the seeds were planted (PHI 49 days) at the growth stage BBCH 14-15 (4 to 5 fully open leaves).

TRR was determined by combustion/liquid scintillation counting (LSC) analysis of homogenized tissue samples were 0.0491 mg/kg for Swiss chard treated with [phenyl-U-^{14}C]sedaxane and 0.0586 mg/kg for Swiss chard treated with [pyrazole-5-^{14}C]sedaxane. The TRR derived from the sum of the radioactivity present in the extracts and the post extraction solids were 0.0452 mg/kg for the phenyl label and 0.0556 mg/kg for the pyrazole label, which are in good agreement (92% for the phenyl label and 95% for the pyrazole label) with the values based on combustion.

The majority of the radioactivity in Swiss chard was released with a series of acetonitrile and acetonitrile:water solvent extractions (95.5% TRR; 0.0431 mg/kg for the phenyl label and 97.1% TRR; 0.0539 mg/kg for the pyrazole label), leaving 4.54% TRR (0.0021 mg/kg for the phenyl label) and 2.95% TRR (0.0016 mg/kg for the pyrazole label) in the unextractable residues.

For the phenyl label, the N-desmethyl parent CSCD667584 was present at 4.5% TRR (0.002 mg/kg) and two components were tentatively identified as glycoside conjugates: CSCD658906 or CSCD659089 at 1.1% TRR (< 0.001 mg/kg) and CSCD668403 at 1.5% TRR (< 0.001 mg/kg). A number of other very minor metabolites were also observed at levels ≤ 2.0% TRR (< 0.001 mg/kg).

For the pyrazole label, CSCC210616 (pyrazole amide; free and conjugated) was present at 12.9% TRR (0.0072 mg/kg), CSCD465008 (N-desmethyl pyrazole acid; free and conjugated) was present at 11.5% TRR (0.0064 mg/kg), the N-desmethyl parent CSCD667584 was present at 2.3% TRR (0.0013 mg/kg) and CSAA798670 (pyrazole acid; free and conjugated) was present at 0.8% TRR (< 0.001 mg/kg). Two glycoside conjugated components tentatively identified as CSCD658906 or CSCD659089, and CSCD668403 were present at 0.9% TRR each.

The principal metabolism transformations include N-demethylation of the pyrazole ring and cleavage between the pyrazole and phenyl ring. In addition, possible minor metabolism transformations involve hydroxylation of the phenyl ring and/or hydroxylation of the cyclopropyl ring and ring opening of the cyclopropyl ring, based on tentative assignments of metabolites, present as glycoside conjugates that were released on hydrolysis with Driselase enzyme.

The sedaxane trans:cis isomer ratio of the administered dose material was 6:1. The same measured ratio in Swiss chard samples was reported as approximately 10:1.

Table 9 Summary of identification of radioactive residues in [^{14}C] Sedaxane treated Swiss chard (in %TRR and mg of sedaxane eq/kg) at BBCH 14-15 (49 DAP)

		Phenyl-U-^{14}C		Pyrazole-5-^{14}C	
TRR by summation, mg/kg		0.0452		0.0556	
TRR by direct quantification, mg/kg		0.0491		0.0586	
Origin of component	Component	%TRR	Residue (mg/kg)	%TRR	Residue (mg/kg)
Pre- and post-hydrolysis Chromatographed	Sedaxane (as conjugates)	52.3 (ND)	0.0236 (ND)	28.5 (0.3)	0.0159 (0.0002)
	CSCD465008	ND	ND	11.5	0.0064

	(as conjugates)			(2.2)	(0.0012)
	CSCD667584 (as conjugates)	4.5 (ND)	0.0020 (ND)	2.3 (ND)	0.0013 (ND)
	CSCC210616 (as conjugates)	ND	ND	12.9 (2.3)	0.0072 (0.0013)
	CSCD658906/ CSCD659089 (as conjugates)	1.1 (1.1)	0.0005 (0.0005)	0.9 (0.9)	0.0005 (0.0005)
	CSCD668403 (as conjugates)	1.5 (1.5)	0.0007 (0.0007)	0.9 (0.9)	0.0005 (0.0005)
	CSAA798670 (as conjugates)	ND	ND	0.8 (0.4)	0.0004 (0.0002)
	Unassigned [a]	6.4	0.0028	9.6	0.0054
	Baseline [b]	27.7	0.0125	22.6	0.0125
	Remainder [c]	0.3	0.0003	0.3	0.0003
	Unextracted [d]	4.5	0.0021	3.0	0.0016
	Accountability	98.3	0.0445	93.3	0.052

Note: Values without parenthesis are the sum of both the free and conjugated forms. The values within parenthesis indicate the proportion of the TRR that is conjugated.

[a] Phenyl label: no discreet components greater than 1.9% TRR (0.008 mg/kg)

Pyrazole label: no discrete components greater than 1.6% TRR (0.001 mg/kg)

[b] Baseline material on 2D TLC,

Phenyl label: further 1D TLC using a more polar solvent system showed this to comprise eight components each less than 11.3% TRR (≤ 0.005 mg/kg)

Pyrazole label: further 1D TLC using a more polar solvent system showed this to comprise nine components each ≤ 10.1% TRR (≤ 0.006 mg/kg)

[c] The remainder consists of areas of the chromatogram which cannot be assigned to discrete radioactive components/ streaks

[d] Radioactivity remaining in the debris after the initial extractions

Rape seed (Canola)

A study was submitted investigating the uptake and translocation of sedaxane in rape seed (canola) plants after treatment of seeds with a suspension concentrate containing either [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane (065, Fletcher & Gilbert, 2009). Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to rape seeds at a nominal concentration of 7.5 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment in a glasshouse. The wheat was grown under greenhouse conditions. Canola seed pods were harvested at growth stage BBCH 85–89 (50–90% of pods brown and about to split). Seeds were separated from the mature pods and analysed for residues. The TRR for the canola seed from both radiolabelled experiments was calculated to be less than the limit of detection of 0.002 mg/kg; therefore no further analysis was conducted. No uptake of sedaxane residues into canola seeds was observed.

Plant Metabolism Summary

Metabolism studies were conducted in wheat, soya bean, and Swiss chard; an uptake study was conducted with canola. For each crop, separate ring-labelled studies were conducted. The nature of the residues in wheat grain and canola seeds were not defined since the radioactive residue was very low in these crop matrices, < 0.007 and < 0.002 mg/kg, respectively. Sedaxane was a predominant

component of the residues in all foliage commodities, but was not found in the soya bean seeds. In Swiss chard, sedaxane was the major component of the residue representing up to 52% TRR, while in wheat and soya bean foliage commodities it represented 10.9–18.3% and 12.0–23.2% TRR, respectively.

Metabolism of sedaxane was similar in all three crops: oxidative metabolism of the phenyl and cyclopropane rings, N-demethylation of the pyrazole ring, and cleavage between the pyrazole and phenyl rings represent the pathways observed in all three crops. There is, however, variation in the significance of the different pathways and the nature of the observed conjugations between crops. Figure 2 presents the proposed metabolic profile of sedaxane in plants.

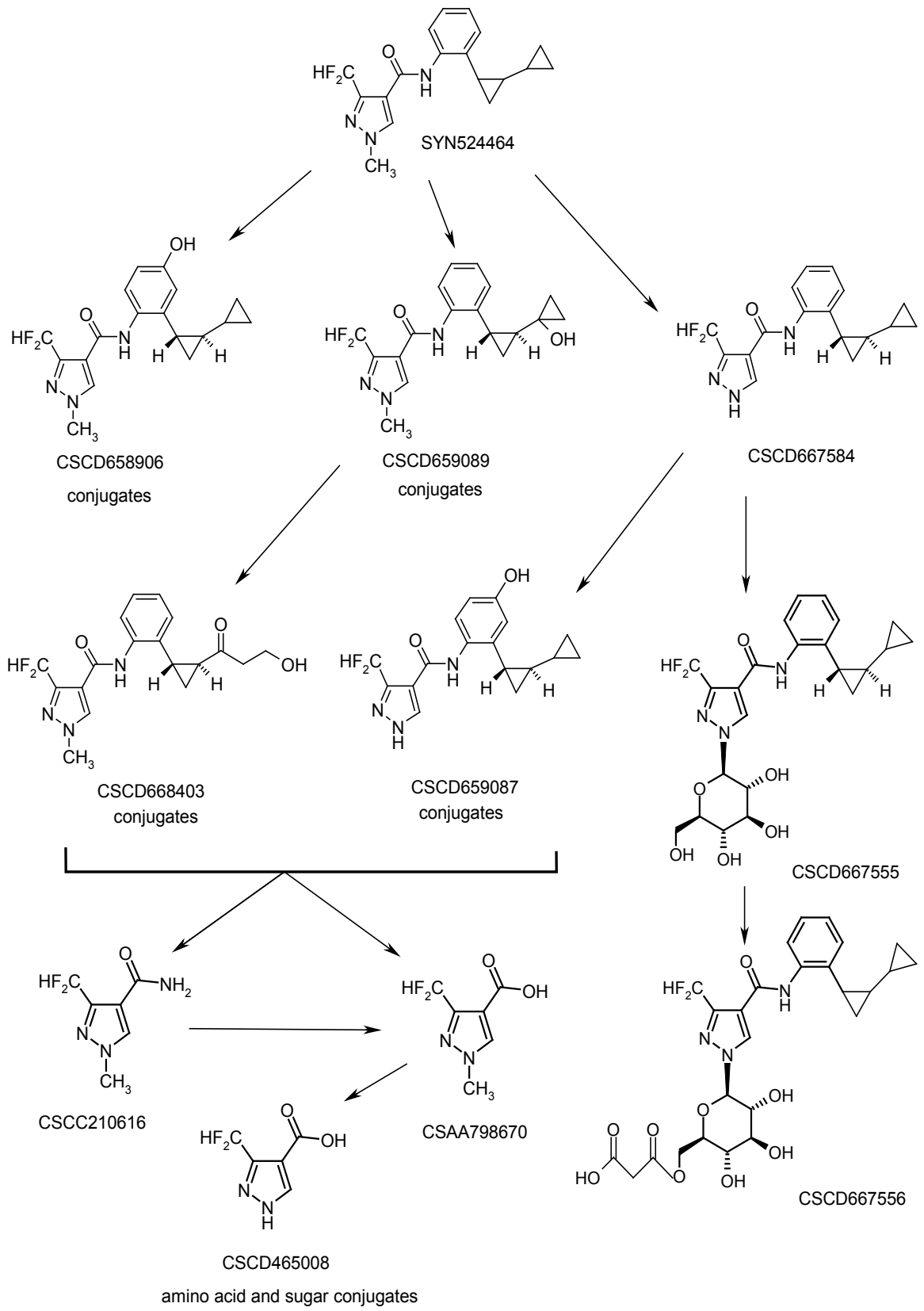


Figure 2 Proposed Metabolic Pathway of Sedaxane in Plants

Environmental Fate

Soil treatment rates in the environmental fate studies were expressed in g ai/ha. In order to compare these rates to the seed treatment rates, the crop sowing rates are needed. Table 10 provides this information for the relevant crops and in the countries where sedaxane is presently registered or intended to be registered, as supplied by the manufacturer. These data demonstrate that most of the environmental fate studies were conducted at significantly exaggerated rates compared to the maximum label seed treatment rates.

Table 10 Conversion of treatment rates to area equivalent rates based on maximum sowing rates

Crop	Country	Treatment Rate (g ai/100 kg seed)	Max Sowing Rate (kg seeds/ha)	Area Equivalent Rate (g ai/ha)
Barley	CAN	5	110	5.5
	USA	5	108	5.5
	France	10	250	25
Oat	CAN	5	110	5.5
	USA	5	168	8.4
	France	10	250	25
Wheat, Triticale, Rye	CAN	5	110	5.5
	USA	5	168	8.4
	France	10	250	25
Canola	CAN	5	6	0.3
	USA	5	9	0.45
Soya bean	CAN	5	72	3.6
	USA	5	72	3.6

Aerobic Soil Degradation

The rate of degradation of [pyrazole-5-^{14}C]-sedaxane and [phenyl-U-^{14}C]- sedaxane has been investigated under aerobic conditions at 20 ± 2 ºC in three soils in the dark for up to 367 days (066, Fitzmaurice & Mackenzie, 2009). The soils were North Dakota sandy clay loam [USA, pH 7.3, 5.6% organic matter], California sand [USA, pH 7.0, 0.6% organic matter] and Gartenacker loam [Switzerland, pH 7.1, 4.0% organic matter]. [^{14}C]-sedaxane was applied either to the surface of individual soil samples at a rate equivalent to 150 g ai/ha, or to spring wheat seeds, which were then sown into soil samples, to achieve a target application rate equivalent to a field rate of 150 g ai/ha [60 g ai/100 kg seed assuming the maximum wheat sowing rate in France].

The levels of sedaxane declined steadily, reaching ≤ 50% of applied radioactivity in all soils by 1 year in directly treated soils. The metabolites CSAA798670 and CSCD465008 were observed in all soils. CSCD465008 reached a maximum value of 32% of applied radioactivity in the North Dakota sandy clay loam following seed treatment application, and CSAA798670 reached a maximum value of 14% of applied radioactivity in the California sand following direct soil application of sedaxane.

Table 11 Composition of Extractable Radioactivity by HPLC in ND Sandy Clay Loam Treated with Seed Applied Sedaxane (Py label)

Time (days)	% in Extract	Sedaxane (%AR)	CSCD465008 (%AR)	CSAA798670 (%AR)
9	100	91	1.6	1.4
50	56	41	11	2.4

80	98	62	25	4.7
122	72	40	24	1.6
237	86	46	32	4.0
365	55	23	27	1.2

Table 12 Composition of Extractable Radioactivity by HPLC in CA Sand Treated with Soil Applied Sedaxane (Py label)

Time (days)	% in Extract	Sedaxane (%AR)	CSCD465008 (%AR)	CSAA798670 (%AR)
10	97	96	0	0.8
60	85	67	4.7	4.4
122	85	67	4.8	5.2
237	86	59	6.2	11
365	83	52	6.4	14

Table 13 DT_{50} and DT_{90} Values in Aerobic Soil Degradation Study for ^{14}C-Sedaxane Using Simple First Order Kinetics

Label	Soil	Seed Applied		Soil Applied	
		DT_{50} (days)	DT_{90} (days)	DT_{50}(days)	DT_{90} (days)
Phenyl	Gartenacker	88	292	296	984
Pyrazole	CA Sand	78	258	343	> 1000
Pyrazole	ND Sandy Clay Loam	160	531	377	> 1000
Phenyl	ND Sandy Clay Loam	105	344	422	> 1000
Mean		104	344	356	–

These results suggest that sedaxane is unlikely to persist in the environment when used as a seed treatment.

Soil photolysis

The photolysis of [^{14}C]-sedaxane (pyrazole and phenyl labelled) on moist soils was investigated under aerobic conditions, at 20 ± 2 ºC, with continuous irradiation by artificial sunlight for 18 days (432 hours), equivalent to > 30 days natural summer sunlight at 30ºN (021, Oddy, 2008; 021a, Oddy & Brett, 2008). The artificial sunlight was provided by a xenon arc lamp with filters to cut off any radiation below 290 nm. A second series of samples was then incubated under the same conditions except using air dry soil. Non-irradiated control samples were prepared concurrently. The nominal treatment rate was based on a single maximum field application rate of 150 g ai/ha. Similar results were obtained from the pyrazole and phenyl label experiments.

Table 14 DT_{50} and DT_{90} Values in Soil Photolysis Study for ^{14}C-Sedaxane Using Simple First Order Kinetics

Soil Condition	System	Pyrazole Label		Phenyl Label	
		DT_{50} (days)	DT_{90} (days)	DT_{50}(days)	DT_{90} (days)
Moist	Irradiated	82	273	73	242

Moist	Non-Irradiated	239	795	127	421
Dry	Irradiated	63	208	136	450
Dry	Non-Irradiated	393	> 1000	> 1000	> 1000

DT_{50} and DT_{90} values determined in this study are summarized in the table above. In both moist and dry soils, irradiation was found to result in faster degradation of sedaxane. Similar values were obtained moist and dry soils, and no significant differences in half-lives were noted when comparing the results from the two radiolabel experiments.

In the irradiated moist soil samples from the phenyl label experiment, the amount of parent sedaxane decreased from 97% of applied radioactivity at time zero to 84% after 432 hours. Over the same time period there was an increase in three minor transformation products which, in total, accounted for a maximum of 6.2% of the applied radioactivity. In the irradiated moist soil samples from the pyrazole label experiment, the amount of parent sedaxane decreased from 100% of applied radioactivity at time zero to 85% after 432 hours. Over the same time period there was an increase in four minor transformation products which, in total, accounted for a maximum of 7.1% of the applied radioactivity. Similar results were found in the dry soil experiments.

The study showed that photolysis may contribute to the degradation of sedaxane in the environment with the rate of degradation being shown to be faster under photolytic conditions than in non-irradiated samples. The effect was relatively small with no unique photodegradation products being identified.

Residues in succeeding crops

Two similar confined rotational crop studies were performed starting in the fall of 2007. The first was performed in outdoor plots in Madera, California, USA (025, Quistad, Kovatchev & LaMar, 2010). This study made use of sedaxane-treated soya bean seeds, grown to maturity and tilled back into the soil, and closely approximates the anticipated rotational crop scenario. The second was performed in a greenhouse in Harrogate, North Yorkshire in the UK. This study involved direct soil treatment with sedaxane followed by sowing of rotational crops, and thus represents a conventional rotational crop study (026, Graham and Gilbert, 2010).

Confined rotational crop study—application as seed treatment

For initial treatment, [pyrazole-5-^{14}C] labelled sedaxane and [phenyl-U-^{14}C] labelled sedaxane radiochemicals were applied to soya beans as a seed treatment. These pre-treated soya bean seeds were sown into eight raised plots filled with sandy loam soil. The seeding rate was 90–93 seeds/plot in order to obtain a target application rate of 100 g ai/ha (actual 99.1–113 g ai/ha).

Soya bean plants were grown, and then tilled back into the soil within a week before crop plant-back (excluding mature pods/seeds). Rotational crops wheat, lettuce and radish were sown 30, 120/151 and 365 days after treatment (DAT). The original 120-day PBI lettuce crop was severely damaged by cold weather; replanting was required and this resulted in a 151-day PBI for lettuce. Samples were harvested at times typical for each of the raw agricultural commodities (RACs): wheat (forage, hay, straw and grain), lettuce (immature and mature) and radish (root and aerial foliage). Table 15 compares the TRR levels determined in the pyrazole and phenyl-labelled sedaxane experiments. With only a few exceptions, higher TRR levels were found in the pyrazole-labelled experiments. Presumably, this results from preferential uptake of pyrazole metabolites resulting from cleavage of the sedaxane amide bridge into the rotational crops.

Table 15 Total Radioactive Residues (TRR) from Sedaxane Confined Accumulation in Rotational Crops (mg of sedaxane equivalents/kg)

Crop	RAC	Pyrazole-^{14}C			Phenyl-^{14}C		
		30 Day PBI	120/151	365 Day	30 Day PBI	120/151	365 Day

			Day PBI	PBI		Day PBI	PBI
Lettuce	Immature	0.058	0.36	0.14	0.007	0.038	0.010
	Mature	0.053	0.15	0.12	0.005	0.029	0.010
Radish	Foliage	0.019	0.20	0.25	0.018	0.044	0.016
	Roots	0.017	0.029	0.027	0.026	0.014	0.003
Wheat	Forage	0.13	0.39	0.18	0.10	0.041	0.054
	Hay	0.16	0.43	0.23	0.13	0.082	0.086
	Straw	0.17	0.58	0.13	0.21	0.23	0.064
	Grain	0.005**	0.028	0.004**	0.003**	0.004**	0.001**

PBI : Plant Back Interval

TRR = sum of fractions (combined ACN/water extracts + PES digestion extracts + PES)

**TRR by combustion

The major extractable ^{14}C-residues (free or conjugated) common to all the RACs are given in Tables 16 and 17. Approximately 87% and 82% TRR extractabilities were achieved by the combination acetonitrile/water extractions for the pyrazole and phenyl RACs, respectively. The major ^{14}C-residues included: parent, three hydroxylated intact metabolites, both free and sugar-conjugated forms (CSCD668403, CSCD659087 and CSCD659089), pyrazole amide (CSCD210616) and two pyrazole acids, both free and conjugated forms (CSAA798670 and CSCD465008). These major residues, especially conjugated forms, were particularly high in the 120 day PBI wheat straw extracted samples allowing for extensive characterization and identification.

