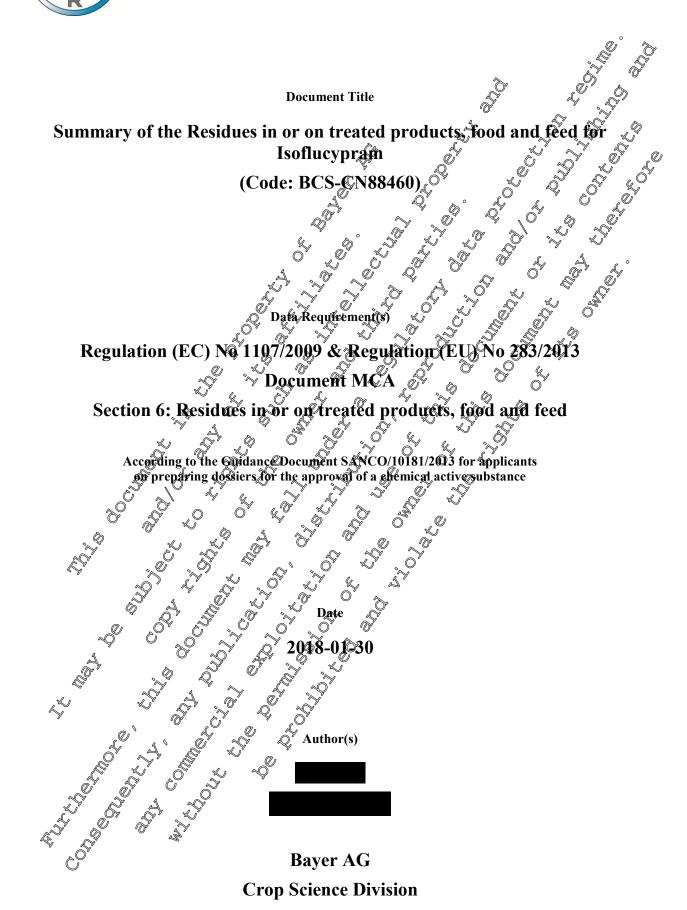


March 12992-01-4



Crop Science Division



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 from other applicants once the period of data agotection has expired basis of the summaries and evaluation of unpublished proprietary data contained in this



Version history

Date [yyyy-mm-dd]	Data points containing amendments or additions ¹ and brief description	Document identifier and version number
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It is suggested in SANCO/101	that applicants adopt a similar approach to showing revision 80/2013 Chapter 4, 'How to revise an Assessment Report'.	and version history as outlined
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E. L	Effect on the residue level in poller and bee products	
× sõ*	Effect on the residue lovel in poller and bee products	
U	Other studies	



CA 6 RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

INTRODUCTION

Isoflucypram (CAS-No. 1255734-28-1) is a new fungicidal active substance developed by Bayer. This document supports the application for regulatory approval of Isoflucypram in Europe, under Regulation (EC) No 1107/2009.

The document MCA Section 6 summarises all metabolism and residue data in or on treated products of plant and animal origin and consumer dietary risk assessments which are relevant for the approval of Isoflucypram and the proposed intended uses, including the representative uses, under Regulation (EC) No 1107/2009 in accordance with the requirements laid down in the Commission Regulation (EU) No 283/2013.

Isoflucypram is a novel broad spectrum fungicide of the chemical class of N-cyclopropyl-N-benzylpyrazole-carboxamides with an outstanding efficacy against the hajor conomically inportant fungal diseases of cereal crops (wheat, triticale, we barley and wats) and excellent cop safety.

Since Isoflucypram is an SDH inhibitor and thus assigned to the FRAC resistance Group 7 the application scope of Isoflucypram-containing products on cereals with only one Gliar spray at a maximum of 75 g a.s./ha supports ar effective anti-resistance management strategy.

Tailor-made and broad spectrum Isoffucyprom combinations show highly beneficial properties in terms of plant physiology beside the long-lasting and certain curative efficacy to control fungal diseases and to maximize the full weld potential of the coreal crops.

Details of the literature search undertaken are summarized in MCA Section 9. For Isoflucypram and its metabolites, no publication and relevant scientifically peer-reviewed open literature reference has been identified which would indicate that a side effect on human health, the environment and nontarget species may exist, which yould then need to be considered in the visk assessment of this new active substance dossier.

Throughout the development of Isoflucypram the following sononymes may have been used and also referred to an individual study reports: Bayer Sode: BCS-CN88460, BCS-CN88460-a.s., '460 and the Bayer-internal short Code: ISX All obtenical substances described by either of these codes refer to the same chemical name and structural formula

In this MCA Summary Section 6, the forthowing codes will be used for the metabolites:

<i>O</i> n		Standard "dossier name"
<u>Name</u> 🔊		<u> Standard "dossier name"</u>
BCS-CR60082	M49 5	BCS-6N88469-N-methyl-cyclopropyl- pyrazole-carboxamide
BCS-DC20298	. № 1	[©] BCS-CN88460-2-propanol
BCS-CY26497	SM124	BCS-CN88460-carboxylic acid
BCS-CY24813	MAN	BCS_6N88460-propanol
BCS-DC22055	M06	BCS-CN88460-desmethyl-propanol
BCS-CX997	~M116 *	BCS-CN88460-desmethyl-carboxylic acid
BCS-CX997®	MO S	BCS-CN88460-propanol-GlucA
~~ ~	M20	BCS-CN88460-2-propanol-GlucA
2 67	≦~M37~	BCS-CN88460-desmethyl-propanol-GlucA
	"O	
°Q3		
\bigcirc		



CA 6.1 Storage stability of residues

Table 6.1- 1:	Periods of frozen storage (approx.	-18°C) of pla	ant-based Samp	les (betwee	n sampling and
	analysis) for matrices relevant to t	his dossier	Q [*]	° 4	4. ^V

• PLANT MATR					
able 6.1- 1: Perio	s of frozen storage of sa ials) are shown in Tabl ods of frozen storage (ap ysis) for matrices relevan	prox18°(gføf plant-based	Ų į	sidue, processing
	ample material		Longest storage	¢ [÷]	Study ? ~
Сгор	Matrix	× ,	o°duration &	Report No.	Reference
Barley	green material		390 St	15-21.18 13-21.15 13-21.15 15-21.15	M-583909-024 KCA 6.3.493 M5883692-02-1 ØKCA 6.3.1/07
	straw		~ 350 ² 7 \$96 6	152118	M-583909-02-1 KCA 6.3.1/03
	grain beer brewet2s grain brewet2s grain brewet2s grain brewet2s grain brewet2s grain brewet2s grain		297 Of	4 *15-3467 *	M-579494-01-1 KCA 6.5.3/01
Wheat	malt sprouts pearl barles pearl barley rub off gereen material		2 398 4 5 5 5 5 5	Ç.	
	Strew of S	<u> </u>	× 5355 ×	15-2119	M-584690-02-1 KCA 6.3.2/07
	grain bran hour whole meal germ nuddlings shorts pasta fresh pasta, dry pasta, dry pasta		<u> </u>	RALNN137	M-600505-02-1 KCA 6.5.3/02



	Sample material		Study			
Crop	Matrix	duration (days)	Report No.	Reference		
Turnip	body	194		Ĵ,		
	leaf	193		& V		
Carrot	root	300	15-2502	M-605725-01-5 KCA 6.6.2/6		
	leaf	299				
Lettuce	head	341				
		C)		× ~ &		

A study was initiated to evaluate the stability of BCS-CN88460 and its metabolite BCS-CR60082, during deep freezing storage (\leq -18°C) for a period of 24 months in tomato (fruit), bean (dry seed), wheat (grain), rape (seed) and orange (fruit). The following interim report describes the effects of deep freezing storage over a period of 18 months.

Donort	KCA 6.1/01; 10 ; 2017; M-605556-01 A
Report:	KCA 0.1/01,, 2019, M-003530-01-4
Title:	Storage stability of residues of RES CNR 2660 and to metabolite RCS CR6008 in
	tomato (fruit), been (dry seed), wheat (grain), rape (seed) and grange (huit) during deep freeze storage for at least 24 months MR-17/244
	deep freeze størage for at leas 24 months 2 2 2
Report No.:	deep freeze storage fot at least 24 months MR-17/244 M-605556-61-1
Document No .:	M-605556-61-1 & & & & & & & & & & & & & & & & & &
Guideline(s):	M-605556-64-1 C C C C C C C C C C C C C C C C C C C
	Regulation (EC) No.1407/2009 of the European Parliament and of the Council as
	regards the data requirements for a give substances [2].
	USEPA Residue/Chemistry Test Guideline OPRTS 860(1/380: Storage Stability Data -
	August 4996 [3]
	August 4996 [3] October 2007 [4]
Guideline deviation(s)	not specified where the second s
Guideline deviation(s)	Yes in it is it is it is
Č (

I. Materials and Methods

To determine the freezer storage stability of the relevant residues of BCS-CN88460 in plant materials, individual 5-g control samples of orange fruit (high acid content), tomato fruit (high water content), wheat grain (high starch content), bean do seed (high protein content) and rape seed (high oil content) were separately spiked with either BCS-CN88460 parent compound or BCS-CR60082 at a level of 0.20 mg/kg. The samples were stored in High Density Poly Ethylene (HDPE) Nalgene containers at an average temperature of -18 °C or below. Jomato (fruit), bean (dry seed), wheat (grain) and rape (seed) were analyzed at the nominal storage intervals of 0 and 6 days, and 1, 3, 8, 13 and 18 months.