Parent was often a minor residue in 30 and 120/151 day PBI RACs or even non-detectable in some 365 day PBI RACs. The highest TRR of parent was found in 30 day PBI phenyl radish root (0.015 mg/kg, 57.7% TRR).

Initial analysis of combined crop extracts took place less than 6 months after harvest. The 120 day PBI wheat straw extract was analysed after 4 months of storage at < 10 °C. Comparison of the initial and final radio-component profiles obtained showed no significant change in the profiles had occurred during the interim period of freezer storage.

Table 16 Levels of major extractable ^{14}C-Residues (free and conjugated) in rotational crops (%TRR) after application as seed treatment–Pyrazole radiolabel (residues in mg of sedaxane equivalents/kg)

Crop–PBI (days)	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD-668403	CSCD-659087	CSCD-659089	CSAA-798670	CSCD-465008	CSCC-210616	Char. Remain
Lettuce–30	Immature	0.058	93	5.2	1.7	ND	ND	55	26	ND	5
	Mature	0.053	93	11	ND	ND	ND	43	32	ND	7
Radish–30	Foliage	0.019	84	11	16	ND	5.3	ND	21	11	20
	Roots	0.017	82	47	ND	ND	ND	ND	ND	ND	35
Wheat–30	Forage	0.13	84	1.5	11	5.3	17	26	21	ND	2
	Hay	0.16	90	1.2	19	1.9	12	11	18	ND	27
	Straw	0.17	83	2.4	7.7	6.0	17	14	11	ND	25
	Grain	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lettuce–151	Immature	0.36	95	1.4	ND	ND	ND	46	19	ND	29
	Mature	0.15	87	1.4	ND	ND	ND	17	43	10	16
Radish–	Foliage	0.20	77	1.0	0.5	7.6	4.0	3.0	40	15	6

Crop–PBI (days)	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD-668403	CSCD-659087	CSCD-659089	CSAA-798670	CSCD-465008	CSCC-210616	Char. Remain
120	Roots	0.029	72	10	ND	ND	ND	ND	35	21	6
Wheat–120	Forage	0.39	81	1.6	14	6.7	14	31	13	ND	1
	Hay	0.43	88	ND	14	5.5	12	31	17	ND	9
	Straw	0.58	88	0.7	10.4	3.3	10	13	16	ND	35
	Grain	0.028	79	ND	ND	ND	ND	ND	11	ND	68
Lettuce–365	Immature	0.14	90	ND	ND	ND	ND	19	54	ND	17
	Mature	0.12	89	ND	ND	ND	ND	16	72	ND	1
Radish–365	Foliage	0.25	85	ND	ND	ND	ND	ND	53	8.0	24
	Roots	0.027	93	3.7	ND	ND	ND	ND	67	15	7
Wheat–365	Forage	0.18	82	2.3	15	1.1	12	17	27	ND	8
	Hay	0.23	89	ND	11	6.3	5.4	13	15	ND	38
	Straw	0.13	86	0.7	4.5	0.7	13	22	10	ND	35
	Grain	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA

PBI : Plant Back Interval

NA: not applicable

ND: not detected

Char. Remain: characterized remainder of the extractable residue.

Table 17 Levels of major extractable ^{14}C-Residues (free and conjugated) in rotational crops (%TRR) after application as seed treatment–Phenyl radiolabel (residues in mg of sedaxane equivalents/kg)

PBI	Crop	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD-668403	CSCD-659087	CSCD-659089	CSAA-798670	CSCD-465008	CSCC-210616	Char. Remain
30	Lettuce	Immature	0.007	86	29	14	ND	ND	ND	ND	ND	29
		Mature	0.005	80	ND	ND	ND	20	ND	ND	ND	60
	Radish	Foliage	0.018	89	17	11	ND	11	ND	ND	ND	50
		Roots	0.026	85	58	ND	ND	ND	ND	ND	ND	17
	Wheat	Forage	0.10	62	4	34	2.0	16	ND	ND	ND	10
		Hay	0.13	70	1.6	21	2.4	14	ND	ND	ND	31
		Straw	0.21	76	3.3	17	9.5	21	ND	ND	ND	25
		Grain	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA
120/151	Lettuce	Immature	0.038	84	18	ND	11	ND	7.9	ND	ND	24
		Mature	0.029	65	3.4	ND	ND	ND	7	ND	ND	54
	Radish	Foliage	0.044	84	2.3	16	11	14	ND	ND	ND	41
		Roots	0.014	57	36	ND	ND	ND	ND	ND	ND	21
	Wheat	Forage	0.041	68	15	24	2.4	17	ND	ND	ND	10
		Hay	0.082	88	ND	ND	11	13	ND	ND	ND	64
		Straw	0.23	85	4.3	21	9.4	23	ND	ND	ND	27
		Grain	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA

PBI	Crop	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD-668403	CSCD-659087	CSCD-659089	CSAA-798670	CSCD-465008	CSCC-210616	Char. Remain
365	Lettuce	Immature	0.010	90	20	ND	10	ND	10	ND	ND	50
		Mature	0.010	40	30	ND	10	ND	ND	ND	ND	NA
	Radish	Foliage	0.016	69	13	ND	ND	ND	ND	ND	ND	56
		Roots	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Wheat	Forage	0.054	69	2.0	19	22	22	ND	ND	ND	4
		Hay	0.086	70	2.0	34	5.8	7.0	ND	ND	ND	22
		Straw	0.064	94	3.1	23	13	22	ND	ND	ND	33
		Grain	ND	NA	NA	NA	NA	NA	NA	NA	NA	NA

PBI: Plant Back Interval

NA: not applicable

ND: not detected

Char. Remain: characterized remainder of the extractable residue.

Uptake of total radioactive residues was generally highest in the 120/151 day PBI rotational crops, particularly in pyrazole wheat foliage RACs, increasing with maturity (and corresponding to dehydration).

Sedaxane is likely to be a major component present at the 30 day planting interval, whilst its more polar half-molecule metabolites (in particular CSAA798670 and CSCD465008) may account for an increasing proportion of the TRR in the soil as time progresses. The low residue levels in the 30 day samples are believed to be a consequence of relatively poor uptake of sedaxane from soil into crops based on its physicochemical properties (logP 3.3, pKa no dissociation at physiological pH) combined with relatively low levels of polar soil metabolites present at this time.

At the second planting interval (120 or 151 days) there is likely to be degradation of sedaxane to the pyrazole specific carboxylic acid metabolites CSAA798670 and CSCD465008. The physicochemical properties of these molecules (more polar and acidic in nature) make them more amenable to uptake into crops relative to the parent molecule. The TRR is therefore higher than at 30 days and the residue comprises primarily these two metabolites. At the final time interval (365 days) the concentration of CSAA798670 and CSCD465008 in the vicinity of the root zone is expected to be significantly lower than at the second time point. This accounts for the lower TRRs at 365 days.

The primary mechanisms for the proposed biotransformation pathway of sedaxane in rotational crops after application by sowing pre-treated soya beans involved: hydroxylation of the bicyclic ring and isopropyl group, hydroxylation of the phenyl ring following N-demethylation of the pyrazole ring, and carbohydrate conjugation of hydroxylated metabolites.

The remaining free pyrazole moieties (predominantly as the pyrazole and/or N-desmethyl pyrazole acids) degraded comparatively slower and reacted via carbohydrate conjugation. CSAA798670 and CSCD465008 were also reported as major soil metabolites, which is consistent with their presence in rotational crops.

The proposed metabolic pathway for sedaxane in rotational crops following seed treatment is presented in Figure 3.

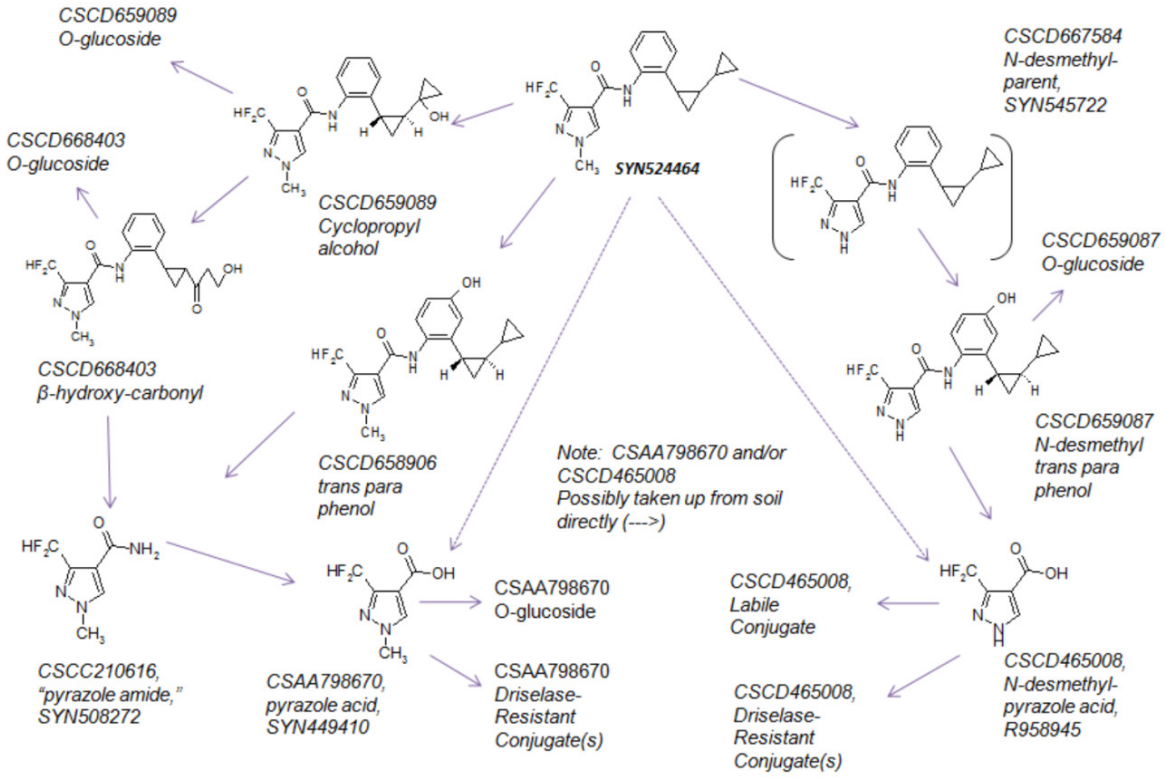


Figure 3 Proposed Metabolic Pathway of Sedaxane in Rotated Crops (Seed Treatment Application)

Confined rotational crop study–application to bare soil

[Pyrazole-5-^{14}C] labelled sedaxane and [phenyl-U-^{14}C] labelled sedaxane, formulated as a flowable concentrate, were applied to the soil at a nominal rate of 100 g ai/ha (achieved application rates 107.7 and 102.6 g ai/ha for the phenyl and pyrazole ring labelled sedaxane, respectively).

Succeeding crops representing cereal, root and leafy vegetable crop groups, i.e., wheat, turnip and lettuce were sown 29, 90 and 300 days after the application of the test substance.

Crops were harvested and separated into typical fractions as follows:

Lettuce—leaves were collected at immature harvest (BBCH 41–43) and at maturity (BBCH 49)

Turnip—leaves and root were collected separately at maturity (BBCH 49)

Wheat—aerial parts of the crop were taken at a suitable forage harvest growth stage (BBCH 22-30) and hay was taken at growth stage BBCH 41–49 (sample cut and dried in glasshouse). Grain and straw were collected separately at maturity (BBCH 89).

Tables 18 and 19 summarize the study results, indicating TRR levels and the results of metabolite identification obtained at the three PBIs.

Table 18 Levels of major extractable ^{14}C-Residues (free and conjugated) in rotational crops (%TRR) after application as soil application treatment-Pyrazole radiolabel (residues in mg of sedaxane equivalents/kg)

Crop - PBI (days)	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD 667584 CSCD 668403 CSCD-668403 CSCD-659087 CSCD-659089	CSAA-798670 CSCD-465008 CSCC-210616	Char. Remain
Lettuce –29	Immature	0.014	91	30	5.0	36	20
	Mature	0.012	93	15	6.2	36	36
Turnip–29	Foliage	0.089	97	8.8	15	35	38
	Roots	0.022	101	48	8.7	22	22
Wheat–29	Forage	0.060	100	17	26	20	37
	Hay	0.47	110	24	29	29	28
	Straw	1.1	91	14	28	4	45
	Grain	0.016	60	6	6	2	46
Lettuce –90	Immature	0.025	88	11	3.0	50	24
	Mature	0.026	88	11	2.7	46	28
Turnip–90	Foliage	0.049	88	6.3	5.0	54	23
	Roots	0.0081	102	43	7.1	30	22
Wheat–90	Forage	0.087	100	33	21	36	10
	Hay	0.43	106	18	19	33	36
	Straw	0.43	130	21	28	34	47
	Grain	< 0.01	NA	NA	NA	NA	NA
Lettuce –300	Immature	0.022	88	8.3	1.4	53	25
	Mature	0.021	85	8.8	1.4	41	34
Turnip–300	Foliage	0.026	90	1.9	1.7	41	48
	Roots	ND	NA	NA	NA	NA	NA
Wheat–300	Forage	0.040	100	21	17	26	36
	Hay	0.19	97	16	16	9	56
	Straw	0.23	97	13	21	5	58
	Grain	< 0.01	NA	NA	NA	NA	NA

PBI: Plant Back Interval

NA: not applicable

ND: not detected

Char. Remain: characterized remainder of the extractable residue.

Table 19 Levels of major extractable ^{14}C-Residues (free and conjugated) in rotational crops (%TRR) after application as soil application—Phenyl radiolabel (residues in mg of sedaxane equivalents/kg)

Crop - PBI (days)	RAC	Total (mg/kg)	Initial extract (%TRR)	Parent	CSCD 667584 CSCD 668403 CSCD-668403 CSCD-659087 CSCD-659089	CSAA-798670 CSCD-465008 CSCC-210616	Char. Remain
Lettuce–29	Immature	< 0.01	NA	NA	NA	NA	NA
	Mature	< 0.01	NA	NA	NA	NA	NA
Turnip–29	Foliage	0.046	77	10	20	ND	47
	Roots	0.013	89	54	11	ND	24
Wheat–29	Forage	0.043	100	42	39	ND	19
	Hay	0.31	115	57	25	ND	33
	Straw	0.53	98	20	40	ND	38
	Grain	< 0.01	NA	NA	NA	NA	NA
Lettuce–90	Immature	< 0.01	NA	NA	NA	NA	NA
	Mature	0.01	89	45	15	ND	29
Turnip–90	Foliage	0.025	92	17	13	ND	62
	Roots	< 0.01	NA	NA	NA	NA	NA
Wheat–90	Forage	0.046	100	41	26	ND	33
	Hay	0.29	88	28	27	ND	33
	Straw	0.36	100	20	29	ND	33
	Grain	< 0.01	NA	NA	NA	NA	NA
Lettuce–300	Immature	< 0.01	NA	NA	NA	NA	NA
	Mature	< 0.01	NA	NA	NA	NA	NA
Turnip–300	Foliage	< 0.01	NA	NA	NA	NA	NA
	Roots	< 0.01	NA	NA	NA	NA	NA
Wheat–300	Forage	0.021	100	36	27	ND	37
	Hay	0.073	100	31	20	ND	49
	Straw	0.13	103	20	32	ND	51
	Grain	< 0.01	NA	NA	NA	NA	NA

PBI: Plant Back Interval

NA: not applicable

ND: not detected

Char. Remain: characterized remainder of the extractable residue.

The proposed metabolic pathway for rotational crops following bare soil application is presented in Figure 4.

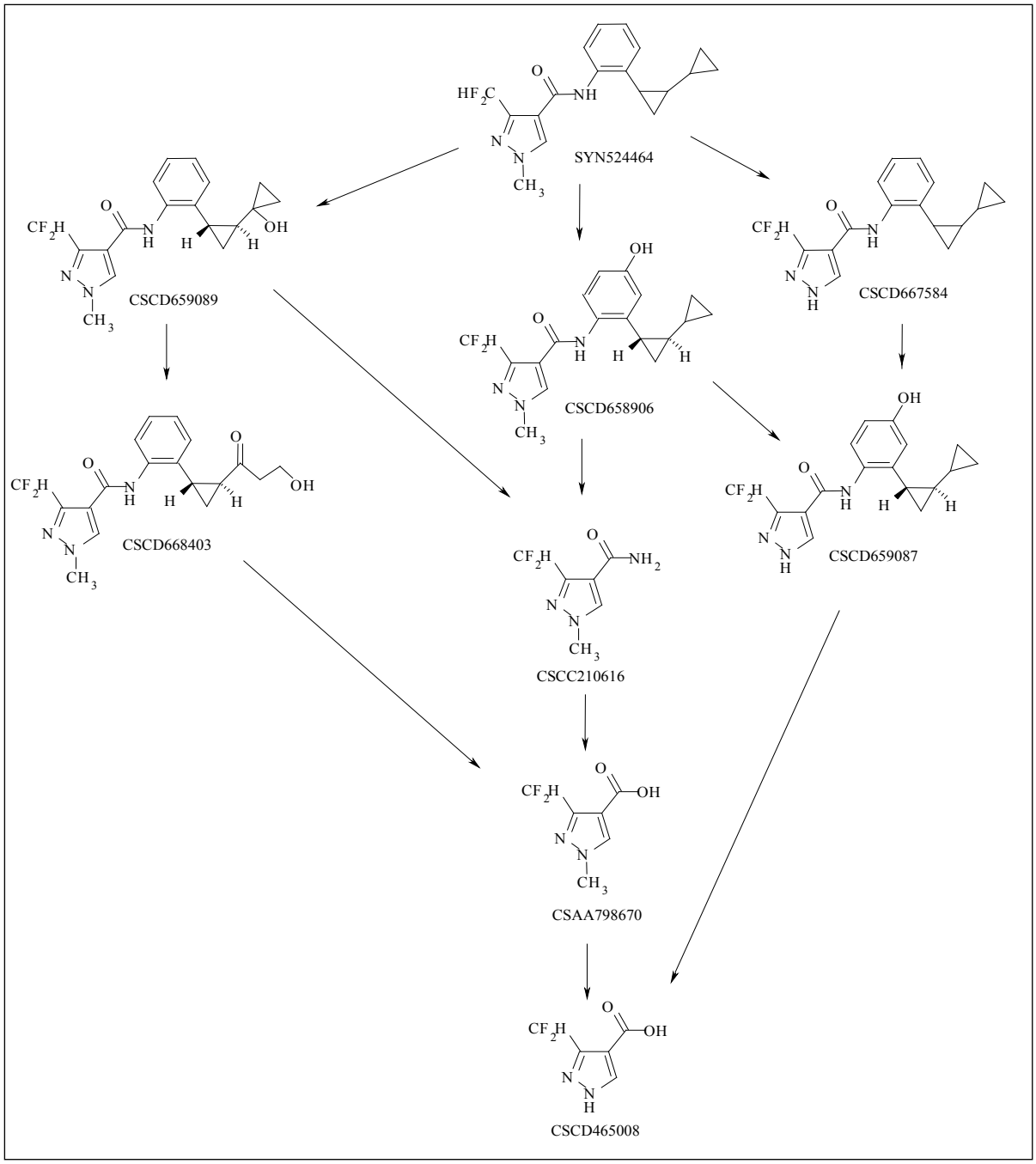


Figure 4 Proposed metabolic pathway of sedaxane in rotated crops (bare soil application)

Consistent with the seed treatment CRC study, higher residue levels were generally found in the samples from the pyrazole labelled experiments. Residues in crops declined over the period of the study and commodities from the 300 DAT plant-back interval were low i.e., wheat grain and turnip roots were < 0.01 mg/kg.

The primary difference noted between the seed treatment and soil application CRC studies was that more parent sedaxane was found in the soil application studies. This result demonstrates that the presence of plant material assists with sedaxane degradation.

Major features of the proposed biotransformation pathway of sedaxane were: N-demethylation of the pyrazole ring, hydroxylation of the phenyl ring, hydroxylation of the cyclopropyl

ring, conjugation of primary metabolites, ring opening of the cyclopropyl ring, cleavage between the phenyl and pyrazole rings.

The results of the confined rotational crop study indicate that pyrazole metabolites may be taken up by plant roots. Therefore, a limited field rotational crop study was conducted to properly assess the potential for accumulation in successive crops at various PBIs.

Field rotational crop studies—application as seed treatment

Two field crop rotation trials were carried out in Northern Europe (France and the United Kingdom) during 2008 and 2009 to determine any residues of sedaxane and its major rotational crop metabolites in crops grown in an area previously treated with sedaxane (027, Klimmek & Gizler, 2010). Further, two similar field crop rotation trials were carried out in Southern Europe (France and Italy) during 2008 and 2009 for the same purpose (028, Klimmek & Gizler, 2010).