For orange (fruit), although the RSDs on Day Oremained acceptable (<20%), the variability of results was higher than for the other phatrices and higher compared to what was observed during the method validation. It was thus decided to increase the number of analyses for the later storage intervals and to start a second set of orange (fruit) sample in order to ensure that sufficient samples would be available to investigate the stability of residues over 24 months. The new set of orange (fruit) was separately fortified with BCS-CN88460 and BCS-CR60082 at 0.20 mg/kg. The samples stored in HDPE Nalgene containers at an average temperature of -18 °C or below, and analyzed at the nominal storage intervals of 0.5° and 10° months for this interim report.

The results covering a storage interval 24 months will be given in the final report.

For Day 0 analysis, three stored spiked samples of each material were analyzed, alongside with one control sample and concurrent recoveries at 0.01 and 0.20 mg/kg. At later storage intervals, two stored spiked samples were analysed (3 for orange fruit) alongside with one control sample and concurrent



recoveries at 0.01 and 0.20 mg/kg. Samples used for concurrent recoveries were prepared at the same time and stored in the same way as the control samples, and spiked on the day of analysis.

Concurrent recoveries at 0.01 and 0.20 mg/kg were conducted for each sample material, at each storage interval.

Residues of BCS-CN88460 and its metabolite BCS-CR60082 were determined according to the analytical method 01475 (2016; M-558986-01-1, referenced in M@A Section 4 under Point 4.1.2 (e)) which had been validated for the sample materials relevant to this study in the method 01475. Samples of orange fruit, tomato fruit, wheat grain, bean dry seed and rape seed were analyzed according to the procedure described in the method for these matrices. The LOQ was 0.01 mg/kg/or BCS-CN88460 and BCS-CR60082, expressed as parent.

II. Findings

At each storage interval, apparent residues of BCS CN88460 and BCS-CR60082 in the control samples were below 30% of the LOQ (LOQ=0.01 mg/kg) for each sample material except for BCS-CR60082 at the storage interval 6 days in manage (fruit), where the control sample was at 0.603 mg/kg. Nevertheless, this result was consider acceptable

For BCS-CN88460, all the concurrent recovery means were within the acceptable range of 70-110% with corresponding RSDs (relative standard deviation) below 20% except the recovery mean of 111% at the storage interval 561 days for bean (dry seed). Novertheless, this was considered acceptable since it only slightly exceeds the criteria laid down in the 5U guidance SANCO 3029/99 rev. 4, but remains within the OECD guidance ENV/JM/MONO(2007)17 criteria.

For BCS-CR60082, all the recovery means were within the acceptable range of 70-110% with corresponding RSDs (relative standard deviation) $\leq 20\%$.

Details on concurrent ecovery data are shown in Table 6.1-2 for BCS CN88460 and Table 6.1-3 for BCS-CR60082.

On Day 0, average residue recoveries of BCS-CN88460 ranged from 96 110% of the nominal spiked concentration in the stored samples; and ranged from 92-110% for BCS-CR60082. In samples analysed after approximately 18 months of frozen storage (558-563 days), storage stability recoveries ranged from 89-104% for BCS-CN88460 and 82-102% for BCS-CR60082. At all sampling dates and in all sample materials, the relevant components of the residue of BCS-CN88460 were above 70%. Even in the case of the lower values in the given ranges, there was no evidence of any continued degradation of any of the analytes in any of the sample materials. Thus, both analytes can be considered stable in all relevant plant matrix types for a period of at least 18 months (558 to 563 days).

All storage stability cesults are summarised below in Table 6.1-4 for BCS-CN88460 and Table 6.1-5 for BCS-CR60082.

The time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours for tomato fruit, bean dry seed, wheat grain and rape seed. For orange fruit and the compound BCS-CR60082, the analysis for time point T=0 was done after a maximum time of 105 hours from the beginning of proparation (most of the samples had to be rediluted from the Extract A to be analysed). This storage period is covered by the stability experiments done in method 01475 (**1990**). This storage period is covered by the stability experiments done in method 01475 (**1990**). This storage period is covered in MCA Section 4 under Point 4.1.2 (e)) which indicated that Extract A are stable for at least a period of 149 hours for orange (fruit).

III. Conclusions

During Storage period of 18 months under deep-freezer conditions, BCS-CN88460 and BCS-CR60082 were stable in orange fruit (high acid content), tomato fruit (high water content), wheat grain (high starch content), bean dry seed (high protein content) and rape seed (high oil content), representing a wide array of plant-based sample materials. According to OECD guideline 506 on the



stability of pesticide residues in stored commodities, it can be concluded that residues of BCS-CN88460 and BCS-CR60082 are stable for 18 months at \leq -18°C in all raw agricultural

commodities and processed commodities. These results validate the residue values reported in all supervised field trials and processing studies of with respect to storage stability of samples frozen prior to analysis.

				6	Ô		-	1 .	K N	
Plant	Fortification	Date of	Storage		S-CN8	-	Mean	DSD	Standard deviation	K 4
material	Level [mg/kg]	Extraction	Interval	Sing	le Reco	veries	wiean [%]	RSD ^O [©]	deviation	× v
materiai	Level [mg/kg]	Extraction	(days) 🖉	A.	[%]	Ŵ,				<i>©</i>
		2016-03-29	0 🔊	100	- ^	¥	© -	°\$ - ∖°	0, %	<u></u>
		2016-07-07	100	86°	-2	-&	×_0	- 2	~~ ~	
Tomato	0.01	2016-12-05	ØĨ	Ø103	×.		~®	Ŕ	s S	0
(fruit)		2017-05-18	A 415 0	106	V -	Q	<u> </u>	- ~	0 -27	
		2017-10-13	563	97	- Ô	- "	♦ - (0	-~	4	Ç ^ı
	Overal	l Mean, RSD and	standard de	viatio	n {Ø]	0	100	A Y	4.2	8
		2016-03	\$0.5	× 98 (\$102	Ø103	\$1 01	\$2.6	2.6	
		2016-67-07	100	82	89	7 - 3	<u>ک 86 ک</u>	- 2		
Tomato	0.20	2016-12-05	2455	A96	1,090	Ś	105	<u>م</u> 0	- -	
(fruit)		2017-05-Ì8	415 ⁴	0 ⁷ 95	≪⁄84	Ŝ.	es ⁹⁰	<u>Öğ</u>	õ -	
		2017-10-13	⁽²⁾ 563	101	103 4	۶ °	¥102			
	Overal	Mean, RSD and				- N	970	8.6	8.3	1
		2006-03-20	Å Å	Ø99	Ô ^y	& ,		- OF	-	
	, C	@016-07-08	a, 100 Q	99	7 -	Ő.	Š - "	<u>у</u> -	-	
Bean	Q.Q.L	2016	246	Ŕ	<u>.</u> @			-	-	
(dry seed)	J ^e vo	2017-05-19	41/5	87	S.	ŵ	ŝ	-	-	
		2017-10-12	C 7561	115>		S-	×°-	-	-	
		KMean, RSD and	standard de	eviatio	n [%] [©]		98	10.9	10.7	
		2046-03-30	ð,	99	Ø 9	<u>98</u> °	99	0.6	0.6	
<u>z</u> q"		2016-07-08	\100 o	ž 97 😵	88	0-	93	-	-	
Bean	0.20>	2016-12-01	Ĵ ^{\$} 246 ≯	98	1013	۶ -	100	-	-	
(dry seed)	J.J. A	2017,05-19	4109	Ø6	~ <u>&</u> 2	-	79	-	-	
		2017-10-10r	°~561 (×113	Q r 09	-	111			
	Overal	l Ŵean, RSD and	standard de	eviatio	n [%]		96	11.2	10.8	
4	Š Č	2016-03-31		Ĵ2	-	-	-	-	-	
Wheet	, D	2006-07-10		9 3	-	-	-	-	-	
Wheat 🦑	0.01	2016-42-05	£ ²⁴⁹ ~Q	104	-	-	-	-	-	
(grain)	J L	2017-05-19	44	88	-	-	-	-	-	
	, O	2007-10-12	se ŏ	108	-	-	-	-	-	
	Overal Overal	l Mean, RSD and	standard de	eviatio	n [%]		97	8.8	8.5	
هر		2016-03-31	y 0	95	94	97	95	1.6	1.5	
, Ś		2016-07-11	102	94	96	-	95	-	-	
Wheat	0.20	16-12-05	249	102	102	-	102	-	-	
(grain)	G A .	2017-05-19	414	97	87	-	92	-	-	
		2017-10-12	560	90	103	-	97	-	-	
	Overal	l Mean, RSD and	standard de	eviatio	n [%]		96	5.2	5.0	
D. C		2016-03-31	0	113	-	-	-	-	-	
	0.01	2016-07-12	103	93	-	-	-	-	-	
(seed)		2016-12-01	245	94	-	-	-	-	-	
	•				•		•			•

Table 6.1- 2:	Concurrent recovery dat	a for BCS-CN88460
	concurrence recovery du	a for Deb ertoutoo



Page 10 of 432 2018-01-30 Document MCA - Section 6: Residues in or on treated products, food and feed Isoflucypram