In each trial, the application was made as a seed treatment to spring wheat at a nominal rate of 10 g ai/100 kg seed, equivalent to 25 g ai/ha.

Ten days before the scheduled plant back interval (either approximately 20 or approximately 50 days after drilling), the primary treated crop (wheat) was treated with glyphosate and incorporated back into the soil. Three representative crops (carrot, spinach and spring barley) were planted back into the treated soil in side by side sub-plots at typical timings and agricultural practice for rotational crops (nominal 30 or 60 days after drilling the primary crop for treated plot 1 and treated plot 2, respectively).

Approximately 10 days before the scheduled 3rd and 4th plant back interval (180 and 365 days, respectively) the cover crop was treated with glyphosate and incorporated back into the soil by light cultivation and harrowing.

Two representative crops (winter barley and winter oil seed rape) were sown into side by side sub-plots of treated plot 1 at typical timings and agricultural practice for winter rotational crops (nominally 180 days after drilling the primary crop).

Four representative crops (carrot, spinach, spring barley and spring oil seed rape) were planted back into the treated soil in side by side sub-plots of treated plot 2 at typical timings and agricultural practice for spring rotational crops (nominally 365 days after drilling the primary crop).

The rotational crops were maintained according to normal agricultural practices. Crops sampled at immature stages were barley forage at BBCH 30–33, barley whole plant at BBCH 59–70 and immature spinach at BBCH 49. All crops were sampled at maturity.

Samples of spinach (immature plant and mature leaves), short-cycle carrot (roots and leaves) and barley (forage, whole plant, grain and straw) were taken by hand (or with a combine harvester for mature barley grain and straw). Oil seed rape seed was sampled using a small plot combine. Samples were stored frozen at <-18 °C prior to analysis. Specimens were stored frozen for a maximum period of 17 months from sampling to analysis for trans-sedaxane and cis-sedaxane and the metabolites CSCD659089, CSCD668403, CSCD659087, CSAA798670 and CSCD465008.

Method GRM023.11A was used for analysis of S\sedaxane residues (trans-sedaxane and cis-sedaxane) and metabolites CSCD659089, CSCD668403, CSCD659087, CSAA798670 and CSCD465008. The limit of quantification (LOQ) has been determined to be 0.005 mg/kg for parent and 0.01 mg/kg for all metabolites.

Northern Europe trials

Residues of sedaxane (both isomers) and metabolites were all below the limit of quantification of the method in all the following crops.

No residues of sedaxane nor any of the metabolites (CSCD659089, CSCD668403, CSCD659087, CSAA798670 and CSCD465008) were found at or above the limits of quantification

in any of the untreated samples of spring barley, winter barley, carrots, spinach, spring and winter rape.

Southern Europe trials

All residues of trans-sedaxane and cis-sedaxane in spring barley, winter barley, carrots, spinach, spring rape and winter rape samples were below the LOQ of 0.005 mg/kg.

All residues of the metabolites CSCD668403, CSCD659089, CSCD659087, CSAA798670 and CSCD465008 in spring barley, winter barley, carrots, spinach, spring rape and winter rape samples were below the LOQ (< 0.01 mg/kg) except for one residue of 0.02 mg/kg (CSCD465008) in one carrot leaf sample taken at the 60 day PBI in a trial conducted in Italy.

Field rotational crop studies—application to bare soil

Six field rotational crop trials following direct soil application of sedaxane were conducted in the USA (029, Hamilton, 2010).

Sedaxane, formulated as a flowable concentrate for seed treatment (FS), was applied to bare-ground at two different rates, 9 and 30 g ai/ha, to cover conventional treatment rates. The test material was incorporated into the soil after application.

Three crop groups were planted back at three intervals: 60, 120 and 270-day Plant Back Intervals (PBIs). The three crop groups planted back were leafy vegetables (spinach), root and tuber vegetables (radish), and small grains (wheat). Untreated control crops were planted back concurrently in untreated areas. Plant back crops were harvested at typical agricultural intervals.

At the target interval, two separate replicate samples were obtained by collecting from several areas of the plot. Spinach and radish samples were collected at standard maturity; wheat was harvested at typical agricultural intervals.

After collection all samples were frozen and stored for a maximum of 7 months at -20 °C until analysis.

Samples were analysed for parent sedaxane, as trans and cis isomers. Samples were also analysed for the following metabolites: CSCD659089, CSCD668403, CSCD465008, CSCD659087 and CSAA798670.

Results for parent, CSCD659089 and CSCD668403 were determined using analytical method GRM023.03A. Results for CSCD465008, CSCD659089 and CSAA798670 were determined using analytical method GRM023.011A. The limit of quantification (LOQ) has been determined to be 0.005 mg/kg for parent and 0.01 mg/kg for all metabolites.

Residues of sedaxane and metabolites were all less than the LOQ of the methods in all the crop matrices tested at both application rates and all PBIs. No residues of sedaxane or any of the metabolites were detected in any of the control samples analysed during this study.

Rotational Crop Summary

The rotational crop studies demonstrate that, at maximum labelled use rates and patterns, no significant levels of sedaxane or its metabolites are expected in succeeding crops. The confined rotational crop study investigating uptake into succeeding crops following a soil application of sedaxane showed that parent sedaxane was a major residue in most plant matrices, although the absolute levels were low. This soil application use pattern does not match the intended use pattern and is primarily for informational purposes. The confined rotational crop study investigating uptake into succeeding crops following a seed treatment application showed essentially no parent sedaxane but primarily uptake of pyrazole metabolites. In order to determine the likely magnitude of these compounds in field scenarios, limited field rotational crop studies were undertaken.

Limited field rotational crop studies confirmed the general findings from the confined rotational crop study. No residues of parent were found at any interval in any crop matrix following

either soil or seed treatment applications at the critical GAP. The only residue detected in these studies was one residue of 0.02 mg/kg of pyrazole metabolite CSCD465008 in a carrot leaf sample taken at a 60 day plant back interval after seed treatment application from the trial conducted in Italy.

METHODS OF RESIDUE ANALYSIS

Several studies were conducted to document the performance of the analytical methods and these are summarized in Table 20. All methods are based on HPLC/MS/MS, as sedaxane is not amenable to GC analysis.

Table 20 Summary of Residue Analytical Methods [a]

Matrix	Analyte	Method No.	Purpose	LOQ
Crop methods				
Validated using various crops: wheat grain, straw, whole plant; carrot; spinach; potato; whole orange; rape seed; lentils; tomato; maize kernels; soya bean seed	TRANS-SEDAXANE CIS-SEDAXANE CSCD667584 CSCD658906 CSCD659089 CSCD668403 CSCD667555 CSCD465008 CSCC210616	GRM023.03A	Data Collection—plants	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE 0.01 mg/kg for metabolites
Validated using various rotated crops: wheat grain, straw, whole plant; carrot; spinach; rape seed	TRANS-SEDAXANE CIS-SEDAXANE CSCD659089 CSCD668403 CSCD659087 CSCD798670 CSCD465008	GRM023.11A	Data Collection—plants	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE 0.01 mg/kg for metabolites
Validated using various crops: Green forage (unspecified), rape seed; wheat grain; orange (whole fruit)	TRANS-SEDAXANE CIS-SEDAXANE	Specht method P-14.141	Enforcement—plants	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE
Validated using wheat green forage and wheat straw	TRANS-SEDAXANE CIS-SEDAXANE	ILV of Specht method P-14.141	Enforcement—plants	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE
Validated using soya bean seed	CSCD465008	GRM023.12A	Data Collection—plants	0.01 mg/kg
Validated using soya bean seed	CSCD465008	ILV of GRM023.12A	Data Collection—plants	0.01 mg/kg

Matrix	Analyte	Method No.	Purpose	LOQ
Crop commodities (wheat) from European field trial studies	TRANS-SEDAXANE CIS-SEDAXANE	GRM023.01A	Data Collection—plants	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE
Livestock methods				
Validated using bovine muscle, kidney, liver, fat, chicken eggs, bovine blood Bovine feeding study	TRANS-SEDAXANE CIS-SEDAXANE CSCD658906 CSCD659087	GRM023.10A	Data Collection—livestock	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE 0.01 mg/kg for metabolites
Validated using bovine muscle, liver, and milk	TRANS-SEDAXANE CIS-SEDAXANE CSCD658906 CSCD659087	ILV of GRM023.10A	Data Collection—livestock	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE 0.01 mg/kg for metabolites
Validated using bovine meat, kidney, liver, fat, milk, blood, and hen egg	TRANS-SEDAXANE CIS-SEDAXANE	Specht method P-14.141	Enforcement—livestock	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE
Validated using bovine milk, liver, and hen egg	TRANS-SEDAXANE CIS-SEDAXANE	ILV of Specht method P-14.141	Enforcement—livestock	0.005 mg/kg for TRANS-SEDAXANE and CIS-SEDAXANE
Multi-residue method				
The behaviour of trans-sedaxane and cis-sedaxane through MRM Protocols A-G of the PAM I Multi-residue Method (MRM) was investigated but low recoveries were obtained.				

The FDA Multi-Residue Method Test guidelines in the Pesticide Analytical Manual (PAM) (Third Edition, January 1994) is not applicable for the analysis of sedaxane (064, Reibach, 2010), due to low recoveries.

Enforcement method in plant matrices

Specht method P-14.141

Specht method P-14.141 (dispersive solid phase extraction/HPLC/MS/MS) was developed for the determination of residues of sedaxane (as its isomers trans-sedaxane and cis-sedaxane) in/on various crops. In this method, crop samples are extracted with acetonitrile:water (80:20, v/v) (049, Specht, 2007). A buffer-salt mixture is added containing magnesium sulphate, sodium chloride, trisodium citrate dehydrate and disodium hydrogen citrate and the extract is shaken, then centrifuged. After centrifugation, an aliquot of the extract is cleaned up with PSA (primary and secondary amines) sorbent and magnesium sulphate prior to analysis. The sedaxane isomers (trans-sedaxane and cis-sedaxane) are quantitatively determined by LC-MS/MS.

The validated limit of quantification (LOQ) reported in the method is 0.005 mg/kg for trans-sedaxane and cis-sedaxane in/on green forage, rape seed, wheat grain and orange (whole fruit) (047, Weber & Gizler, 2009). Acceptable mean recoveries ranging from 74% to 104% with relative standard deviations less than 20% were found using the quantification (primary) and confirmatory transitions for each of green forage, rape seed, wheat grain, and orange (whole fruit) fortified with trans-sedaxane and cis-sedaxane at 0.005 and 0.05 mg/kg.

An independent laboratory validation (ILV) study was also conducted on Specht method P-14.141_using samples of wheat green forage and wheat straw fortified with trans-sedaxane and cis-sedaxane at 0.005 and 0.05 mg/kg (048, Toledo & Rodriguez, 2010). Acceptable mean recoveries ranging from 80% to 107% with relative standard deviations less than 20% were found using the quantification (primary) [m/z 332→159] and confirmatory [m/z 332→292] transitions for each analyte and each matrix tested.

Data generation methods in plants

GRM023.03A

GRM023.03A is an HPLC/MS/MS data collection method for the determination of residues of sedaxane (as its isomers trans-sedaxane and cis-sedaxane) and its metabolites in/on a variety of crops (050, Klimmek & Gizler, 2009). In this method, samples are extracted with acetonitrile:water (80:20, v/v), centrifuged, and separate aliquots are taken and cleaned up using slightly different protocols for determination of the metabolites.

For trans-sedaxane and cis-sedaxane an aliquot is diluted with water and loaded onto a solid phase extraction (SPE) Oasis® HLB cartridge. The cartridge is washed with water and the two isomers are eluted with acetonitrile. The analytes are quantitatively determined by LC-MS/MS.

For the analysis of CSCD667584, CSCD658906, CSCD659089, CSCD668403 and CSCC210616, an aliquot is evaporated then buffered to pH 5. Samples are hydrolysed using Driselase® from *Basidiomycetes sp* (crude powder containing cellulose, laminarinase and xylanase activity), by incubation overnight in a water bath at 37 °C. Samples are centrifuged and taken through a SPE procedure. For the analysis of CSCD667555, an aliquot is made basic with 0.1M sodium hydroxide and hydrolysed at 60 ºC for 3 hours. Samples are cooled to room temperature and diluted with pure water. For the analysis of CSCD465008, an aliquot is evaporated and partitioned with isohexane, then acidified and taken through an SPE clean-up procedure. Final determinations are by LC-MS/MS.

The validated LOQ reported in the method is 0.005 mg/kg for trans-sedaxane and cis-sedaxane and 0.01 mg/kg for all metabolites in/on wheat (grain, straw and whole plant), carrots, spinach, potatoes, oranges, rape seed, lentils, tomatoes, maize kernels and soya bean seeds. Acceptable mean recoveries ranging from 70% to 111% with relative standard deviations less than 20% were found using the quantification (primary) and confirmatory transitions for each analyte and each matrix tested.

GRM023.03A was also radiovalidated for the extraction of [pyrazole-5-^{14}C]sedaxane and metabolites from wheat (forage and straw) and soya bean (forage and hay). The radiovalidation study proved the efficiency of the extraction methodology used in Method GRM023.03A (051, Fletcher & Gilbert, 2010). The residue method was shown to extract > 80% of the radioactivity in wheat forage and 95% in wheat straw compared to the wheat metabolism study. The residue method was also shown to extract ≥ 81% of the radioactivity in soya bean forage and 88% in soya bean hay compared to the soya bean metabolism study.

GRM023.11

GRM023.11 is an HPLC/MS/MS data collection method for the determination of residues of sedaxane (as its isomers trans-sedaxane and cis-sedaxane) and its metabolites in/on rotational crops (052, Lin, 2010). In this method, crop samples are extracted twice with acetonitrile:de-ionized water

(80:20, v/v) and the extracts are combined and centrifuged. Separate aliquots are taken from the combined extract and cleaned up separately for the determination of different analytes.

For determination of trans-sedaxane and cis-sedaxane the aliquots are evaporated to remove the acetonitrile, diluted with water:acetonitrile (90:10, v/v) and cleaned up on an SPE cartridge. The two isomers are eluted from the SPE cartridge with acetonitrile and diluted with deionized water:methanol (60:40, v/v). The analytes are quantitatively determined by LC-MS/MS.

For analysis of CSCD659089, CSCD668403, and CSCD659087, an aliquot of the extract is evaporated to approximately1 mL. The sample is buffered with sodium acetate and hydrolysed with Driselase® by incubation at 37 ºC for a minimum of 6 hours to liberate free CSCD659089, CSCD668403, and CSCD659087 from the conjugates. The sample is taken through an SPE clean-up and CSCD659089, CSCD668403 and CSCD659087 are eluted from the SPE cartridge with 60/40 (v/v) DIW/acetonitrile and diluted for LC-MS/MS analysis.

For analysis of CSAA798670 and CSCD465008, an aliquot of the primary extract is evaporated and then buffered with sodium acetate and hydrolysed with Driselase® by incubation at 37 ºC for a minimum of 6 hours to liberate free CSCD659089, CSCD668403 and CSCD659087 from the conjugates. Trans-sedaxane, cis-sedaxane, CSCD659089, CSCD668403and CSCD659087 are extracted from the aqueous sample by liquid-liquid partition with diethyl ether. The remaining aqueous fraction containing a mixture of free and conjugated CSAA798670 and CSCD465008 is acidified with concentrated HCl and refluxed for 2 hours to liberate free pyrazole acids from the conjugates. The diethyl ether partitions collected are evaporated to near-dryness and combined with the cooled, acidic aqueous fraction. An aliquot is taken through an SPE procedure. CSAA798670 and CSCD465008 are eluted from the SPE cartridge with 80/20 (v/v) DIW/acetonitrile. The eluate is evaporated to remove the acetonitrile and then diluted with an appropriate amount of DIW for quantification by LC-MS/MS.

The validated LOQ reported in the method is 0.005 mg/kg for trans-sedaxane and cis-sedaxane and 0.01 mg/kg for all metabolites in/on wheat (grain, straw and whole plant), carrots, spinach and rape seed. Acceptable mean recoveries ranging from 70% to 110% with relative standard deviations ≤ 20% were found using the quantification (primary) and confirmatory transitions for each analyte and each matrix tested.

Method GRM023.11A was radiovalidated for the extraction of [pyrazole-5-^{14}C]sedaxane and metabolites from wheat straw samples from a confined accumulation rotational crop study (051, Fletcher & Gilbert, 2010). The radiovalidation study proved the efficiency of the extraction methodology used in the residue method. The residue method was shown to extract 97% of the radioactivity in wheat straw compared to the confined accumulation rotational crop study.

GRM023.12A

GRM023.12A is an LC-MS/MS data collection method for the determination of combined residues of CSCD465008 from free and conjugated CSCD465008 in soya bean seed (054, Braid, 2010). Soya bean seed samples are extracted in 50/50 v/v acetonitrile/water by homogenization. After centrifugation, aliquots of the soya bean seed extracts are evaporated to remove all the acetonitrile then acidified with 2M HCl. Samples are heated at 90 °C to hydrolyse the conjugates of CSCD465008. The cooled, acidic sample is centrifuged then taken through a SPE clean-up procedure. CSCD465008 is eluted from the cartridge with 50/50 v/v acetonitrile/ultra pure water and the eluate is evaporated to remove the acetonitrile. Final determination is by LC-MS/MS.

Enforcement method in livestock matrices

The Specht method was used for determination of residues of sedaxane (as its isomers trans-sedaxane and cis-sedaxane) in animal matrices and body fluids using LC-MS/MS and was validated as a potential enforcement method (056, Weber & Gizler, 2009).

In this method, animal matrices and body fluid samples are extracted with acetonitrile:water (80:20, v/v). A buffer-salt mixture is added containing magnesium sulphate, sodium chloride,

trisodium citrate dehydrate and disodium hydrogen citrate and the extract is shaken by hand for 1 minute, and then centrifuged. After centrifugation, an aliquot of the extract of each matrix (except meat) is cleaned up with magnesium sulphate, PSA and chromabond sorbents (C18). For meat samples, an aliquot of the extract is cleaned up with magnesium sulphate and PSA sorbent. The samples are then centrifuged and the extracts are diluted with water prior to analysis. The sedaxane isomers (trans-sedaxane and cis-sedaxane) are quantitatively determined by LC-MS/MS.

The validated LOQ reported in the method is 0.005 mg/kg for trans-sedaxane and cis-sedaxane in bovine meat, liver, kidney, fat, milk and whole blood, and hen egg. The Specht method was successfully validated for the isomers trans-sedaxane and cis-sedaxane in bovine meat, liver, kidney, fat, milk and whole blood, and hen egg. Acceptable mean recoveries ranging from 80% to 106% with relative standard deviations less than 20% were found using the quantification (primary) and confirmatory transitions for each analyte and each matrix tested.

A successful ILV trial was conducted on the Specht method using samples of milk, egg and liver in sets consisting of one blank, two unfortified control samples, five samples fortified at the LOQ (0.005 mg/kg) and five samples fortified at ten times the LOQ (0.05 mg/kg) (057, Class & Senciuc, 2010). Acceptable mean recoveries ranging from 86% to 102% with relative standard deviations less than 20% were found using the quantification (primary) [m/z 332→159] and confirmatory [m/z 332→292] transitions for each analyte and each matrix tested.

Data generation methods in livestock

GRM023.10A

GRM023.10A is an HPLC/MS/MS method for the determination of residues of trans-sedaxane and cis-sedaxane and metabolites CSCD658906 and CSCD659087 in animal tissues, blood, milk and poultry eggs (055, Lin, 2009).

In this method, composite animal tissue samples are homogenized, with dry ice if needed, using a suitable food processor or bowl chopper. A subsample (10 g) is extracted with acetonitrile:water (80:20, v/v) for approximately 3 minutes and the extract is centrifuged. For determination of trans-sedaxane and cis-sedaxane, an aliquot (0.5 mL) is taken from the extract, mixed with water, diluted with an appropriate amount of water:methanol (60:40, v/v) and the isomers are determined by LC-MS/MS.

For determination of CSCD658906 and CSCD659087, an aliquot (2 mL) is taken from the extract, mixed with water and evaporated to ≤ 1 mL using an N_2 evaporator. The extract is adjusted to pH 5 and β-glucuronidase is used for hydrolysis in an incubator at 37 °C for a minimum of 6 hours. After the hydrolysis, samples are mixed with acetonitrile:water (50:50, v/v) and the sample is filtered through a 0.45 µm Acrodisc® GHP filter. The filtered sample is then diluted to an appropriate volume with water:acetonitrile (70:30, v/v) and analysed by LC-MS/MS.