Plant material	Fortification Level [mg/kg]	Date of Extraction	Storage Interval (days)		S-CN88 le Reco [%]		Mean [%]	RSD [%]	Standard deviation	Ŷ
		2017-05-22	417	86	-	-	-	-	- %	
		2017-10-10	558	97	-	-	-	ð	- "?	Ô
	Overall	Mean, RSD and		1	n [%]		97	10.4	10.6	Ş
		2016-03-31	0	100	99	96	98	2.1	QN A	
		2016-07-12	103	92	83	-	**	-	· · · · · · · · · · · · · · · · · · ·	
Rape	0.20	2016-12-01	245	98	Ø96	-	Ø7	-		, Ô
(seed)		2017-05-22	417	91 [×]	93		2, 92	- 0	J.	
		2017-10-10	558	<i>8</i> 1	83	L of g	85	O``		, v
	Overall	Mean, RSD and	4//	í –	n [%]	~~	∂9 [°] 3	6.5	6.1	
		2016-03-29	0 0	82	- 0	y - 🗞	~ - / ~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>		Ş
		2016-04-04	<u>k</u>	<u>B</u> D	Ň	-V			°∼∕- ≪	
Orange		2016-05-02	94 🔬	9 ⁸⁷	Ò-	ď	<u> </u>	Ø,		L°
(fruit)	0.01	2016-07-13	A 106 0		-	Q>-	- 4	> -	l de	"Q"
()		2016-12-08	<u>`A.</u>	<u>9</u> 4/	J.	- 🞸	<u> -</u> >>y	2 Q	<u></u>	N'
		2017-05-18	(4) ⁵	()85	°	KJ Ø	Č.	<u> </u>	~~ O`	
		2017-10-99	³ √559 °√	106	r	ý- (\$~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	6	\$ -\$	
	Overall	Mean, R SD and				<u></u>	89°C	' <u>10.</u> ♣	°,9,3	
		2006-03-2%	<u> </u>	\$ 76	1001	- ZÔV	83	1 9 4	<u>د</u> 16.1	
		2916-04-04	~~~ 6	92	≈ 82	@9 4	<i>©</i> 89	7.2	©° 6.4	
		2016-05-02	34	1040		88	y [≫] 90 ∿y	15.1Q	13.6	
Orange	0.20 🦄	2016-07-13	1406	~92	29	88	23 S	60	5.6	
(fruit)	Ž	2016-12-08	Q54 2	<u> </u>	Q 83	\$108	93 م	94 .5	13.4	
	Ũ,	2017-05-18	Ø 415 S	89%	80	96 (D ⁸ 88 4	/	8.0	
		201700-09	<u>559</u>	AQ)	105	105	105	3.8	4.0	
		Mean, RSD and		6		<u>v</u>	Ĵ ⁹²	12.0	10.9	
	0.64	2016-12002		108	¢ - 4	° -	-	-	-	
Orange *	0.09	2017 205-18	1.67	Ð	-	- 45	-	-	-	
(fruit)		2017-10-130	315	103	, C	<u></u>	-	-	-	
R. Y	Qeral	Mean, RSD and	standard 🛈	eviatio	n∕[%] ∿	0 >	101	7.5	7.6	
	\$° '	Ç [°] 2016 2-02	D' 0KJ	181	106	104	104	2.4	2.5	
Orange *	2 ^{9.20} A	2010-05-18	<u>, 197</u>	94	<u>8</u> 2	89	88	6.8	6.0	
(fruit)		2017-10-19	315	101	Ş×Î02	97	100	2.6	2.6	
4	O veral	Mean, ŘSD ant	standard de	eviatio	n [%]		97	8.0	7.8	
(fruit) RSD: relatives New set of D Fortification as 1): value not re	Overall tandard deviation range (fruit) BCS-CN88460 I etained	2016-1202 2017-05-18 2017-10-120 Mean, RSD and 2016-2-02 2016-2-02 2010-05-18 3917-10-93 Mean, RSD and Determination as:	Bes-CN884	7 101 eviation	Tio2 n [%]	97 as: BCS	100 97 3-CN8846	2.6 8.0		



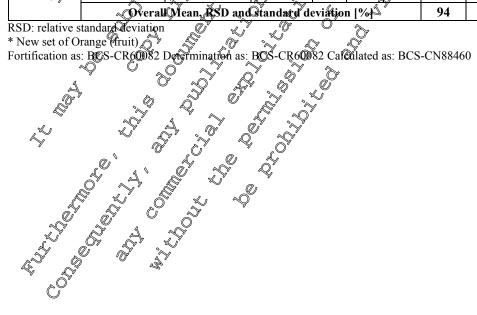
Plant material	Fortification Level [mg/kg]	Date of Extraction	Storage Interval (days)		S-CR6 le Reco [%]		Mean [%]	RSD [%]	Standard deviation	, Å
		2016-03-29	0	88	-	-	-	ð	- 0	Ô
		2016-07-07	100	101	-	-	- 6	- '		Į.
Tomato	0.01	2016-12-05	251	100	-	-	- 1	-		Ô
(fruit)		2017-05-18	415	97	»	-	s s	-	<u></u> - x	L.
		2017-10-13	563	90 🔊	2r -	-	ŵ-	- (Ů,	
	Overal	l Mean, RSD and	standard d	eviatio	n [%]	Ô	₽ 95	6.2 Ø		"Ć
		2016-03-29	0	₄ @4	95	8	94	, Q	1.0 O	
		2016-07-07	100	× 84	86 🔊	-	28 5	Q - .		Ş
Tomato	0.20	2016-12-05	251	102.	97@	× - ×	¥ 100			<i>,</i>
(fruit)		2017-05-18	458	<i>f</i> 2	.87	L.	87	<i>Q</i>		
		2017-10-13	<u>م</u> 563 ه	95	Q102	<u>a</u>	399	102		ç°
	Overal	l Mean, RSD and	standard d	eviatio	n [%]		93 着	7.1	6.6	, ^v
		2016-03-30	L D	84		- Á	_^^	<i>Q</i>	×- 4	
		2016-07-0	004	⁶ 99 ,	<u> </u>	×,	. Č	<u>_</u>	6	
Bean	0.01	2016-12-01	@ 246 ×	87 [%]	Ž _ ^	y - %	Q - ,	ð - 4		
(dry seed)		2017-08-19 @	4166	Ô	2	0 _	ā0	-0	۶ ۲	
		20 7-10-12	581	A 10	"Ø″	Ŵ.	<u>Ö</u>	°\$₽	& -	
	Overal	l Mean, RSD and	-	1Q/	n [%] /		<u>92</u>	13.1	[©] 12.1	
	(5 0 <u>0</u>	93	94	94	94 💙	0,69	0.6	
	°~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	2016-07-08	190	Å 94	&	<u> </u>	89	Â, Ç	-	
Bean	0.20 🖑	2016-12-09	246	۶ 91 ک	≫95	×-	<u>د</u> 93 (-	
(dry seed)		2017	Q 415	74	77	- (D 76	-	-	
,		2018-10-12	561	. 97	94	Å	.98	-	-	
		l Mean, RSP and	standard d	wiatio	n [%]	L.	×90	8.7	7.8	
	Operal Operal	2016-03-31	\$ 0 Å	87		S - 0	Pn -	-	-	
Ô		201,6-07-11	1927	Ŷ		Ŵ	-	-	-	
Wheat 🔊	0.01	2016-12-05	249 a	≫95	<i>.</i> .	\sim	_	-	-	
(grain)	. U	> 2017-05-19	\$ 414°	80	у - %	0' V -	-	-	-	
	0.01 Č	✓ 2017Qr0-12 %	560	101	- 4	-	-	-	_	
	Overal	l Mean, RSD and			n. 🍂 I		91	8.8	8.0	
		2016-0301		90 @	93	92	92	1.7	1.5	
	φ°Ŭ,	0 2016 07-11	× 102×	89 7	93	-	91	-	-	
Wheat 🗳	0.20	2010-12-05	、249 、	, G 9	97	-	98	-	_	
(grain)	, Q	2017-05-19	A14	89	81	-	85	-	_	
(grain) and a second						_	87	-		
- North Contraction of the second sec	Overail	Mean RSD and	standard d	eviatio	n [%]	l	<u>91</u>	5.7	5.2	
¢		2017, 0-12 Mean, RSD and 2016-03-24 2016-07-12 2016-12-01 2017-10-10 Mean, RSD and		116	- [/ 0]	-	-	-	-	
	A A	\$016-97-12	Q103	110	_	-	-	-	-	
Dana		2016-12-01	245	Q1	_		-			
(seed)		2040312-0400	24J /17	07	-	-		-	-	
		×(3017 10 10	41/	9/ 110	-	-	-	-	-	
s, s		$\sim 201/-10-10$	JJ0			-	- 105	- 9.9		
	ww or word	uviean KND and	standard d	evistio	11 1 7/01		105	9.9	10.4	