The validated LOQ reported in the method is 0.005 mg/kg for trans-sedaxane and cis-sedaxane and 0.01 mg/kg for both metabolites in all matrices. The method was successfully validated using samples of bovine muscle, fat, kidney, liver, blood, milk and chicken eggs fortified at the LOQ and at 10 times the LOQ: 0.005 mg/kg and 0.05 mg/kg each for trans-sedaxane and cis-sedaxane and at 0.1 mg/kg for the metabolites CSCD658906 and CSCD659087. Acceptable mean recoveries ranging from 82% to 102% with relative standard deviations less than 20% were found using the quantification (primary) and confirmatory transitions for each analyte and each matrix tested.

The extraction method described in Method GRM023.10A was also radiovalidated for the extraction of [pyrazole-5-^{14}C]sedaxane and metabolites from livestock tissues and milk samples from a goat metabolism study. GRM023.10A was shown to extract 106%, 110%, and 86.4–99.6% of the radioactivity from milk, fat, and liver, respectively, compared to the metabolism study.

A successful ILV trial was conducted using samples of milk, liver and muscle fortified at the LOQ and 10 times the LOQ (059, Ward, 2009). Acceptable mean recoveries ranging from 79% to

111% with relative standard deviations less than 20% were found using the quantification (primary) and confirmatory transitions for each analyte and each matrix tested.

Summary of Analytical Methods

Adequate validation data and independent laboratory validation data were reported supporting the LOQ and LOD of 0.010 and 0.003 mg/kg, respectively, for sedaxane and its metabolites in all plant and animal matrices. Radiovalidation results demonstrated that the proposed methods are able to adequately extract aged residues.

Stability of pesticide residues in stored analytical samples

Results were available to evaluate the stability of sedaxane (060, Lakaschus & Gizler, 2010) and its metabolites (061, Klimmek & Gizler, 2010) in various crop matrices stored under frozen conditions up to 24 months. Individual aliquots of the homogenised sample materials were fortified with the indicated analytes at 0.20 mg/kg. Table 21 summarizes the findings from the studies; in total, they demonstrate that residues of sedaxane and its metabolites were stable for the time samples were stored in the magnitude of the residue studies (062, Lakaschus & Gizler, 2009; 063, Bennet, 2010).

Table 21 Summary of Sedaxane Storage Stability Studies

Matrix	Analyte	Storage Duration	Results
wheat grain and straw, spinach, potato, orange, lentils, and soya beans	Sedaxane isomers: Trans-sedaxane Cis-sedaxane	24-month	Residues of trans-sedaxane and cis-sedaxane are stable under frozen conditions (–18 °C) for at least 24 months.
wheat grain and straw, spinach, potato, orange, dried broad beans, and soya bean seeds	Metabolites: CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616, CSCD465008	24-month	Results indicate stability of all metabolites in all matrices tested for at least 24 months in frozen storage.
wheat grain and straw, barley forage, spinach, and carrots (leaves and roots)	Metabolite: CSAA798670	12-month	Residues of CSAA798670 are stable under frozen conditions (–18 °C) for at least 12 months
processed commodities of wheat (flour, germ, and bran), soya bean (meal, hulls, and oil), and orange (dried pulp, juice, and oil)	Sedaxane isomers: Trans-sedaxane Cis-sedaxane Metabolite: CSCD465008	12-month	Results indicate stability of all residues tested in all processed commodity matrices for at least 12 months in frozen storage.

Table 22 presents the results of the two-year storage stability study for the trans- and cis-isomers of sedaxane.

Table 22 Stability of Sedaxane Residues in Plants Following Storage at ≤ -18 °C

Commodity	Spike Level (mg/kg)	Storage Interval (days)	Measured Residues at Storage Interval (mg/kg)	Mean Residues at Storage Interval (mg/kg)	Mean % Remaining (%)

Commodity	Spike Level (mg/kg)	Storage Interval (days)	Measured Residues at Storage Interval (mg/kg)	Mean Residues at Storage Interval (mg/kg)	Mean % Remaining (%)
Trans-sedaxane					
Wheat grain	0.20	0	0.211, 0.206, 0.204	0.207	104
		99/114 [c]	0.174, 0.209	0.192	96
		182	0.212, 0.216	0.214	107
		365	0.152, 0.162	0.157	79
		552	0.182, 0.201	0.192	96
		719	0.192, 0.207	0.200	100
Wheat straw	0.20	0	0.202, 0.193, 0.187	0.194	97
		99	0.159, 0.167	0.163	82
		182	0.187, 0.187	0.187	94
		365	0.150, 0.140	0.145	73
		509 [d]	0.198, 0.204	0.201	101
		552	0.167, 0.183	0.175	88
		719	0.189, 0.187	0.188	94
Spinach	0.20	0	0.215, 0.213, 0.214	0.214	107
		99	0.203, 0.206	0.205	102
		182	0.212, 0.214	0.213	107
		365	0.183, 0.187	0.185	93
		552	0.200, 0.202	0.201	101
		719	0.220, 0.218	0.219	110
Potato	0.20	0	0.211, 0.200, 0.198	0.203	102
		99	0.203, 0.211	0.207	104
		182	0.210, 0.222	0.216	108
		365	0.182, 0.185	0.184	92
		552	0.190, 0.212	0.201	101
		719	0.205, 0.203	0.204	102
Orange	0.20	0	0.220, 0.204, 0.220	0.215	107
		99/114 [c]	0.211, 0.214	0.213	106
		182	0.206, 0.192	0.199	100
		365	0.194, 0.183	0.189	94
		552	0.177, 0.211	0.194	97
		719	0.215, 0.203	0.209	105
Lentils	0.20	0	0.211, 0.217, 0.196	0.208	104

Commodity	Spike Level (mg/kg)	Storage Interval (days)	Measured Residues at Storage Interval (mg/kg)	Mean Residues at Storage Interval (mg/kg)	Mean % Remaining (%)
		99	0.149, 0.204	0.177	88
		182	0.174, 0.208	0.191	96
		365	0.204, 0.226	0.215	108
		552	0.190, 0.204	0.197	99
		719	0.203, 0.216	0.210	105
Soya beans	0.20	0	0.205, 0.208, 0.210	0.208	104
		99	0.145, 0.155	0.150	75
		182	0.203, 0.171	0.187	94
		365	0.189, 0.191	0.190	95
		552	0.217, 0.182	0.200	100
		719	0.210, 0.208	0.209	105
Cis-sedaxane					
Wheat grain	0.20	0	0.211, 0.204, 0.208	0.208	104
		99/114 [c]	0.171, 0.208	0.190	95
		182	0.202, 0.204	0.203	102
		365	0.159, 0.167	0.163	82
		552	0.177, 0.183	0.180	90
		719	0.176, 0.192	0.184	92
Wheat straw	0.20	0	0.198, 0.194, 0.190	0.194	97
		98	0.162, 0.164	0.163	82
		187	0.184, 0.179	0.182	91
		365	0.181, 0.158	0.170	85
		552	0.163, 0.179	0.171	86
		719	0.184, 0.182	0.183	92
Spinach	0.20	0	0.205, 0.204, 0.208	0.206	103
		99	0.205, 0.209	0.207	104
		182	0.206, 0.213	0.210	105
		365	0.200, 0.207	0.204	102
		552	0.189, 0.205	0.197	99
		719	0.213, 0.209	0.211	106
Potato	0.20	0	0.210, 0.204, 0.203	0.206	103
		99	0.206, 0.209	0.208	104
		182	0.206, 0.222	0.214	107

Commodity	Spike Level (mg/kg)	Storage Interval (days)	Measured Residues at Storage Interval (mg/kg)	Mean Residues at Storage Interval (mg/kg)	Mean % Remaining (%)
		365	0.198, 0.201	0.200	100
		552	0.180, 0.205	0.193	96
		719	0.199, 0.191	0.195	98
Orange	0.20	0	0.193, 0.193, 0.199	0.195	98
		99/114 [c]	0.220, 0.207	0.214	107
		182	0.210, 0.186	0.198	99
		365	0.207, 0.223	0.215	108
		552	0.169, 0.214	0.192	96
		719	0.206, 0.196	0.201	101
Lentils	0.20	0	0.213, 0.218, 0.197	0.209	105
		99	0.141, 0.192	0.167	83
		182	0.156, 0.185	0.171	85
		365	0.207, 0.213	0.210	105
		552	0.175, 0.212	0.194	97
		719	0.193, 0.198	0.196	98
Soya beans	0.20	0	0.206, 0.206, 0.211	0.208	104
		99	0.140, 0.151	0.146	73
		182	0.197, 0.165	0.181	91
		365	0.196, 0.197	0.197	98
		552	0.198, 0.200	0.199	100
		719	0.195, 0.194	0.195	97

Similar results were obtained in the two-year storage stability study conducted for the following metabolites: CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616, and CSCD465008. Thus, mean percentage remaining values determined for CSCD667584 in the seven crop matrices tested (wheat grain, wheat straw, spinach, potato, orange, broad bean and soya bean) ranged from 70–107%. For CSCD658906, the percentage remaining values were 73–105%. For CSCD659089, the percentage remaining values were 73–110%. For CSCD668403, the percentage remaining values were 68–120%. For CSCD667555, the percentage remaining values were 65–116%. For CSCC210616, the percentage remaining values were 71–110%. For CSCD465008, the % remaining values were 74–103%.

No separate storage stability studies were submitted for animal commodities. However, all samples were analysed within 30 days of collection in the bovine feeding study, and no significant changes were noted in the radio-profiles of the principle extracts from milk, liver, kidney, muscle and fat samples at the end of the analytical phase of the animal metabolism studies.

Summary of storage stability results

The submitted storage stability results indicate that residues of sedaxane and its metabolites are stable in frozen storage for at least 2 years in plant matrices, and 1 year in processed commodities. These intervals are adequate to cover the sample storage intervals in the plant magnitude of the residue studies, the processing studies, and the animal studies.

USE PATTERN

Sedaxane is registered for use as a FS (flowable concentrate) formulation in several countries as a seed treatment application. The use patterns relevant for this evaluation are summarized in Table 23.

Table 23 Identification of Critical GAPs for Sedaxane

Crop	Country	GAP Specification	
		Treatment Rate (g as/100 kg seed)	Pre Grazing/Feeding Interval (days)[a]
Barley	CAN	5	45
	USA	5	45
	France	10	NS
Oat	CAN	5	45
	USA	5	45
	France	10	NS
Wheat, Triticale, Rye	CAN	5	45
	USA	5	45
	France	10	NS
Canola	CAN	5	45
	USA	5	45
Soya bean	CAN	5	45
	USA	5	45

[a] Do not graze or feed livestock on seeded areas for 45 days after planting.

RESIDUES RESULTING FROM SUPERVISED TRIALS

One hundred and forty-five supervised sedaxane residue trials were conducted in Australia (AUS), the European Union (EU), the United States of America (USA), Canada (CAN) and Brazil (BRZ), as summarized below.

Table 24 Index of tables summarizing sedaxane seed treatment crop field trials

Table No.	Crop	Country	# of Trials
25	Soya bean	BRZ, USA	22
26	Barley grain	AUS, EU, USA	28
27	Oat grain	AUS	4
28	Wheat grain	AUS, EU, USA, CAN	67
29	Rape seed	AUS, EU, USA, CAN	24
Animal Feeds			
30	Soya bean (forage & hay)	BRZ, USA	20
31	Barley (straw & hay)	AUS, EU, USA	28

Table No.	Crop	Country	# of Trials
32	Oat (forage, hay & straw)	AUS	4
33	Wheat (forage, hay & straw)	AUS, EU, USA, CAN	67

Results from the supervised trials are shown in Tables 25–33. Residues of sedaxane and its metabolites were determined by LC-MS/MS, with a LOQ of 0.005 mg/kg for *trans*- and *cis-sedaxane* (totalled to 0.010 mg/kg), and an LOQ of 0.010 mg/kg for all sedaxane metabolites. The data gathering method for plants was used for sample analysis. Unless stated otherwise, in all trials, untreated control plots gave residues < LOQ.

All field trials involved seed treatment applications to the seeds, and most were conducted according to the GAP use pattern. The data tables that follow are arranged according to crop groupings, with human food RACs first, followed by animal feed commodity tables.

The Meeting received extensive residue data on residue levels of parent sedaxane and its metabolites. Because no detectable residues of sedaxane or any of its metabolites were found in any human food RAC, these tables were simplified to depict only sedaxane residue levels, as the sum of the *trans*- and *cis*-isomers. For the livestock feedstuffs, detectable levels of sedaxane and several metabolites were found in some samples. For these tables, levels of sedaxane and the major metabolite(s) are indicated.

Soya bean

Table 25 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on Soya beans at maturity (Reference 044, 045)

Country Year Soya bean	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Quitman, Georgia USA, 2008	NK/S73-Z5	2	40	89-99	138	Seed	< 0.01
Sycamore, Georgia USA, 2008	NK/S76-L9	2	40	89-99	161	Seed	< 0.01
Cheneyville, Louisiana USA, 2008	NK/S49-Q9	4	40	89-99	145	Seed	< 0.01
Cheneyville, Louisiana USA, 2008	NK/S49-Q9	4	40	89-99	144	Seed	< 0.01
Cheneyville, Louisiana USA, 2008	NK/S52-F2	4	40	89	145	Seed	< 0.01
Oregon, Missouri USA, 2008	NK/S36-C7	5	40	89	133	Seed	< 0.01
St. Joseph, Missouri USA, 2008	NK/S36-C7	5	40	89	131	Seed	< 0.01
Fitchburg, Wisconsin USA, 2008	NK/H-1604	5	40	89	128	Seed	< 0.01
Fitchburg, Wisconsin USA, 2008	H1604RR	5	40	89	127	Seed	< 0.01
Northwood, North Dakota USA, 2008	NK/S01-C9	5	40	89	143	Seed	< 0.01

Country Year Soya bean	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
York, Nebraska USA, 2008	S27-C4	5	40	89	124	Seed	< 0.01
Osceola, Nebraska USA, 2008	S27-C4	5	40	89	117	Seed	< 0.01
Bagley, Iowa USA, 2008	NK/S32-E2	5	40	89	131	Seed	< 0.01
Berkley, Iowa USA, 2008	NK/S32-E2	5	40	89	121	Seed	< 0.01
Lime Springs, Iowa USA, 2008	NK/21-N6	5	40	89	122	Seed	< 0.01
Lime Springs, Iowa USA, 2008	NK/S21-N6	5	40	89	121	Seed	< 0.01
Richland, Iowa USA, 2008	NK/S32-E2	5	40	89	138	Seed	< 0.01
Laplata, Missouri USA, 2008	NK/S32-E2	5	40	89	122	Seed	< 0.01
Perley, Minnesota USA, 2008	NK/S02-M9	5	40	89	127	Seed	< 0.01
Perley, Minnesota USA, 2008	NK/S02-M9	5	40	89	131	Seed	< 0.01
Holambra, São Paulo, Brazil 2008	CD219RR		120	89	167	Seed	< 0.01
Uberlândia, Minas Gerais, Brazil 2008	NK9047RR		120	89	95	Seed	< 0.01

Cereal grains

Table 26 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on barley, grain at maturity (Reference 030-033)

Country Year Barley	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Toodyay, Western Australia, 2008	Yagan	AUS	5 10	89-99	162 162	Grain	< 0.01 < 0.01
Templers, South Australia, 2008	Flagship	AUS	5 10	89-99	147 147	Grain	< 0.01 < 0.01
Moorilim, Victoria, 2008	Gairdner	AUS	5 10	89-99	164 164	Grain	< 0.01 < 0.01

Country Year Barley	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Boggabilla, Northern New South Wales, 2008	Grimmett	AUS	5 10	89-99	169 169	Grain	< 0.01 < 0.01
Bagley, IA USA 2009	Unknown	5	5	89	84	Grain	< 0.01
Richland, IA USA 2008	Robust	5	5	89	102	Grain	< 0.01
Northwood, ND USA 2008	Tradition	7	5	89	101	Grain	< 0.01
Carrington, ND USA 2008	Tradition	7	5	89	110	Grain	< 0.01
New Rockford, ND USA 2008	Tradition	7	5	89	112	Grain	< 0.01
Eldridge, ND USA 2008	Tradition	7	5	89	103	Grain	< 0.01
Adrian, ND USA 2008	Tradition	7	5	89	99	Grain	< 0.01
Monte Vista, CO USA 2008	Drummond	9	5	89	113	Grain	< 0.01
Fresno, CA USA 2008	Tradition	10	5	89	310	Grain	< 0.01
Hermiston, OR USA 2008	Tradition	11	5	89	99	Grain	< 0.01
Rupert, ID USA, 2008	IDA Gold II	11	5	89	104	Grain	< 0.01
North Rose, NY USA 2009	Robust	1	5	89	102	Grain	< 0.01
Elm Creek, MB Canada, 2008	Legacy	5	5	87-99	95	Grain	< 0.01
St. Marc-sur-Richelieu, QC, Canada, 2008	AC Metcalfe	5	5	87-99	102	Grain	< 0.01
Vanscoy, SK, Canada, 2008	Legacy	7	5	87-99	104	Grain	< 0.01
Delisle, SK, Canada 2008	AC Metcalfe	7	5	87-99	111	Grain	< 0.01
Minto, MB, Canada 2008	Legacy	14	5	87-99	98	Grain	< 0.01
Boissevain, MB, Canada 2008	AC Metcalfe	14	5	87-99	98	Grain	< 0.01
Rosthern, SK, Canada 2008	Legacy	14	5	87-99	105	Grain	< 0.01

Country Year Barley	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Hepburn, SK, Canada 2008	AC Metcalfe	14	5	87-99	108	Grain	< 0.01
Innisfail, AB, Canada 2008	AC Metcalfe	14	5	87-99	119	Grain	< 0.01
Penhold, AB, Canada 2008	Legacy	14	5	87-99	99	Grain	< 0.01
Josephburg, AB. Canada 2008	Legacy	14	5	87-99	110	Grain	< 0.01
Alvena, SK, Canada 2008	AC Metcalfe	14	5	87-99	105 113 119 126	Grain	< 0.01 < 0.01 < 0.01 < 0.01

Table 27 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on oats at maturity (Reference 033)

Country Year Oats	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Toodyay, Western Australia, 2008	Winjardie	AUS	5 10	89-99	162 162	Grain	< 0.01 < 0.01
Templers, South Australia, 2008	Wintaroo	AUS	5 10	89-99	140 140	Grain	< 0.01 < 0.01
Moorilim, Victoria, 2008	Yarran	AUS	5 10	89-99	164 164	Grain	< 0.01 < 0.01
Walla Walla, Northern New South Wales, 2008	Bimbal	AUS	5 10	89-99	154 154	Grain	< 0.01 < 0.01

Table 28 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on wheat, grain at maturity (Reference 033-041)

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Toodyay Western Australia, Australia, 2008	Spring Wheat (Millewa)	AUS	5 10	89-99	162 162	Grain	< 0.01 < 0.01
Southern River, Western Australia, Australia, 2008	Spring Wheat (Millewa)	AUS	5 10	89-99	160 160	Grain	< 0.01 < 0.01
Templers, South Australia, 2008	Spring Wheat (Yitpi)	AUS	5 10	89-99	157 157	Grain	< 0.01 < 0.01
Moorilim, Victoria Australia, 2008 Clay loam	Spring Wheat (Whistler)	AUS	5 10	89-99	164 164	Grain	< 0.01 < 0.01
Moorilim, Victoria Australia, 2008 Sandy loam	Spring Wheat (Whistler)	AUS	5 10	89-99	163 163	Grain	< 0.01 < 0.01
Walla Walla, NSW Australia2008	Spring Wheat (Ventura)	AUS	5 10	89-99	154 154	Grain	< 0.01 < 0.01
Boggabilla, NSW Australia, 2008	Spring Wheat (Gregory)	AUS	5 10	89-99	169 169	Grain	< 0.01 < 0.01
Goondiwindi, Qld Australia, 2008	Spring Wheat (Gregory)	AUS	5 10	89-99	169 169	Grain	< 0.01 < 0.01
Goldbeck, Germany 2007	Spring Wheat (Leguan)	EU-N	10	89	137	Grain	< 0.01
Burweg, Germany 2007	Spring Wheat (Leguan)	EU-N	10	89	137	Grain	< 0.01
Roinvilliers, N. France 2007	Spring Wheat (Leguan)	EU-N	10	89	122	Grain	< 0.01

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Kings Newton, Derbyshire, UK 2007	Spring Wheat (Leguan)	EU-N	10	89	132	Grain	< 0.01
Grivesnes, N. France 2007-2008	Winter Wheat (Apache)	EU-N	10	89	299	Grain	< 0.01
Rogy, N. France 2007-2008	Winter Wheat (Apache)	EU-N	10	89	273	Grain	< 0.01
Ormes, N. France 2007-2008	Winter Wheat (Apache)	EU-N	10	89	283	Grain	< 0.01
Sept Saulx, N. France 2007-2008	Winter Wheat (Apache)	EU-N	10	89	286	Grain	< 0.01
Roinvilliers, N. France 2008	Spring Wheat (Granary)	EU-N	10	89	120	Grain	< 0.01
Mulsum, Niedersachsen, Germany 2008	Spring Wheat (Granary)	EU-N	10	89	100	Grain	< 0.01
Goldbeck, Niedersachsen, Germany 2008	Spring Wheat (Granary)	EU-N	10	89	120	Grain	< 0.01
Pilling, Lancashire, UK 2008	Spring Wheat (Granary)	EU-N	10	89	157	Grain	< 0.01
Hemington, Derbyshire, UK 2008	Spring Wheat (Granary)	EU-N	10	89	153	Grain	< 0.01
Meauzac, S. France 2007	Spring Wheat (Leguan)	EU-S	10	89	89	Grain	< 0.01
Montauban, S. France 2007	Spring Wheat (Leguan)	EU-S	10	89	112	Grain	< 0.01

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
S. Maria Codifiume, Italy 2007	Spring Wheat (Leguan)	EU-S	10	89	97	Grain	< 0.01
Marsillargues, S. France 2007	Winter Wheat (Apache)	EU-S	10	89	238	Grain	< 0.01
Pompignan, S. France 2007 Loamy sand, pH 8.2	Winter Wheat (Apache)	EU-S	10	89	239	Grain	< 0.01
Pompignan, S. France 2007 Sandy clay, pH 5.9	Winter Wheat (Apache)	EU-S	10	89	246	Grain	< 0.01
Cordes Tolosannes, S. France 2008	Spring Wheat (Palesio)	EU-S	10	89	119	Grain	< 0.01
Montbeton, S. France 2008	Spring Wheat (Palesio)	EU-S	10	89	127	Grain	< 0.01
Castelguelfo, Bologna, Italy 2008	Spring Wheat (Palesio)	EU-S	10	89	104	Grain	< 0.01
Budrio, Bologna, Italy 2008	Spring Wheat (Palesio)	EU-S	10	89	95	Grain	< 0.01
Mebane, NC USA 2008/2009	Winter Wheat (Coker)	2	5	89	268	Grain	< 0.01
Cheneyville, LA USA 2008/2009	Winter Wheat (Terral)	4	5	89	185	Grain	< 0.01
Oregon, MO USA 2008/2009	Winter Wheat (Santa Fe)	5	5	89	215	Grain	< 0.01
Troy, KS USA 2008	Winter Wheat (Danby)	5	5	89	236	Grain	< 0.01

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Bagley, IA USA 2008	Winter Wheat (Arapahoe)	5	5	89	299	Grain	< 0.01
Lime Springs, IA USA 2008	Spring Wheat (Granger HRS)	5	5	89	108 112 119 126	Grain	< 0.01 < 0.01 < 0.01 < 0.01
Lime Springs, IA USA 2008	Spring Wheat (Granger HRS)	5	5	89	113	Grain	< 0.01
Wharton, TX USA 2008	Winter Wheat (Fannin)	6	5	89	188	Grain	< 0.01
Eldridge, ND USA 2008	Spring Wheat (Penewawa)	7	5	89	103	Grain	< 0.01
Eldridge, ND USA 2008	Spring Wheat (Argent)	7	5	89	96	Grain	< 0.01
New Rockford, ND USA 2008	Winter Wheat (Hawken)	7	5	89	334	Grain	< 0.01
Carrington, ND USA 2008	Spring Wheat (Divide)	7	5	89	110	Grain	< 0.01
Adrian, ND USA 2008	Spring Wheat (Alsen)	7	5	89	99	Grain	< 0.01
Claude, TX USA 2008	Winter Wheat (Deliver)	8	5	89	287	Grain	< 0.01
Groom, TX USA 2008	Winter Wheat (Cutter)	8	5	89	287	Grain	< 0.01
Groom. TX USA 2008	Winter Wheat (Deliver)	8	5	89	287	Grain	< 0.01
Levelland, TX USA 2008	Winter Wheat (TAM 111)	8	5	89	266	Grain	< 0.01

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Wolforth, TX USA 2008	Winter Wheat (TAM 112)	8	5	89	253	Grain	< 0.01
New Home, TX USA 2008	Winter Wheat (TAM 105)	8	5	89	258	Grain	< 0.01
Hermiston, OR USA 2008	Winter Wheat (Stephens)	11	5	89	273	Grain	< 0.01
Elm Creek, MB Canada 2008	Spring Wheat (Lillian)	5	5	89	97	Grain	< 0.01
Portage la Prairie, MB Canada 2008	Spring Wheat (Infinity)	5	5	89	114	Grain	< 0.01
Delisle, SK Canada 2008	Spring Wheat (Lillian)	7	5	89	111	Grain	< 0.01
Delisle, SK Canada 2008	Spring Wheat (Infinity)	7	5	89	111	Grain	< 0.01
Variscoy, SK Canada 2008	Spring Wheat (Lillian)	7	5	89	106 113 120 127	Grain	< 0.01 < 0.01 < 0.01 < 0.01
Variscoy, SK Canada 2008	Spring Wheat (Infinity)	7	5	89	106	Grain	< 0.01
Dundum, SK Canada 2008	Spring Wheat (Lillian)	7	5	89	109	Grain	< 0.01
Dundum, SK Canada 2008	Spring Wheat (Infinity)	7	5	89	109	Grain	< 0.01
Taber, AB Canada 2008	Spring Wheat (Infinity)	7A	5	89	130	Grain	< 0.01
Boissevain, MB Canada 2008	Spring Wheat (Lillian)	14	5	89	104	Grain	< 0.01
Minto, MB Canada 2008	Spring Wheat (Infinity)	14	5	89	98 105 112 119	Grain	< 0.01 < 0.01 < 0.01 < 0.01

Country Year WHEAT	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Rosthern, SK Canada 2008	Spring Wheat (Lillian)	14	5	89	118	Grain	< 0.01
Hepburn, SK Canada 2008	Spring Wheat (Lillian)	14	5	89	108	Grain	< 0.01
Hepburn, SK Canada 2008	Spring Wheat (Infinity)	14	5	89	108	Grain	< 0.01
Innisfail, AB Canada 2008	Spring Wheat (Lillian)	14	5	89	127	Grain	< 0.01
Josephburg, AB Canada 2008	Spring Wheat (Infinity)	14	5	89	99	Grain	< 0.01

Oilseed

Table 29 Results of residue trials conducted with seed treatment application of Sedaxane 500 FS in/on rape seed at maturity (Reference 042, 043)

Country Year Rape (canola)	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Sycamore, GA USA 2008	Flint	2	7.5	89	232	Seed	< 0.01
Verona, WI USA 2008	DKL 38-25	5	7.5	89	171	Seed	< 0.01
Fitchburg, WI USA 2008	DKL 38-25	5	7.5	89	117 124 131 138 145	Seed	< 0.01 < 0.01 < 0.01 < 0.01 < 0.01
Carrington, ND USA 2008	Croplan 924RR	7	7.5 22.5	89	109 109	Seed	< 0.01 < 0.01
Adrian, ND USA 2008	DKL 52-10	7	7.5 22.5	89	100 100	Seed	< 0.01 < 0.01
Hermiston, OR USA 2008	Cropland Hyclass 712RR	11	7.5	89	84	Seed	< 0.01

Country Year Rape (canola)	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Rupert, ID USA 2008	Cropland Hyclass 712RR	11	7.5	89	132	Seed	< 0.01
Parkdale, Oregon USA 2008	DKL 52-10	11	7.5	89	92	Seed	< 0.01
Elm Creek, Manitoba, Canada 2008	1841RR	CAN	5	89	91	Seed	< 0.01
Vanscoy, Saskatchewan, Canada 2008	45H26RR	CAN	5	89	113	Seed	< 0.01
Minto, Manitoba, Canada 2008	45H26RR	CAN	5	89	94	Seed	< 0.01
Boissetrain, Manitoba, Canada 2008	1841RR	CAN	5	87	98	Seed	< 0.01
Boissetrain, Manitoba, Canada 2008	45H26RR	CAN	5	88	98	Seed	< 0.01
Elgin, Manitoba, Canada 2008	1841RR	CAN	5	87	98	Seed	< 0.01
Elgin, Manitoba, Canada 2008	45H26RR	CAN	5	87	98	Seed	< 0.01
Rosthern, Saskatchewan, Canada 2008	1841RR	CAN	5 15	89 89	99 99	Seed	< 0.01 < 0.01
Rosthern, Saskatchewan, Canada 2008	45H26RR	CAN	5	89	99	Seed	< 0.01
Hepburn, Saskatchewan, Canada 2008	1841RR	CAN	5	97	110	Seed	< 0.01
Hepburn, Saskatchewan, Canada 2008	45H26RR	CAN	5	97	110	Seed	< 0.01
Innisfail, Alberta, Canada 2008	1841RR	CAN	5	89	127	Seed	< 0.01
Spruce View, Alberta, Canada 2008	1841RR	CAN	5	89	132	Seed	< 0.01
Spruce View, Alberta, Canada 2008	45H26RR	CAN	5 15	89 89	132 132	Seed	< 0.01 < 0.01
Minto, Manitoba, Canada 2008	1841RR	CAN	5	80 83-86 86-88 89	86 93 99 105	Seed	< 0.01 < 0.01 < 0.01 < 0.01

Country Year Rape (canola)	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Innisfail, Alberta, Canada 2008	45H26RR	CAN	5	80-81 82-83 85-89 86-89	90 97 105 111	Seed	< 0.01 < 0.01 < 0.01 < 0.01

Animal feeds

Table 30 Results of residue trials conducted with seed treatment application of sedaxane in/on soya bean feeds (Reference 044, 045)

Country Year Soya bean Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667555 Residues (mg/kg)
Quitman, Georgia USA, 2008	NK/S73-Z5	2	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 < 0.01
Sycamore, Georgia USA, 2008	NK/S76-L9	2	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 < 0.01
Cheneyville, Louisiana USA, 2008	NK/S49-Q9	4	40 40	45 45	Forage Hay	< 0.01 0.025	0.060 < 0.01
Cheneyville, Louisiana USA, 2008	NK/S49-Q9	4	40 40	45 45	Forage Hay	0.014 0.035	< 0.01 0.050
Cheneyville, Louisiana USA, 2008	NK/S52-F2	4	40 40	45 45	Forage Hay	< 0.01 < 0.01	0.020 0.040
Oregon, Missouri USA, 2008	NK/S36-C7	5	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 0.030
St. Joseph, Missouri USA, 2008	NK/S36-C7	5	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 0.020
Fitchburg, Wisconsin USA, 2008	NK/H-1604	5	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 0.030
Fitchburg, Wisconsin USA, 2008	H1604RR	5	40 40	45 45	Forage Hay	< 0.01 0.012	0.040 0.15
Northwood, North Dakota USA, 2008	NK/S01-C9	5	40 40	45 45	Forage Hay	0.050 0.30 [a]	0.14 0.17
York, Nebraska USA, 2008	S27-C4	5	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 < 0.01
Osceola, Nebraska USA, 2008	S27-C4	5	40 40	45 45	Forage Hay	< 0.01 < 0.01	< 0.01 < 0.01

Country Year Soya bean Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667555 Residues (mg/kg)
Bagley, Iowa USA, 2008	NK/S32-E2	5	40	31	Forage	< 0.01	0.02
				38		< 0.01	< 0.01
				45		< 0.01	< 0.01
				52		< 0.01	< 0.01
				59		< 0.01	< 0.01
			40	31	Hay	< 0.01	0.06
				38		< 0.01	0.01
				45		< 0.01	0.01
				52		< 0.01	< 0.01
				59		< 0.01	< 0.01
Berkley, Iowa USA, 02008	NK/S32-E2	5	40	31	Forage	0.014	0.070
				38		< 0.01	0.010
				45		< 0.01	< 0.01
				52		< 0.01	< 0.01
				59		< 0.01	< 0.01
			40	31	Hay	0.025	0.22
				38		< 0.01	0.040
				45		< 0.01	0.030
				52		< 0.01	< 0.01
				59		< 0.01	< 0.01
Lime Springs, Iowa USA, 2008	NK/21-N6	5	40	45	Forage	< 0.01	< 0.01
			40	45	Hay	< 0.01	< 0.01
Lime Springs, Iowa USA, 2008	NK/S21-N6	5	40	45	Forage	< 0.01	< 0.01
			40	45	Hay	< 0.01	0.020
Richland, Iowa USA, 2008	NK/S32-E2	5	40	45	Forage	< 0.01	< 0.01
			40	45	Hay	< 0.01	< 0.01
Laplata, Missouri USA, 2008	NK/S32-E2	5	40	45	Forage	< 0.01	< 0.01
			40	45	Hay	< 0.01	< 0.01
Perley, Minnesota USA, 2008	NK/S02-M9	5	40	45	Forage	< 0.01	0.010
			40	45	Hay	< 0.01	0.050
Perley, Minnesota USA, 2008	NK/S02-M9	5	40	45	Forage	< 0.01	0.020
			40	45	Hay	< 0.01	0.060

[a] At the timing of sampling on the USA label (45 days after planting) the soya bean crop in the North Dakota trial was only about 6 inches tall, more immature than the soya bean crop at other trial sites, due to unusually cold weather. It is very unlikely that hay would be harvested commercially at this growth stage (BBCH 13). For this reason the North Dakota hay data should not be included in the overall residue data set. For comparison, in nearby trials (WI and MN) the soya bean plants were at growth stages BBCH 41-61 at 45 days after sowing and approximately 12 inches in height.

Table 31 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on barley feeds (Reference 030-033)

Country Year Barley Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Toodyay, Western Australia, 2008	Yagan	AUS	5	89-99	162	Straw	< 0.01
			10		162		< 0.01
			5	11-20	70	Forage	< 0.01
			10		70		< 0.01
Templers, South Australia, 2008	Flagship	AUS	5	89-99	147	Straw	< 0.01
			10		147		< 0.01
			5	11-20	70	Forage	< 0.01
			10		70		< 0.01
Moorilim, Victoria, 2008	Gairdner	AUS	5	89-99	164	Straw	< 0.01
			10		164		< 0.01
			5	11-20	70	Forage	< 0.01
			10		70		< 0.01
Boggabilla, Northern New South Wales, 2008	Grimmett	AUS	5	89-99	169	Straw	< 0.01
			10		169		< 0.01
			5	11-20	70	Forage	< 0.01
			10		70		< 0.01
Bagley, IA USA 2009	Unknown	5	5	89	84	Straw	< 0.01
					45	Hay	< 0.01
Richland, IA USA 2008	Robust	5	5	89	102	Straw	< 0.01
					45	Hay	< 0.01
Northwood, ND USA 2008	Tradition	7	5	89	101	Straw	< 0.01
					45	Hay	< 0.01
Carrington, ND USA 2008	Tradition	7	5	89	110	Straw	< 0.01
					45	Hay	0.011
New Rockford, ND USA 2008	Tradition	7	5	89	112	Straw	< 0.01
					31	Hay	0.1
					38		0.045
					45		0.025
					52		< 0.01
					59		< 0.01
Eldridge, ND USA 2008	Tradition	7	5	89	103	Straw	< 0.01
					45	Hay	< 0.01
Adrian, ND USA 2008	Tradition	7	5	89	99	Straw	< 0.01
					45	Hay	0.011

Country Year Barley Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Monte Vista, CO USA 2008	Drummond	9	5	89	113 45	Straw Hay	< 0.01 < 0.01
Fresno, CA USA 2008	Tradition	10	5	89	310 45	Straw Hay	< 0.01 0.025
Hermiston, OR USA 2008	Tradition	11	5	89	99 45	Straw Hay	< 0.01 < 0.01
Rupert, ID USA, 2008	IDA Gold II	11	5	89	104 45	Straw Hay	< 0.01 0.025
North Rose, NY USA 2009	Robust	1	5	89	102 45	Straw Hay	< 0.01 < 0.01
Elm Creek, MB Canada, 2008	Legacy	5	5	87-99 73-85	95 60	Straw Hay	< 0.01 < 0.01
St. Marc-sur-Richelieu, QC, Canada, 2008	AC Metcalfe	5	5	87-99 73-85	102 67	Straw Hay	< 0.01 < 0.01
Vanscoy, SK, Canada, 2008	Legacy	7	5	87-99 73-85	104 64	Straw Hay	< 0.01 < 0.01
Delisle, SK, Canada 2008	AC Metcalfe	7	5	87-99 73-85	111 72	Straw Hay	< 0.01 < 0.01
Minto, MB, Canada 2008	Legacy	14	5	87-99 73-85	98 68	Straw Hay	< 0.01 < 0.01
Boissevain, MB, Canada 2008	AC Metcalfe	14	5	87-99 73-85	98 69	Straw Hay	< 0.01 < 0.01
Rosthern, SK, Canada 2008	Legacy	14	5	87-99 73-85	105 65	Straw Hay	< 0.01 < 0.01
Hepburn, SK, Canada 2008	AC Metcalfe	14	5	87-99 73-85	108 70	Straw Hay	< 0.01 < 0.01
Innisfail, AB, Canada 2008	AC Metcalfe	14	5	87-99 73-85	119 75	Straw Hay	< 0.01 < 0.01
Penhold, AB, Canada 2008	Legacy	14	5	87-99 73-85	99 71	Straw Hay	< 0.01 < 0.01
Josephburg, AB. Canada 2008	Legacy	14	5	87-99 73-85	110 66	Straw Hay	< 0.01 < 0.01

Country Year Barley Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)
Alvena, SK, Canada 2008	AC Metcalfe	14	5	87-99	105	Straw	< 0.01
					113		< 0.01
					119		< 0.01
					126		< 0.01
				73-85	63	Hay	< 0.01
					70		< 0.01
					77		< 0.01
					84		< 0.01
					91		< 0.01

Table 32 Results of residue trials conducted with seed treatment application of sedaxane in/on oat feeds (Reference 033)

Country Year Oat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Toodyay, Western Australia, 2008	Winjardie	AUS	5	89-99	162	Straw	< 0.01	< 0.01
			10		162		< 0.01	< 0.01
			5	11-29	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		< 0.01	< 0.01
			5		40		< 0.01	< 0.01
			10		40		0.015	< 0.01
			5		28		< 0.01	< 0.01
			10		28		0.035	0.05
Templers, South Australia, 2008	Wintaroo	AUS	5	89-99	140	Straw	< 0.01	0.02
			10		140		< 0.01	0.04
			5	11-29	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		41		0.015	0.01
			10		41		0.025	0.02
			5		28		0.045	0.05
			10		28		0.085	0.09

Country Year Oat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Moorilim, Victoria, 2008	Yarran	AUS	5	89-99	164	Straw	< 0.01	0.01
			10		164		< 0.01	0.02
			5	11-29	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		41		0.015	0.01
			10		41		0.045	0.02
			5		28		0.035	0.05
			10		28		0.10	0.06
Walla Walla, Northern New South Wales, 2008	Bimbal	AUS	5	89-99	154	Straw	< 0.01	0.01
			10		154		< 0.01	0.03
			5	11-29	69	Forage	< 0.01	< 0.01
			10		69		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	0.01
			5		42		0.015	0.01
			10		42		0.035	0.02
			5		28		0.045	0.05
			10		28		0. 10	0.09

Table 33 Results of residue trials conducted with seed treatment application of sedaxane 500 FS in/on wheat feeds (Reference 033-041)