Table 6.1- 3:	Concurrent recover	ry data for BCS-CR60082
	Concurrent recover	



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Plant material	Fortification Level [mg/kg]	Date of Extraction	Storage Interval (days)		S-CR6 le Reco [%]		Mean [%]	RSD [%]	Standard deviation
		2016-03-31	0	99	94	97	97	2.6	2.5 🗞
		2016-07-12	103	87	81	-	84	ð	- ,
Rape	0.20	2016-12-01	245	101	94	-	98	- 2	- 4
(seed)		2017-05-22	417	92	94	-	93 ₄	-	\$ \$
		2017-10-10	558	81	. 81	-	A	-	
	Overall	Mean, RSD and	standard d	eviatio	\$ %]		19 1	8.1	7.4
		2016-03-29	0	82	-	- 🦾	Ş -	0	j j
		2016-04-04	6	. ØŽ	-	Å	-	.0	Q0
		2016-05-02	34	78	-	Q.	Ø-	<u> </u>	62-52 63-50 63-50 75 75 75 75 75 75 75 75 75 75 75 75 75
Orange	0.01	2016-07-13	106	63	- 🧖	> - 🗞	Ø - 🔍	\ 	
(fruit)		2016-12-08	2\$4	<u>کې</u>	, N	- K	~	, ^o	°~- ~
		2017-05-18	A95 🐇	9 74	õ-	Ĩ	×	- Ož	x - A
		2017-10-09	A.559 0	106	Ľ	Q	- d	Ç -	O LO.
	Overall	Mean, RSD and	standard d	eviatio	n [%)	Ś	ັ 83√	165	13.6
		2016-03-20	_&0 [×]	LJ 15	2°87	×67		112	\$10.1 O
		2016-04-04	6 %	× 84 🗶	J ⁶ 5 ∧	79	Å76 ,	S13.0 🔬	§ 9.8Q
		2016-05-02	34	9 3 ,	69	810	9 ⁶ 81	14.8	\$1,2.0
Orange	0.20	2016-07-136	106	\$84	<i>.</i> Ø	814	80	~3 ⁹⁶	§ 3.0
(fruit)		2916-12-08	~ <u>254</u>	80	^%76	¢%	گ%84	12.6	O ^v 10.6
		2017-05-18	¥150	830	78	87~~	83 %	5.5 G	4.5
	2	2017-10-09 🖗	559	<u>_</u> 92	27 ^	104	97 S	A.T	4.5
	Overall	Mean, RSD and	standard @	sviatio	n∲%]	×	83	. D .6	9.7
	í, s	2016-12-02	0 0 \$	93%	-	0 - (D - 4	- V	-
Orange*		2017-05-18	167	Ô	ß	4	-@1	-	-
(fruit)		2647-10-13	~3/15 "	<u>9</u> 1	Ň	Ű	Č.	-	-
	S Qverall	Mean, RO and	standard d	* eviatiô	r [%] _	Š [×]	. 87	10.0	8.7
ĵ	, Ø	2016 2-02	× Q	9	99	94	96	3.0	2.9
Orange*	0.20	2017-05-180	107	86	8 8	~85	83	5.3	4.3
(fruit)	O	<u>0</u> 017-10-13	~ %15, Ö	, W	U101.	Q ₀₀	103	3.7	3.8
- V		Mean, RSD and	and are d		n 10/1	7	94	9.8	9.2



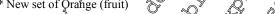


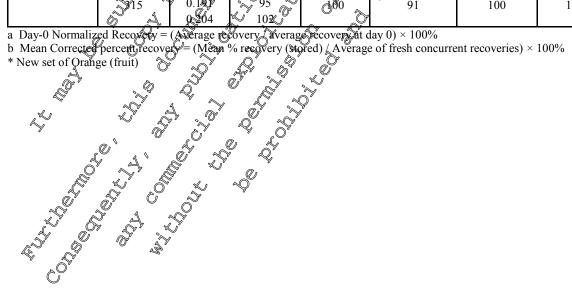
Commodity	Storage Period (days)		Level in Store % of	-	Day 0 Normalized %	Average % of Fresh Concurrent	Mean Connected	
	(22,52)	mg/kg	nominal spiking level	Mean % recovery	Recovery	Recoveries	Recovery	2
	0	0.197 0.199 0.207	99 99 104	201				
	100	0.199 0.193	9/ 🐄	99	2 98 0 2 98 0 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	\$ 86 O		
Tomato (fruit)	251	0.198 0.204	99 & 102		2 98 0 3 400 0 400 0 2 400	\$105 L	0 115 0 96 296	
	415	0.172 0.180	2 90 ~	88	87		43° 98 43°	
	563	0.192		\$ 99 \$ \$		Q102 Q	97	
	0	0.204 0.200 0.200	100 100 102 102 102				≪Ĵ У 103	
Bean	100	≪0.205 0.206	2103 Q	× 1085×		\$2 93 7 93	111	
(dry seed)	246	0,195 	98 980 980	~~ ⁹⁸ ~~	97 5	<u>5</u> 100	98	
	QU5	0.168 0.160	\$4 \$ ⁸⁴		2 83 ⁰	√√ 79	106	
~	564	0.208	104 100 97	× 104 ×	102 L	111	93	
		0.194 0.189 20194	95 ° 97	S S		95	101	
		0.187 0.1 87	094° ×	`	<u>م</u> م 98	95	99	
Wheat (grain)	^{\$249}	0.301 		5 ^{3 99} 5	102	102	97	
~ A	414	0.1279	89 91 91		93	92	98	
A BUY	560	0.170 0.200		<u>مَ</u> مَّ 90	93	97	93	
		0.200 07,88 09.189	94 94 95	97	100	98	98	
Rape (seed)	103 E	0.160 0.194	80 ~~97	89	92	88	101	
Rape (sæð)	245 245 0417 5	0.200	92 100	96	99	97	99	
	Ø417 ×	0.193 0.186	97 93	95	98	92	103	
e Correction	558	0.180 0.175	90 88	89	92	85	105	