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Toodyay Western Australia, Australia, 2008	Spring Wheat (Millewa)	AUS	5	89-99	162	Straw	< 0.01	< 0.01
			10		162		< 0.01	< 0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		40		< 0.01	< 0.01
			10		40		0.025	< 0.01
			5		28		0.015	< 0.01
			10		28		0.065	0.01
Southern River, Western Australia, Australia, 2008	Spring Wheat (Millewa)	AUS	5	89-99	160	Straw	< 0.01	< 0.01
			10		160		< 0.01	0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		40		0.015	< 0.01
			10		40		0.035	0.01
			5		28		0.025	0.01
			10		28		0.065	0.03
Templers, South Australia, 2008	Spring Wheat (Yitpi)	AUS	5	89-99	157	Straw	< 0.01	< 0.01
			10		157		< 0.01	0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		41		< 0.01	< 0.01
			10		41		0.015	< 0.01
			5		28		0.025	0.01
			10		28		0.010	0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Moorilim, Victoria Australia, 2008 Clay loam	Spring Wheat (Whistler)	AUS	5	89-99	164	Straw	< 0.01	< 0.01
			10		164		< 0.01	0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		41		0.015	< 0.01
			10		41		0.025	0.01
			5		28		0.010	< 0.01
			10		28		0.065	0.03
Moorilim, Victoria Australia, 2008 Sandy loam	Spring Wheat (Whistler)	AUS	5	89-99	163	Straw	< 0.01	< 0.01
			10		163		< 0.01	0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	0.015
			5		41		0.015	0.015
			10		41		0.025	0.010
			5		28		0.025	0.010
			10		28		0.065	0.020
Walla Walla, NSW Australia2008	Spring Wheat (Ventura)	AUS	5	89-99	154	Straw	< 0.01	< 0.01
			10		154		< 0.01	0.010
			5	11-20	69	Forage	< 0.01	< 0.01
			10		69		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		42		0.015	< 0.01
			10		42		0.035	0.010
			5		28		0.025	0.010
			10		28		0.065	0.040

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Boggabilla, NSW Australia, 2008	Spring Wheat (Gregory)	AUS	5	89-99	169	Straw	< 0.01	< 0.01
			10		169		< 0.01	< 0.01
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		< 0.015	< 0.01
			5		42		< 0.015	0.010
			10		42		< 0.035	0.010
			5		28		< 0.035	0.010
			10		28		< 0.065	0.030
Goondiwindi, Qld Australia, 2008	Spring Wheat (Gregory)	AUS	5	89-99	169	Straw	< 0.01	0.010
			10		169		< 0.01	0.020
			5	11-20	70	Forage	< 0.01	< 0.01
			10		70		< 0.01	< 0.01
			5		56		< 0.01	< 0.01
			10		56		0.015	< 0.01
			5		42		0.015	0.010
			10		42		0.035	0.020
			5		28		0.025	< 0.01
			10		28		0.085	0.04
Goldbeck, Germany 2007	Spring Wheat (Leguan)	EU-N	10	89	137	Straw	< 0.01	< 0.01
				77-79	112	Forage	< 0.01	< 0.01
				59	80		< 0.01	< 0.01
				39	63		< 0.01	< 0.01
				22-30	34		0.016 [a]	< 0.01
Burweg, Germany 2007	Spring Wheat (Leguan)	EU-N	10	89	137	Straw	< 0.01	< 0.01
				77-79	106	Forage	< 0.01	< 0.01
				59	75		< 0.01	< 0.01
				39	67		< 0.01	< 0.01
				22-30	55		< 0.01	< 0.01
Roinvilliers, N. France 2007	Spring Wheat (Leguan)	EU-N	10	89	122	Straw	< 0.01	< 0.01
				77-79	102	Forage	< 0.01	< 0.01
				59	70		< 0.01	< 0.01
				39	59		< 0.01	< 0.01
				22-30	42		< 0.01	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Kings Newton, Derbyshire, UK 2007	Spring Wheat (Leguan)	EU-N	10	89	132	Straw	< 0.01	< 0.01
				77-79	86	Forage	< 0.01	< 0.01
				59	65		< 0.01	< 0.01
				39	54		< 0.01	< 0.01
				22-30	41		< 0.01	< 0.01
Grivesnes, N. France 2007–2008	Winter Wheat (Apache)	EU-N	10	89	299	Straw	< 0.01	< 0.01
				77-79	252	Forage	< 0.01	< 0.01
				59	228		< 0.01	< 0.01
				39	216		< 0.01	< 0.01
				22-30	168		< 0.01	< 0.01
Rogy, N. France 2007–2008	Winter Wheat (Apache)	EU-N	10	89	273	Straw	< 0.01	< 0.01
				77-79	239	Forage	< 0.01	< 0.01
				59	214		< 0.01	< 0.01
				39	202		< 0.01	< 0.01
				22-30	159		< 0.01	< 0.01
Ormes, N. France 2007–2008	Winter Wheat (Apache)	EU-N	10	89	283	Straw	< 0.01	< 0.01
				59	240	Forage	< 0.01	< 0.01
				39	217		< 0.01	< 0.01
				22-30	163		< 0.01	< 0.01
Sept Saulx, N. France 2007-2008	Winter Wheat (Apache)	EU-N	10	89	286	Straw	< 0.01	< 0.01
				77-79	243	Forage	< 0.01	< 0.01
				59	218		< 0.01	< 0.01
				39	208		< 0.01	< 0.01
				22-30	160		< 0.017	< 0.01
Roinvilliers, N. France 2008	Spring Wheat (Granary)	EU-N	10	89	120	Straw	< 0.01	< 0.01
				77-79	92	Forage	< 0.01	< 0.01
				59	69		< 0.01	< 0.01
				39	51		< 0.01	< 0.01
				22-30	34		< 0.01	< 0.01
Mulsum, Niedersachsen, Germany 2008	Spring Wheat (Granary)	EU-N	10	89	100	Straw	< 0.01	< 0.01
				77-79	92	Forage	< 0.01	< 0.01
				59	62		< 0.01	< 0.01
				39	48		< 0.01	< 0.01
				22-30	36		< 0.01	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Goldbeck, Niedersachsen, Germany 2008	Spring Wheat (Granary)	EU-N	10	89	120	Straw	< 0.01	< 0.01
				77-79	91	Forage	< 0.01	< 0.01
				59	61		< 0.01	< 0.01
				39	48		< 0.01	< 0.01
				22-30	35		0.013	< 0.01
Pilling, Lancashire, UK 2008	Spring Wheat (Granary)	EU-N	10	89	157	Straw	< 0.01	< 0.01
				77-79	109	Forage	< 0.01	< 0.01
				59	80		< 0.01	< 0.01
				39	63		< 0.01	< 0.01
				22-30	38		0.013	< 0.01
Hemington, Derbyshire, UK 2008	Spring Wheat (Granary)	EU-N	10	89	153	Straw	< 0.01	< 0.01
				77-79	104	Forage	< 0.01	< 0.01
				59	92		< 0.01	< 0.01
				39	56		< 0.01	< 0.01
				22-30	38		< 0.01	< 0.01
Meauzac, S. France 2007	Spring Wheat (Leguan)	EU-S	10	89	89	Straw	< 0.01	< 0.01
				77-79	79	Forage	< 0.01	< 0.01
				59	59		< 0.01	< 0.01
				39	56		< 0.01	< 0.01
				22-30	48		< 0.01	< 0.01
Montauban, S. France 2007	Spring Wheat (Leguan)	EU-S	10	89	112	Straw	< 0.01	< 0.01
				77-79	75	Forage	< 0.01	< 0.01
				59	54		< 0.01	< 0.01
				39	39		< 0.01	< 0.01
				22-30	25		0.013 [b]	< 0.01
S. Maria Codifiume, Italy 2007	Spring Wheat (Leguan)	EU-S	10	89	97	Straw	< 0.01	< 0.01
				77-79	85	Forage	< 0.01	< 0.01
				59	64		< 0.01	< 0.01
				39	57		< 0.01	< 0.01
				22-30	48		< 0.01	< 0.01
Marsillargues, S. France 2007	Winter Wheat (Apache)	EU-S	10	89	238	Straw	< 0.01	< 0.01
				77-79	202	Forage	< 0.01	< 0.01
				59	187		< 0.01	< 0.01
				39	168		< 0.01	< 0.01
				22-30	106		< 0.01	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Pompignan, S. France 2007 Loamy sand, pH 8.2	Winter Wheat (Apache)	EU-S	10	89	239	Straw	< 0.01	< 0.01
				77-79	217	Forage	< 0.01	< 0.01
				59	185		< 0.01	< 0.01
				39	167		< 0.01	< 0.01
				22-30	119		0.023	< 0.01
Pompignan, S. France 2007 Sandy clay, pH 5.9	Winter Wheat (Apache)	EU-S	10	89	246	Straw	< 0.01	< 0.01
				77-79	211	Forage	< 0.01	< 0.01
				59	189		< 0.01	< 0.01
				39	171		< 0.01	< 0.01
				22-30	119		0.023	< 0.01
Cordes Tolosannes, S. France 2008	Spring Wheat (Palesio)	EU-S	10	89	119	Straw	< 0.011	< 0.01
				77-79	75	Forage	< 0.01	< 0.01
				59	61		< 0.01	< 0.01
				39	49		< 0.01	< 0.01
				22-30	39		< 0.01	< 0.01
Montbeton, S. France 2008	Spring Wheat (Palesio)	EU-S	10	89	127	Straw	0.012	< 0.01
				77-79	85	Forage	< 0.01	< 0.01
				59	76		< 0.01	< 0.01
				39	59		< 0.01	< 0.01
				22-30	50		< 0.01	< 0.01
Castelguelfo, Bologna, Italy 2008	Spring Wheat (Palesio)	EU-S	10	89	104	Straw	< 0.01	< 0.01
				77-79	84	Forage	< 0.01	< 0.01
				59	60		< 0.01	< 0.01
				39	54		< 0.01	< 0.01
				22-30	32		< 0.01	< 0.01
Budrio, Bologna, Italy 2008	Spring Wheat (Palesio)	EU-S	10	89	95	Straw	< 0.01	< 0.01
				77-79	75	Forage	< 0.01	< 0.01
				59	59		< 0.01	< 0.01
				39	46		< 0.01	< 0.01
				22-30	30		0.011	< 0.01
Mebane, NC USA 2008/2009	Winter Wheat (Coker)	2	5	89	268	Straw	< 0.01	< 0.01
					45	Forage	0.012	< 0.01
					45	Hay	0.025	0.02
Cheneyville, LA USA 2008/2009	Winter Wheat (Terral)	4	5	89	185	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	0.013	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Oregon, MO USA 2008/2009	Winter Wheat (Santa Fe)	5	5	89	215	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	0.014	< 0.01
Troy, KS USA 2008	Winter Wheat (Danby)	5	5	89	236	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Bagley, IA USA 2008	Winter Wheat (Arapahoe)	5	5	89	299	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Lime Springs, IA USA 2008	Spring Wheat (Granger HRS)	5	5	89	108	Straw	< 0.01	< 0.01
					112		< 0.01	< 0.01
					119		< 0.01	< 0.01
					126		< 0.01	< 0.01
					31	Forage	< 0.01	< 0.01
					38		< 0.01	< 0.01
					45		< 0.01	< 0.01
					52		< 0.01	< 0.01
					59		< 0.01	< 0.01
					31	Hay	< 0.01	< 0.01
					38		< 0.01	< 0.01
					45		< 0.01	< 0.01
					52		< 0.01	< 0.01
					59		< 0.01	< 0.01
Lime Springs, IA USA 2008	Spring Wheat (Granger HRS)	5	5	89	113	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Wharton, TX USA 2008	Winter Wheat (Fannin)	6	5	89	188	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Eldridge, ND USA 2008	Spring Wheat (Penewawa)	7	5	89	103	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Eldridge, ND USA 2008	Spring Wheat (Argent)	7	5	89	96	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
New Rockford, ND USA 2008	Winter Wheat (Hawken)	7	5	89	96	Straw	< 0.01	< 0.01
					31	Forage	0.015	< 0.01
					38		0.012	< 0.01
					45		0.013	< 0.01
					31	Hay	0.065 [c]	0.040
					38		0.035 [d]	0.030
					45		0.025	0.020
Carrington, ND USA 2008	Spring Wheat (Divide)	7	5	89	110	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	0.014	< 0.01
Adrian, ND USA 2008	Spring Wheat (Alsen)	7	5	89	99	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Claude, TX USA 2008	Winter Wheat (Deliver)	8	5	89	287	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Groom, TX USA 2008	Winter Wheat (Cutter)	8	5	89	287	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Groom. TX USA 2008	Winter Wheat (Deliver)	8	5	89	287	Straw	< 0.01	< 0.01
					45	Forage	< 0.01	< 0.01
					45	Hay	< 0.01	< 0.01
Levelland, TX USA 2008	Winter Wheat (TAM 111)	8	5	89	266	Straw	< 0.01	< 0.01
					45	Forage	0.012	< 0.01
					45	Hay	0.035	< 0.01
Wolforth, TX USA 2008	Winter Wheat (TAM 112)	8	5	89	253	Straw	< 0.01	< 0.01
					45	Forage	0.014	< 0.01
					45	Hay	0.025	< 0.01
New Home, TX USA 2008	Winter Wheat (TAM 105)	8	5	89	258	Straw	< 0.01	< 0.01
					45	Forage	0.015	< 0.01
					45	Hay	0.075 [e]	0.02
Hermiston, OR USA 2008	Winter Wheat (Stephens)	11	5	89	273	Straw	< 0.01	< 0.01
					45	Forage	0.013	< 0.01
					45	Hay	0.045 [f]	0.05

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Elm Creek, MB Canada 2008	Spring Wheat (Lillian)	5	5	89	97	Straw	< 0.01	< 0.01
				30-32	47	Forage	< 0.01	< 0.01
				71	67	Hay	< 0.01	< 0.01
Portage la Prairie, MB Canada 2008	Spring Wheat (Infinity)	5	5	99	114	Straw	< 0.01	< 0.01
				22-23	32	Forage	< 0.01	< 0.01
				67-69	62	Hay	< 0.01	< 0.01
Delisle, SK Canada 2008	Spring Wheat (Lillian)	7	5	89-93	111	Straw	< 0.01	< 0.01
				30	45	Forage	< 0.01	< 0.01
				61-69	72	Hay	< 0.01	< 0.01
Delisle, SK Canada 2008	Spring Wheat (Infinity)	7	5	89-93	111	Straw	< 0.01	< 0.01
				30	45	Forage	< 0.01	< 0.01
				61-69	72	Hay	< 0.01	< 0.01
Variscoy, SK Canada 2008	Spring Wheat (Lillian)	7	5	87-89	106	Straw	< 0.01	< 0.01
				89-93	113		< 0.01	< 0.01
				92-97	120		< 0.01	< 0.01
				92-97	127		< 0.01	< 0.01
				14	36	Forage	< 0.01	< 0.01
				32	43		< 0.01	< 0.01
				30	43		< 0.01	< 0.01
				37	50		< 0.01	< 0.01
				47	57		< 0.01	< 0.01
				65	64		< 0.01	< 0.01
				65-69	71	Hay	< 0.01	< 0.01
				69-73	78		< 0.01	< 0.01
				83-85	86		< 0.01	< 0.01
				85-89	93		< 0.01	< 0.01
				85-89	100		< 0.01	< 0.01
Variscoy, SK Canada 2008	Spring Wheat (Infinity)	7	5	89-93	106	Straw	< 0.01	< 0.01
				30	36	Forage	< 0.01	< 0.01
				69	69	Hay	< 0.01	< 0.01
Dundum, SK Canada 2008	Spring Wheat (Lillian)	7	5	99	109	Straw	< 0.01	< 0.01
				22-23	38	Forage	< 0.01	< 0.01
				69	65	Hay	< 0.01	< 0.01
Dundum, SK Canada 2008	Spring Wheat (Infinity)	7	5	99	109	Straw	< 0.01	< 0.01
				22-23	38	Forage	< 0.01	< 0.01
				69	65	Hay	< 0.01	< 0.01

Country Year Wheat Feeds	Variety	Region	Application Rate (g ai/100 kg seed)	Growth Stage at Sampling (BBCH)	Days After Sowing	Portion	Sedaxane Residues (mg/kg)	CSCD667584 Residues (mg/kg)
Taber, AB Canada 2008	Spring Wheat (Infinity)	7A	5	92-97	130	Straw	< 0.01	< 0.01
				23-25	47	Forage	< 0.01	< 0.01
				61	61	Hay	< 0.01	< 0.01
Boissevain, MB Canada 2008	Spring Wheat (Lillian)	14	5	89	104	Straw	< 0.01	< 0.01
				30-31	40	Forage	< 0.01	< 0.01
				69	69	Hay	< 0.01	< 0.01
Minto, MB Canada 2008	Spring Wheat (Infinity)	14	5	87-89	98	Straw	< 0.01	< 0.01
				89	105		< 0.01	< 0.01
				89-93	112		< 0.01	< 0.01
				92-93	119		< 0.01	< 0.01
				13-14	37	Forage	< 0.01	< 0.01
				31-37	44		< 0.01	< 0.01
				32-41	50		< 0.01	< 0.01
				43-59	58		< 0.01	< 0.01
				58-65	64		< 0.01	< 0.01
				41-59	56	Hay	< 0.01	< 0.01
				58-65	63		< 0.01	< 0.01
				61-69	70		< 0.01	< 0.01
				71-75	77		< 0.01	< 0.01
				77-83	84		< 0.01	< 0.01
Rosthern, SK Canada 2008	Spring Wheat (Lillian)	14	5	89-92	118	Straw	< 0.01	< 0.01
				23-30	35	Forage	< 0.01	< 0.01
				69-75	69	Hay	< 0.01	< 0.01
Hepburn, SK Canada 2008	Spring Wheat (Lillian)	14	5	89-93	108	Straw	< 0.01	< 0.01
				30	42	Forage	< 0.01	< 0.01
				69-71	72	Hay	< 0.01	< 0.01
Hepburn, SK Canada 2008	Spring Wheat (Infinity)	14	5	89-93	108	Straw	< 0.01	< 0.01
				30	42	Forage	< 0.01	< 0.01
				69-73	72	Hay	< 0.01	< 0.01
Innisfail, AB Canada 2008	Spring Wheat (Lillian)	14	5	89	127	Straw	< 0.01	< 0.01
				24-26	43	Forage	< 0.01	< 0.01
				73	78	Hay	< 0.01	< 0.01
Josephburg, AB Canada 2008	Spring Wheat (Infinity)	14	5	89	99	Straw	< 0.01	< 0.01
				25-28	31	Forage	< 0.01	< 0.01
				61	51	Hay	< 0.01	< 0.01

[a] Residues for metabolites CSCD658906, CSCD668403 and CSCD659089 found at 0.02, 0.02 and 0.02 mg/kg.

[b] Residues for metabolites CSCD658906, CSCD668403, and CSCD659089 at 0.03, 0.02 and 0.04 mg/kg.

[c] Residue for metabolite CSCD658906 found at 0.03 mg/kg.
[d] Residue for metabolite CSCD658906 found at 0.03 mg/kg.
[e] Residue for metabolite CSCD658906 found at 0.02 mg/kg.
[f] Residue for metabolite CSCD658906 found at 0.02 mg/kg.

FATE OF RESIDUES IN PROCESSING

Effects on the nature of residues

A high-temperature aqueous hydrolysis study was conducted to determine the nature of any sedaxane-derived residues in processed crop commodities or by-products under conditions typical of industrial or household processing (046, Lewis & Gilbert, 2009). These conditions are summarized in Table 34.

Table 34 Experimental conditions typical of industrial or household processing

Temperature (ºC)	Time (min)	pH	Process Represented
90	20	4	Pasteurization
100	60	5	Baking, boiling, brewing
120	20	6	Sterilization

Individual aqueous solutions of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane (nominal concentration 1 µg/mL) were prepared in sterile citrate buffers at pH 4, 5 and 6. Duplicate samples for each buffer solution were treated. The initial concentration of radiolabelled sedaxane, based upon the applied radioactivity and the nominal volume (3 mL), ranged from 0.989 to 1.036 mg/L.

The total recovery of radioactivity for all initial and hydrolysed samples was ≥ 96.1% (mean of two replicates) for all hydrolysed samples, indicating that there were no significant losses of radioactivity during the experimental procedures. In both the initial and hydrolysed samples the major component was determined to be sedaxane which, represented ≥ 97.4% of the radioactivity. Unidentified components were present at very low levels, representing ≤ 2.6% of the radioactivity. No significant differences were observed between the initial samples and the incubated test samples. Sedaxane is concluded to be hydrolytically stable under conditions representative of pasteurization, baking/brewing/boiling and sterilization.

Processing studies

Processing studies were conducted on barley, canola, soya bean and wheat in the U.S. and on barley in the U.K. In all studies, residues of sedaxane and its metabolites were determined using high performance liquid chromatographic with quadrupole mass spectrometric detection (HPLC-MS/MS), Method GRM023.03A.

Barley

In two field trials conducted in ND (Carrington and Adrian), sedaxane, formulated as flowable concentrate for seed treatment (FS), was applied to barley seeds at an exaggerated rate of 15 g ai/100 kg seed (3× the US GAP rate of 5 g ai/100 kg seed) (030, Hamilton, 2010). Barley grain was harvested at maturity and processed into pearled barley, bran, and flour using simulated commercial procedures. Neither sedaxane nor any metabolites were detected above the LOQ for any RAC or processed commodity sample. Thus, no concentration factors were determined for processed commodities based on processed barley studies conducted in the U.S.

In one field trial conducted in the U.K., sedaxane, formulated as flowable concentrate for seed treatment (FS), was applied to barley at an exaggerated rate of 36 g ai/100 kg seed (3.6× the cGAP rate of 10 g ai/100 kg seed) (032, Klimmek & Gizler, 2010). Barley grain was harvested at maturity

and processed into pot barley, bran, and flour using simulated commercial procedures. Neither sedaxane nor any metabolites were detected above the LOQ for any RAC or processed commodity sample. Thus, no concentration factors were determined for processed commodities based on processed barley studies conducted in the U.K.

Oilseed rape (Canola)

In two field trials conducted in ND (Carrington and Adrian), sedaxane, formulated as flowable concentrate for seed treatment (FS), was applied to rape seeds at an exaggerated rate of 22.5 g ai/100 kg seed (4.5× the US GAP rate of 5 g ai/100 kg seed) (042, Hamilton, 2009). Rape seed was harvested at maturity and processed into meal and oil using simulated commercial procedures. Neither sedaxane nor any metabolites were detected above the LOQ for any RAC or processed commodity sample. Thus, no concentration factors were determined for processed commodities based on processed rape seed studies conducted in the U.S.

Soya bean

In two field trials conducted in GA and ND, sedaxane, formulated as flowable concentrate for seed treatment (FS), was applied to soya bean seeds at an exaggerated rate of 120 g ai/100 kg seed (24× the US GAP rate of 5 g ai/100 kg seed) (044, Hamilton, 2010). Soya bean seed was harvested at maturity and processed into meal, hulls and refined oil using simulated commercial procedures. Neither sedaxane nor any metabolites were detected above the LOQ for any RAC or processed commodity sample. Thus, no concentration factors were determined for processed commodities based on processed soya bean studies conducted in the U.S.

Wheat

In two field trials conducted in IA and ND, sedaxane, formulated as flowable concentrate for seed treatment (FS), was applied to wheat seeds at an exaggerated rate of 15 g ai/100 kg seed (3× the US GAP rate of 5 g ai/100 kg seed) (034, Hamilton, 2010). Wheat grain was harvested at maturity and processed into bran, flour, middlings, shorts and germ using simulated commercial procedures. Neither sedaxane nor any metabolites were detected above the LOQ for any RAC or processed commodity sample. Thus, no concentration factors were determined for processed commodities based on processed wheat studies conducted in the U.S.

Residues in animal commodities

Cattle

Eleven lactating Friesian/Holstein dairy cows (*Bos taurus*; three cows/treatment group, three treatment groups and two control cows) were administered gelatin capsules containing sedaxane for 29 or 30 consecutive days (058, MacDougall & Roberts, 2009).

Milk was collected twice daily and combined for analysis on days -1, 1, 2, 3, 5, 7, 10, 14, 17, 21, 24 and 28. On days 1, 3, 7, 14, 21 and 28, aliquots of milk from one animal in the highest treatment group were mechanically separated into cream and skim milk fractions and analysed. Cows from the three treatment groups and the control group were sacrificed within 24 hours of administration of the final dose. The following tissue samples were collected immediately after slaughter: muscle (including hind leg and loin), liver, kidney and fat (including mesenteric, subcutaneous and perirenal). Tissue and milk samples were analysed for residue by LC-MS/MS according to method GRM023.010A. This method was used to determine residues of parent sedaxane and structurally-related metabolites CSCD658906 and CSCD659087 in bovine tissues and milk. All milk, cream, skimmed milk and tissue samples were stored frozen at approximately -20 °C following tissue processing. All residue analysis was completed within 30 days of sample collection.

Residues of sedaxane and metabolites CSCD658906 and CSCD659087 in milk, cream and cow tissues are summarized in Table 35. No sedaxane or CSCD659087 residues were found in any livestock matrix at any of the three dose levels. No sedaxane or metabolites were found in milk, skim

milk, or cream at any dose level. Muscle and fat samples from the 0.1 mg/kg and 0.5 mg/kg sedaxane dose level cow groups were not analysed, as no residues greater than the LOQ were detected in any muscle or fat samples from the 2.2 mg/kg sedaxane dose level. The only residues detected were CSCD658906 in two liver samples at the 2.2 mg/kg dose level (animal 9 = 0.03 mg/kg and animal 11 = 0.01 mg/kg) and CSCD658906 in two kidney samples at the 2.2 mg/kg dose level (animal 9 = 0.01 mg/kg and animal 10 = 0.02 mg/kg).

Table 35 Summary of Sedaxane Bovine Feeding Study

	Dose Level (mg/kg)	n	Sedaxane Residue (mg/kg)	CSCD658906 Residue (mg/kg)	CSCD659087 Residue (mg/kg)
Milk	0.11	33	< 0.010	< 0.010	< 0.010
	0.54	33	< 0.010	< 0.010	< 0.010
	2.2	33	< 0.010	< 0.010	< 0.010
Cream	2.2	6	< 0.010	< 0.010	< 0.010
Liver	0.11	3	< 0.010	< 0.010	< 0.010
	0.54	3	< 0.010	< 0.010	< 0.010
	2.2	3	< 0.010	0.027	< 0.010
Kidney	0.11	3	< 0.010	< 0.010	< 0.010
	0.54	3	< 0.010	< 0.010	< 0.010
	2.2	3	< 0.010	0.018	< 0.010
Muscle	0.11	NA	NA	NA	NA
	0.54	NA	NA	NA	NA
	2.2	3	< 0.010	< 0.010	< 0.010
Fat	0.11	NA	NA	NA	NA
	0.54	NA	NA	NA	NA
	2.2	3	< 0.010	< 0.010	< 0.010

Poultry

A poultry feeding study was not submitted. In the barley, oats, wheat, rape and soya bean field trials residues of sedaxane were below the LOQ in/on all samples of grain and seed. No quantifiable residues were found in canola, soya bean and wheat processed commodities. Based on the low dietary burden and the results of the poultry metabolism studies, there is no need for a poultry feeding study for sedaxane.

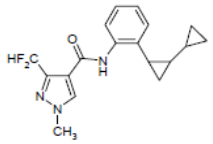
APPRAISAL

Sedaxane is a novel seed treatment fungicide. It is a succinate dehydrogenase inhibitor and affords broad spectrum control of pathogens such as Ascomycete and Oomycete species in crops. It has been registered in France, Canada, and the USA. At the Forty-third Session of the CCPR, it was scheduled for evaluation as a new compound by the 2012 JMPR.

The Meeting received information from the manufacturer on identity, metabolism, storage stability, residue analysis, use pattern, fate of residues during processing, livestock feeding studies, and residues resulting from supervised trials on cereal grains (wheat, oats, and barley), soya bean, and rape.

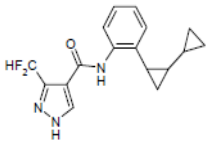
The IUPAC name for sedaxane recognizes a mixture of two *cis*-isomers 2'-[(RS,2RS)-1,1'-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide and two *trans*-isomers 2'-[(RS,2SR)-1,1'-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide. The CA name is *N*-[2-[1,1′-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide.

Sedaxane labelled in the pyrazole and phenyl rings was used in the metabolism and environmental fate studies. The chemical structures of sedaxane and its metabolites/degradates are shown below. Sedaxane is a mixture of *trans* and *cis* isomers, in an approximate 6:1 ratio.



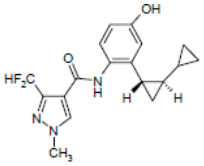
SYN524464

Sedaxane



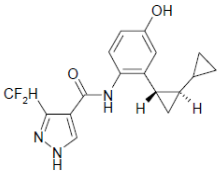
CSCD667584

N-desmethyl sedaxane



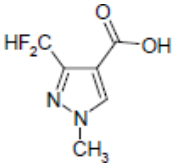
CSCD658906

Trans-para phenol sedaxane



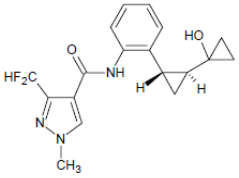
CSCD659087

N-desmethyl trans para phenol sedaxane



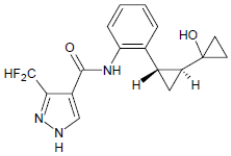
CSAA798670

Pyrazole acid



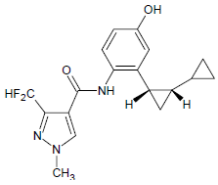
CSCD659089

Cyclopropyl alcohol sedaxane



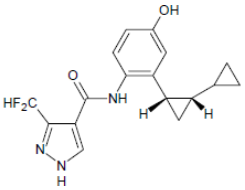
CSCD659088

Desmethyl cyclopropyl alcohol sedaxane



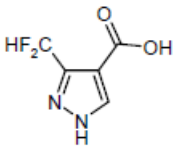
CSCD659090

Cis para phenol sedaxane



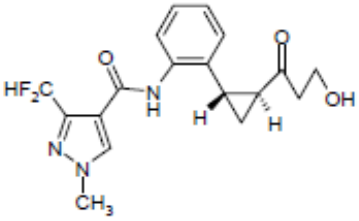
CSCD668404

Cis desmethyl para phenol sedaxane



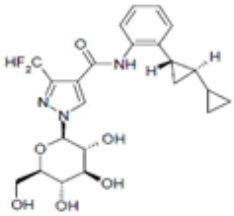
CSCD465008

N-desmethyl pyrazole acid



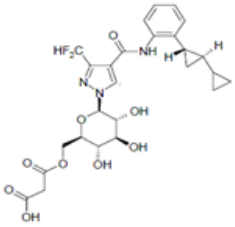
CSCD668403

β-hydroxy carbonyl sedaxane



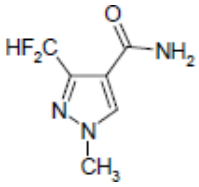
CSCD667555

N-glucoside (trans) sedaxane



CSCD667556

N-malonyl-glucoside of sedaxane



CSCC210616

pyrazole amide

Animal metabolism

Information was available on metabolism of sedaxane in laboratory animals, lactating goats and laying hens.

Sedaxane metabolism in rats was reviewed by the WHO panel of the JMPR in 2012. The sedaxane administered to rats was rapidly excreted, predominantly in the faeces (75–88%) and in urine (12–20%). Sedaxane was extensively metabolized in rats by demethylation, hydroxylation, oxidation and conjugation, resulting in many hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. The major metabolites have been identified as the trans

para phenol sedaxane and the desmethyl trans para phenol sedaxane, which together with the equivalent cis para phenol isomers of sedaxane account for approximately half of the administered dose. There appear to be no major sex or dose related differences in the qualitative metabolite profile of sedaxane and the position of radiolabelling. There is little evidence of any cleavage between the phenyl and pyrazole moieties of the sedaxane molecule. A small amount (< 1%) of a pyrazole amide metabolite of sedaxane also found in plants can be found in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane are subject to glucuronic acid, sulphate and glutathione conjugation.

Two studies were conducted to investigate the nature of residues in milk and tissues from lactating goats, involving dosing of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane. Two goats were treated (one per radiolabel) at a dose rate equivalent to a dietary concentration of 20 ppm (in dry matter) daily for 7 consecutive days. Of the total administered radioactivity (TAR), 49–62% and 18–26% was eliminated in the faeces and urine, respectively. Total recovered radioactivity was 85% of the TAR.

The highest total radioactive residues (TRRs) were found in liver (0.47–0.61 mg eq/kg) and kidney (0.080–0.19 mg eq/kg) and the lowest in fat (0.011–0.015 mg eq/kg) and muscle (0.004–0.006 mg eq/kg). Results for milk indicated that a plateau was reached after approximately 2 days, at 0.033 and 0.045 mg eq/kg in the pyrazole and phenyl experiments, respectively.

In the milk, kidney, and muscle samples, sedaxane was not detected. Low TRR levels in muscle (0.004–0.006 mg eq/kg) precluded metabolite identification. In the liver, sedaxane was found at low levels: 0.009 mg/kg [2.0 % TRR] and 0.034 mg/kg [5.5% TRR] in the pyrazole and phenyl experiments, respectively. In the fat, sedaxane was the predominant residue at 28–44% TRR, but at low concentrations of 0.004–0.005 mg/kg.

Metabolites were present mainly as conjugates except in fat and milk. The principle metabolites identified were the *trans* para phenols CSCD658906 and CSCD659087 and the *cis* para phenol isomer CSCD668404. CSCD658906 was the major component in liver (13–19% TRR, 0.063–0.12 mg eq/kg) and kidney (14–22% TRR, 0.011–0.042 mg eq/kg). CSCD659087 and CSCD668404 were found in milk (9–10% TRR, 0.003–0.004 mg eq/kg), and kidney (11–13% TRR, 0.008–0.024 mg eq/kg).

Two studies were conducted to investigate the nature of residues in eggs and tissues from laying hens, involving dosing of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane. The test substances were administered at a dose rate equivalent to a dietary concentration of 20 ppm (in dry matter) daily for 14 consecutive days. Of the total administered radioactivity (TAR), 89–94% was eliminated in the excreta. Total recovered radioactivity was 94–98% of the TAR.

Total radioactivity results for egg indicated that a plateau was reached after approximately 9 days. TRRs in the egg white and yolk samples were 0.007–0.009 and 0.070–0.078 mg eq/kg, respectively, in the phenyl and pyrazole studies.

The TRR in tissues after sacrifice (12 hours after the last dose) were 0.19–0.26 mg eq/kg, 0.005 mg eq/kg, 0.12–0.24 mg eq/kg, and 0.008–0.016 mg eq/kg in liver, muscle, skin and attached fat, and abdominal fat, respectively.

Sedaxane was found at low levels (< 0.01 mg/kg) in all hen matrices except liver, where no sedaxane residues were detected. Sedaxane was the predominant residue in hen abdominal fat (46–53% TRR, 0.004–0.007 mg/kg).

Metabolites were present mainly as conjugates in liver and egg yolk. CSCD658906 was the principle metabolite identified in liver (14–16% TRR, 0.031–0.036 mg eq/kg) and egg yolk (13–16% TRR, 0.009–0.013 mg eq/kg).

Animal metabolism summary

Metabolism studies in the laying hen and lactating goat demonstrated similar metabolic pathways. Specifically, oxidation reactions at the phenyl and cyclopropyl rings were noted, as well as

demethylation, either prior to or after oxidation. No major differences were noted in the metabolic profiles resulting from the two radiolabelled experiments. There was no indication of significant cleavage between the phenyl and pyrazole moieties. The primary mechanisms for the proposed biotransformation pathway of sedaxane in animals were: N-demethylation to form CSCD667584; hydroxylation of sedaxane to give the para phenols CSCD658906 and CSCD659090, and the cyclopropyl alcohol CSCD659089; hydroxylation of desmethyl sedaxane to give the para phenols CSCD659087 and CSCD668404, and the desmethyl cyclopropyl alcohol CSCD659088. Metabolites were present mainly as conjugates.

The distribution of sedaxane residues in tissues was consistent, with lowest residues in muscle, and highest in liver. Parent sedaxane was the predominant residue in fat tissues at up to 53% TRR in hen fat, although the absolute level was low (0.004 mg/kg). No sedaxane was found in goat muscle samples; trace levels were reported in hen muscle samples (0.001 mg/kg). Overall, the metabolism found in livestock was qualitatively similar to that observed in the rat.

Plant metabolism

Information was available on the metabolism of sedaxane from seed treatment uses in wheat, Swiss chard, and soya bean. Separate studies were reported using phenyl and pyrazole labelled sedaxane for all three crops. In addition, an uptake study in oilseed rape was conducted.

The oilseed rape uptake study demonstrated no residue uptake into oilseed rape seed when a sedaxane seed treatment application rate of 7.5 g ai/100 kg seed is used to grow oilseed rape plants to maturity.

Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to spring wheat seeds at a concentration of 40 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The wheat was grown under greenhouse conditions and harvested at the following intervals: forage, 27 days after planting (DAP), BBCH 22; hay, 56 DAP, BBCH 41–57; and grain and straw, 111 DAP, BBCH 89.

The total radioactive residues in wheat grain RAC samples from both radiolabels were < 0.01 mg eq/kg and were not further analysed. The TRR of the remaining wheat commodities ranged from 0.45 mg eq/kg for wheat forage (phenyl label) to 1.1 mg eq/kg for wheat straw (phenyl label). The residue profiles for wheat forage, hay, and straw were all similar.

The highest residue level of sedaxane was in wheat forage (16% TRR, 0.16 mg/kg). Parent sedaxane was found in all commodities at 11 to 18% TRR (0.066 to 0.16 mg/kg). The N-demethylated compound, CSCD667584, was also found in all commodities at 2.9–5.1% TRR (0.019–0.036 mg eq/kg). The *trans* para phenol metabolite CSCD658906, in both free and conjugated forms, was a major residue in all commodities with residues between 9.5–17% (0.069–0.18 mg eq/kg). Other significant metabolites in forage, hay and straw were the cyclopropyl alcohol CSCD659089 (4.3–12% TRR, 0.042–0.068 mg eq/kg), the β-hydroxyl carbonyl compound CSCD668403 (4.9–11% TRR, 0.036–0.083 mg eq/kg), and the N-desmethyl *trans* para phenol metabolite CSCD659087 (5.0–7.2% TRR, 0.032–0.062 mg eq/kg). Trace levels [< 1% TRR & < 0.01 mg/kg] of the N-desmethyl pyrazole acid CSCD465008, the pyrazole acid CSAA798670 and the pyrazole amide CSCC210616 were also observed.

Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to soya bean seeds at a nominal concentration of 110 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The soya bean plants were grown under greenhouse conditions and harvested at the following intervals: forage, 28 DAP, BBCH 16; hay, 35–42 DAP, BBCH 61; and seed, 96–103 DAP, BBCH 89.

The highest residue levels of sedaxane were in soya bean hay (23% TRR, 0.082 mg/kg) and soya bean forage (17% TRR, 0.020 mg/kg). The parent compound was not detected in the soya bean seeds; the only metabolite identified in this matrix was CSCD465008, free and conjugated, at a level of 0.017 mg eq/kg. The N-glucoside metabolite (CSCD667555) and N-malonyl glucoside metabolite (CSCD667556) were major metabolites in forage and hay (13–28% TRR, 0.018–0.098 mg eq/kg),

resulting from N-demethylation of sedaxane and subsequent conjugation with glucose and then malonic acid. CSCC210616 and CSCD465008, resulting from the cleavage of the amide bridge, were also observed in pyrazole label forage and hay samples, at levels ranging from 1.0–4.2% TRR (0.004–0.014 mg eq/kg).

The metabolism of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane was investigated in Swiss chard after treatment of seeds with a suspension concentrate containing either [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane. Swiss chard seeds were treated at a nominal application rate of 40 g ai/100 kg seeds and sown into containers of soil on the same day as treatment. Swiss chard plants were grown under greenhouse conditions and harvested 49 days after the seeds were planted at the growth stage BBCH 14–15 (4 to 5 fully open leaves).

The predominant residue identified in Swiss chard was sedaxane: 29% TRR and 0.016 mg/kg in the pyrazole-label experiment, and 52% TRR and 0.024 mg/kg in the phenyl-label experiment.

In the phenyl-label study, N-desmethyl sedaxane, CSCD667584, was present at 4.5% TRR (0.002 mg eq/kg) and two components were tentatively identified as glycoside conjugates: CSCD658906/CSCD659089 at 1.1% TRR (< 0.001 mg eq/kg) and CSCD668403 at 1.5% TRR (< 0.001 mg eq/kg).

In the pyrazole label study, CSCC210616 (pyrazole amide; free and conjugated) was present at 12.9% TRR (0.0072 mg eq/kg), CSCD465008 (N-desmethyl pyrazole acid; free and conjugated) was present at 12% TRR (0.0064 mg eq/kg), the N-desmethyl parent CSCD667584 was present at 2.3% TRR (0.0013 mg eq/kg) and CSAA798670 (pyrazole acid; free and conjugated) was present at 0.8% TRR (< 0.001 mg eq/kg). Two glycoside conjugated components tentatively identified as CSCD658906/CSCD659089, and CSCD668403 were present at 0.9% TRR and < 0.001 mg eq/kg each.

Plant metabolism summary

Metabolism of sedaxane was similar in wheat, Swiss chard, and soya bean, although different major metabolites were found among the plants studied. Residues in wheat grain were too low for analysis. In soya bean seed, the only identified compound was CSCD465008, free and conjugated. In Swiss chard, parent sedaxane was the predominant residue.

The two most abundant compounds in wheat feedstuffs were parent sedaxane and CSCD658906; in soya feedstuffs were sedaxane and conjugates of CSCD667584; and in Swiss chard were sedaxane and the pyrazole metabolites. Although cleavage of the amide bond was relatively more important in Swiss chard in comparison to wheat or soya, the absolute levels were low (≤ 0.01 mg eq/kg).

Metabolism of sedaxane in plants occurs via the following reactions: oxidative metabolism of the phenyl and cyclopropane rings, N-demethylation of the pyrazole ring, and cleavage between the pyrazole and phenyl rings. There was variation in the significance of the different pathways and the nature of the observed conjugations between crops.

Environmental fate in soil

The Meeting reviewed aerobic soil degradation, soil photolysis, and succeeding crop studies.

Aerobic Soil Degradation

The rate of degradation of radiolabelled sedaxane was investigated under aerobic conditions at in three soils in the dark for up to 367 days. The levels of sedaxane declined steadily, reaching ≤ 50% of total applied radioactivity (TAR) in all soils by 1 year in soil treated directly and generally by 100 days in soils where sedaxane-treated seeds had been sown. Two major metabolites, identified as CSAA798670 and CSCD465008, were observed in all soils. CSCD465008 reached a maximum value of 32% of TAR in North Dakota sandy clay loam after 237 days following seed treatment application of sedaxane. CSAA798670 reached a maximum value of 14% of TAR in California sand after 365 days following direct soil application of sedaxane.

Soil Photolysis

The photolysis of [^{14}C]-sedaxane (both labels) on moist and dry soils was investigated under aerobic conditions, with continuous irradiation by artificial sunlight. No photodegradation products were detected at more than4.3% of the applied radioactivity at any analysis time in moist or dry soils. These studies suggest that photolysis is not a significant pathway for degradation of sedaxane.

Rotational crops

Confined rotational crop studies demonstrated that sedaxane pyrazole metabolites may be taken up by plant roots of succeeding crops. Therefore, a field rotational crop study was conducted to assess the potential for accumulation in successive crops at typical plant back intervals. This study was conducted at application rates matching GAP, and showed that no residues of sedaxane or its metabolites are likely in succeeding crops resulting from the use of sedaxane as a seed treatment.

Methods of analysis

Acceptable analytical methods were developed and validated for determination of sedaxane and its metabolites in plant and animal matrices.

The methods for enforcement and data generation involve homogenization and extraction with a mixture of acetonitrile and water (80:20, v/v), clean-up with solid phase extraction, centrifugation and dilution; then determination of analytes using LC-MS/MS. Additional clean up procedures, often including hydrolysis reactions, were made as necessary to improve analytical results for the metabolites. The reported LOQ for the sedaxane isomers was 0.005 mg/kg, while the LOQ for all metabolites was 0.01 mg/kg in all matrices (plant and animal).

The FDA Multi-Residue Method Test guidelines in the Pesticide Analytical Manual (PAM) (Third Edition, January 1994) is not applicable for the analysis of sedaxane, due to low recoveries.

Stability of residues in stored analytical samples

The stability of sedaxane residues during frozen storage (approximately -18 ºC) was investigated in plant matrices and processed commodities. The plant matrices tested were: wheat grain and straw, spinach, potato, orange, lentils, and soya beans. The processed commodities were derived from wheat (flour, germ, and bran), soya bean (meal, hulls, and oil), and orange (dried pulp, juice, and oil).

Compounds tested on plants were: both isomers of sedaxane, CSAA798670, CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616, and CSCD465008. For the processed commodities, the testing was limited to both isomers of sedaxane and CSCD456008. Each compound was added to matrices at 0.2 mg/kg.

No stability problems were found in any of the studies. Sedaxane and all isomers are stable for at least 24 months in frozen plant matrices, except for CSAA798670, which was only studied for 12 months. Similarly, stability for 12 months was demonstrated for sedaxane and CSCD456008 in processed commodities.

The periods of demonstrated stability cover the frozen storage intervals in the residue studies.

No separate storage stability studies were submitted for animal commodities. However, all samples were analysed within 30 days of collection in the bovine feeding study, and no significant changes were noted in the radio-profiles of the principle extracts from milk, liver, kidney, muscle and fat samples at the end of the analytical phase of the animal metabolism studies.

Definition of the residue

Results of the goat and hen metabolism studies were similar, indicating that residue levels are highest in liver and kidney, lower in milk, egg, and fat, and nearly undetectable in muscle. Parent sedaxane was found in fat, liver, egg, and hen muscle at levels ≤ 0.034 mg/kg. Sedaxane was the predominant residue in fat tissues at up to 53% TRR in hen fat, although the absolute level was low (0.004 mg/kg).

No sedaxane was found in goat muscle samples; trace levels were reported in hen muscle samples (0.001 mg/kg).

The predominant metabolites in kidney and liver are CSCD658906 and CSCD659087. Hence the bovine feeding study analysed for these compounds and for parent sedaxane. Although metabolite CSCD658906 was the only residue detected in the bovine feeding study, it was only found in liver and kidney samples from animals dosed at the most exaggerated rate (~24× the maximum dietary burden), and was present at ≤ 0.027 mg eq/kg. Because CSCD658906 is found in liver and kidney as glucose conjugates, inclusion in the residue definition would require an analytical method using hydrolysis procedures. Based on practical considerations regarding the analytical enforcement method together with the expectation of residue levels below the LOQ, it is not appropriate to include metabolite CSCD658906 in the residue definition for enforcement. Noting the low levels of sedaxane residues expected in animal tissues following sedaxane seed treatment uses, the Meeting concluded that the residue definition for animal commodities for purposes of enforcement and dietary intake is sedaxane.

The plant metabolism studies demonstrated that no sedaxane residues are found in grains or seeds. Low level residues may occur in the forage, hay and straw of plants grown from treated seeds. Predominant residues consist of parent sedaxane and CSCD658906 in wheat feedstuffs; sedaxane and conjugates of CSCD667584 in soya feedstuffs; and sedaxane and the pyrazole metabolites in Swiss chard.

The Meeting agreed that parent sedaxane is the best marker compound for plants as it was the only compound found at significant levels (> 10% TRR and 0.01 mg/kg) in all three plant metabolism studies, and is appropriate for both MRL enforcement and dietary intake assessments.

Sedaxane has a log K_{ow} of 3.3. In the goat and hen metabolism studies, sedaxane was the predominant residue found in fat, and was present only in trace amounts in muscle. The Meeting considered sedaxane to be a fat-soluble compound.

The Meeting recommended the following residue definition for sedaxane, when used as a seed-treatment.

For plants and animals: Definition of the residue (for compliance with the MRL and for estimation of dietary intake): *sedaxane*.

The residue is fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised field trials data for sedaxane uses on rape, cereal grains (barley, oats, and wheat), and soya bean.

The OECD MRL calculator was used as a tool in the estimation of the maximum residue level from the selected residue data set obtained from trials conducted according to proposed GAP. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgement. Then, the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the JMPR, a brief explanation of the deviation was provided.

Soya bean (immature seeds)

The GAP for soya bean is from Canada and the USA, and specifies seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed. Trials from the USA were conducted at a rate of 40 g ai/100 kg seed. As no residues were detected, the Meeting agreed to make use of these exaggerated rate trials.

A total of 20 trials were available from the USA. Sedaxane residue concentrations in soya bean seed from the USA were: < 0.01 (20) mg/kg.

Based on the results of the soya bean metabolism study, which showed that parent sedaxane residues are not found in soya bean seed, together with the results of the 20 field trials from the USA, the Meeting agreed that no sedaxane residues are expected in soya bean seed.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane on soya bean (immature seeds), and an STMR of 0 mg/kg.

Cereal grains

Supervised trials data were available for barley, oats, and wheat.

Barley

The critical GAP for barley is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

A total of 28 trials on barley grain were available from Australia (4), Canada (12), and USA (12). However, only the four trials from Australia match the GAP of France.

Sedaxane residue concentrations in barley grain from Australia were: < 0.010 (4) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the four field trials from Australia, the Meeting agreed that no sedaxane residues are expected in barley grain.

The Meeting estimated a maximum residue level for sedaxane in barley grain of 0.01* mg/kg, and an STMR of 0 mg/kg.

Oats

The critical GAP for oats is from France and specifies seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

A total of four trials on oat grain were available from Australia matching the GAP of France.

Sedaxane residue concentrations in oat grain from Australia were: < 0.010 (4) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the results of the field trials from Australia, the Meeting agreed that no sedaxane residues are expected in oat grain.

The Meeting estimated a maximum residue level for sedaxane in oat grain of 0.01* mg/kg, an STMR of 0 mg/kg, and an HR of 0 mg/kg.

Wheat

The critical GAP for wheat is from France and specifies seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. GAP rates in Canada and the USA were 5 g ai/100 kg seed. Single and double rate trials were conducted in Australia.

A total of 31 trials on wheat grain matching GAP were available from Australia (8), North Europe (13), and South Europe (10).

Sedaxane residue concentrations in wheat grain from Australia were: < 0.010 (8) mg/kg.

Sedaxane residue concentrations in wheat grain from North Europe were: < 0.010 (13) mg/kg.

Sedaxane residue concentrations in wheat grain from South Europe were: < 0.010 (10) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the results of the field trials from Australia and Europe, the Meeting agreed that no sedaxane residues are expected in wheat grain.

The Meeting estimated a maximum residue level for sedaxane in wheat grain of 0.01* mg/kg, and an STMR of 0 mg/kg.

The Meeting decided to extrapolate the maximum residue level, median residue and highest residue for wheat to rye and triticale, noting that these crops have an identical GAP.

Rape seed

The GAP for rape seed from Canada and the USA lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 16 trials on rape seed matching Canadian GAP were available from Canada.

Sedaxane residue concentrations in rape seed from Canada were: < 0.01 (16) mg/kg.

Based on the results of the rape seed metabolism study, which showed no transfer of radioactivity to the seed, together with the results of the rape field trials, the Meeting agreed that no sedaxane residues are expected in rape seed.

The Meeting estimated a maximum residue level for sedaxane in rape seed of 0.01* mg/kg, and an STMR of 0 mg/kg.

Animal feedstuffs

Soya bean forage and hay (fodder)

The GAP for soya bean is from Canada and the USA specifies seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed. Trials from the USA were conducted at a rate of 40 g ai/100 kg seed (8 × USA GAP rate). As residues were detected in soya bean forage and hay samples, the Meeting determined that no maximum residue estimates could be made for these commodities on the basis of the exaggerated rate trials.

Forages (Barley, Oats, and Wheat)

The critical GAP for forages is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. Because there is no label feeding/grazing restriction for forages in France, the Meeting selected the highest residue concentration from each trial conducted that matched GAP.

Australian trials for barely and oat forage were submitted but not used for residue estimates since an Australian GAP for sedaxane is not available.

Barley straw and fodder

The critical GAP for barley is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

Barley straw

A total of four trials on barley straw matching France GAP were available from Australia. Sedaxane residue concentrations in barley straw from Australia were: < 0.010 (4) mg/kg.

Barley hay

No barley hay trials matching the GAP of France were available. The Canadian and USA GAP lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 24 trials on barley hay matching the GAP of the USA were available from Canada (12) and USA (12).

Sedaxane residue concentrations in barley hay from Canada and the USA were (n = 24): < 0.010 (19), 0.011 (2), 0.025 (3) mg/kg.

Oat straw

The critical GAP for oat is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. A total of 4 trials on oat straw matching France GAP were available from Australia.

Sedaxane residue concentrations in oat straw from Australia were: < 0.010 (4) mg/kg.

Wheat straw, fodder, and forage

The critical GAP for wheat is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. Supervised trials data were available for wheat straw, hay, and forage.

Wheat forage

A total of 23 trials on wheat forage matching France GAP were available from North Europe (13), and South Europe (10).

Sedaxane residue concentrations in wheat forage from North Europe were: < 0.010 (9), 0.013 (2), 0.016, and 0.017 mg/kg.

Sedaxane residue concentrations in wheat forage from South Europe were: < 0.010 (6), 0.011, 0.013, and 0.023 (2) mg/kg.

As the results from North and South Europe are similar, the Meeting decided to combine these datasets (n = 23): < 0.010 (15), 0.011, 0.013 (3), 0.016, 0.017, and 0.023 (2) mg/kg.

Based on the trials conducted in Europe, the Meeting estimated an STMR of 0.01 mg/kg and a HR of 0.023 mg/kg for wheat forage. The Meeting agreed to extrapolate the residue estimates from wheat forage to the other forages (barley, oats, rye, and triticale).

Wheat straw

A total of 23 trials on wheat straw matching GAP from France were available from North Europe (13) and South Europe (10).

Sedaxane residue concentrations in wheat grain from Europe were: < 0.010 (21), 0.011, and 0.012 mg/kg.

Wheat hay

No wheat hay trials matching the French GAP were available. The Canadian and USA GAP lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 36 trials on wheat hay matching Canadian and US GAP were available from Canada (16) and USA (20).

Rank-order sedaxane residues in wheat hay from Canada and USA were (n = 36): < 0.01 (27), 0.013, 0.014 (2), 0.025 (3), 0.035, 0.045, 0.075 mg/kg.

Summary of straw and fodder from barley, oats, rye, triticale, and wheat

Straw and fodder from barley, oats, rye, triticale, and wheat, may not always be readily distinguishable from each other in trade. Thus, it is preferable for these commodities to have the same MRLs. For sedaxane, residues in wheat hay were found to have the highest residue levels among the straw and fodder feedstuffs from small grains. The Meeting agreed to use the wheat hay data from Canada and the USA as a basis for estimating the maximum residue levels of these livestock feedstuffs.

On a dry-weight basis (DM = 88%), sedaxane residues in wheat hay were (n = 36): < 0.011 (27), 0.015, 0.016 (2), 0.028 (3), 0.040, 0.051 and 0.085 mg/kg.

The Meeting estimated a maximum residue level of 0.10 mg/kg for sedaxane on barley, oats, rye, triticale, and wheat straw and fodder, dry. The Meeting estimated median and highest residue values of 0.01 and 0.075 mg/kg (as received), respectively, for sedaxane residues in straw and fodder of barley, oats, rye, triticale, and wheat, for the purposes of calculating livestock dietary burdens.

Fate of residues during food processing

High temperature hydrolysis

A high-temperature aqueous hydrolysis study was conducted to determine the nature of any sedaxane-derived residues in processed crop commodities or by-products under conditions typical of industrial or household processing.

In experiments conducted at 90, 100, and 120 ºC over a range of pHs, no significant degradation of sedaxane was found. Thus, sedaxane is hydrolytically stable under conditions representative of pasteurization, baking/brewing/boiling, and sterilization.

Processing

The Meeting received information on the processing of barley, oilseed rape, soya bean, and wheat. Neither sedaxane nor any metabolites were detected above the LOQ in any RAC or processed commodity sample. Thus, no processing factors for sedaxane could be determined.

Residues in animal commodities

The Meeting received a lactating dairy cow feeding study, which provided information on potential residues resulting in ruminant tissues and milk from sedaxane residues in the animal diet.

Lactating Holstein dairy cows were dosed for 28–30 days once daily via gelatin capsule with sedaxane. The sedaxane dosing rates were 0.11, 0.54, and 2.2 ppm in the dry-weight diet.

No sedaxane transferred into any tissue or milk at any dose level.

Due to low dietary burdens to poultry and low residue transfer noted in the poultry metabolism study, no poultry feeding study was conducted.

Livestock dietary burden

The Meeting estimated the dietary burden of sedaxane in livestock on the basis of the diets listed in OECD Feed Table 2009 (available from the FAO website: http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmpr/jmpr-docs/en/). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating maximum residue levels, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

Estimated maximum and mean dietary burdens of livestock

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the livestock diets from US-Canada, EU, Australia and Japan in the OECD Feed Table 2009.

		Livestock dietary burden, sedaxane, ppm of dry matter diet			
		US-Canada	EU	Australia	Japan
Max	beef cattle	0.013	0.028	**0.092** [a]	0.002
	dairy cattle	0.028	0.028	**0.081** [c]	0.001
	poultry - broiler	0.002	0.002	0.002	0.000
	poultry - layer	0.002	**0.011** [e]	0.002	0.000

		Livestock dietary burden, sedaxane, ppm of dry matter diet			
		US-Canada	EU	Australia	Japan
Mean	beef cattle	0.002	0.011	**0.040** [b]	0.000
	dairy cattle	0.011	0.011	**0.034** [d]	0.000
	poultry - broiler	0.000	0.000	0.000	0.000
	poultry - layer	0.000	**0.004** [f]	0.000	0.000

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues.
[b] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.
[c] Highest maximum dairy cattle dietary burden suitable for MRL estimates for milk.
[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.
[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.
[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

Animal commodities, maximum residue level estimation

Cattle

The sedaxane maximum dietary burden for beef and dairy cattle is 0.09 and 0.08 ppm, respectively. Sedaxane residues in all tissues in the bovine feeding study were below the LOQ of 0.01 mg/kg at all three dosing levels (highest of 2.2 ppm). No detectable residues of sedaxane are expected in any ruminant tissue from seed-treatment uses of sedaxane.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane in/on: edible offal (mammalian); mammalian fats (except milk fats); meat (from mammals other than marine mammals); milks; and milk fats.

Based on no detectable levels of sedaxane being found in any tissue in the bovine feeding study, and the results of the goat metabolism studies demonstrating sedaxane levels are < 0.01 mg/kg in all tissues at exaggerated dose rates, the Meeting estimated STMR and HR values of 0 for mammalian commodities.

Poultry

The sedaxane maximum dietary burden for layer and broiler poultry is 0.01 and 0 ppm, respectively. No detectable residues of sedaxane are expected in any poultry tissue from seed-treatment uses of sedaxane.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane in/on: poultry fats; poultry meat; poultry, edible offal of; and eggs.

Based on the results of the hen metabolism studies demonstrating sedaxane levels are < 0.01 mg/kg in all tissues at exaggerated dose rates, the Meeting estimated STMR and HR values of 0 for poultry commodities.

RECOMMENDATIONS

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

For plants and animals. Definition of the residue (for compliance with the MRL and for estimation of dietary intake): *sedaxane*.

The residue is fat soluble.

CCN	Commodity Name	MRL, mg/kg	STMR mg/kg	HR mg/kg
GC 0640	Barley	0.01*	0	
AS 0640	Barley straw and fodder, dry	0.1	0.01	0.075
MO 0105	Edible offal (Mammalian)	0.01*	0	0
MF 0100	Mammalian fats (except milk fat)	0.01*	0	0
MM 0095	Meat (from mammals other than marine mammals)	0.01* (fat)	0	0
ML 0106	Milks	0.01*	0	
FM 0183	Milk fats	0.01*	0	
GC 0647	Oat	0.01*	0	
AS 0647	Oat straw and fodder, dry	0.1	0.01	0.075
PF 0111	Poultry fats	0.01*	0	0
PM 0110	Poultry meat	0.01*	0	0
PO 0111	Poultry, edible offal of	0.01*	0	0
PE 0112	Eggs	0.01*	0	0
SO 0495	Rape seed	0.01*	0	
GC 0650	Rye	0.01*	0	
AS 0650	Rye straw and fodder, dry	0.1	0.01	0.075
GC 0653	Triticale	0.01*	0	
AS 0653	Triticale straw and fodder, dry	0.1	0.01	0.075
GC 0654	Wheat	0.01*	0	
AS 0654	Wheat straw and fodder, dry	0.1	0.01	0.075

* At the limit of quantification.

Commodity Name	STMR, mg/kg	HR, mg/kg
Barley forage	0.01	0.023
Oat forage	0.01	0.023
Rye forage	0.01	0.023
Triticale forage	0.01	0.023
Wheat forage	0.01	0.023

DIETARY RISK ASSESSMENT

Long-term intake

The ADI for sedaxane is 0–0.11 mg/kg bw. No long-term intake dietary risk assessment is needed for sedaxane because no uses result in residues in human foods. The Meeting concluded that the long-term intake of residues of sedaxane, from uses that have been considered by the JMPR, is unlikely to present a public health concern.

Short-term intake

The ARfD for sedaxane is 0.3 mg/kg bw. No short-term intake dietary risk assessment is needed for sedaxane because no sedaxane uses result in residues in human foods. The Meeting concluded that the short-term intake of residues of sedaxane, from uses that have been considered by the JMPR, is

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