Table 6.1- 4: Storage stability data and concurrent recovery data for BCS-CN88460



	Storage	Residue	Level in Store	d Samples	Day 0 Normalized	Average % of Fresh	Mean_° Corrected
Commodity	Period (days)	mg/kg	% of nominal spiking level	Mean % recovery	% Recovery ^a	Concurrent Recoveries	Recovery
	0	0.251 0.175 0.194	126 88 97	104		83 2 83 2 2 2 89 2 4 89 2 4 89 2 4 89 2 4 89 2 4 89 2 4 89 2 4 89 2 4 89 2 89 2 80 2	×7125 55
	6	0.189 0.182 0.175	95 91 88	A 91	Q88 0°	× 89 44	
	34	0.213 0.203 0.183					
Orange (fruit)	106	0.121 0.173 0.186					
	254	0.181 0.18 0 0 200	94 <u>2</u> <u>100</u> <u>2</u> <u>2</u> <u>3</u> <u>3</u> <u>3</u> <u>3</u> <u>4</u> <u>5</u> <u>5</u> <u>6</u> <u>6</u> <u>7</u> <u>8</u> <u>8</u> <u>8</u> <u>8</u> <u>8</u> <u>8</u> <u>8</u> <u>8</u>				¥ 102
	415	0.183 0.183		, , , , , , , , , , , , , , , , , , , ,			101
	558	0-207 0.195 0.201	103 97 \$400 \si			105	95
ŝ		0:228 0:208 (k 0.223 ()	104 104 201			104	106
Orange*	167 🛫	0.185 0472 3.167	93 86 83	87 0 67 5 67 5 77 5 87 5 87 5 87 5 87 5 87 5 87 5 8		88	99
~ ¥	3915 A	> 0.204 0.10 0.10 0.4			91	100	100





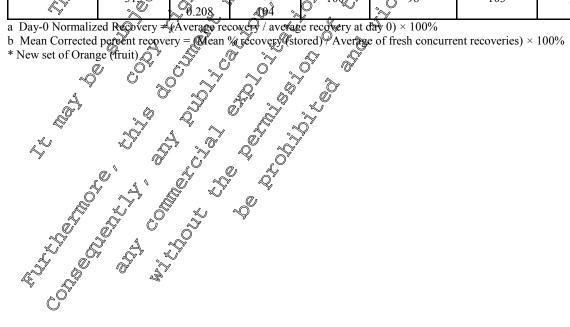


		Residue	Level in Store	d Samples	Day 0	Average %	Mean
Commodity	Storage Period (days)	mg/kg	% of nominal spiking level	Average % recovery	Normalized % Recovery ^a	of Fresh Concurrent Recoveries	Corrected
	0	0.192 0.186 0.189	96 93 94	94 čo	100	94 50 94	
	100	0.196 0.191	98 96	\$97 4	103	85 G	
Tomato (fruit)	251	0.199 0.203	100 102	101	~ 107@	\$ 1000 [°]	\$ 102 °
	415	0.175 0.174	88 & 87 O	88 2	107¢ 93 93 5 5 5 5 5 5 5 5 5 5 5 5 5	87 A	$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & &$
	563	0.180 0.184	<u>\$0</u> 92	N NY	96 <u>1</u>	99 0 ⁴ 99	\$ 92 \$ \$
	0	0.183 0.191 0.183	91, ~~ 91, ~~ 95, ~~ 91, ~~ 91, ~~	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$		94 OF	99 29 27
D	100	0.189	94 102 102 102 102	5 ⁹⁸) A06 O		∀ 110
Bean (dry seed)	246	≪0.193 0.196		1 985		\$ 93 }	105
	415	0,154 0,169	2 77 5 850	\$ ⁷⁸¹	88	£76	107
	Se d	0.171 0.170	86 87 87		94 ⁰	م ب 96	91
ŝ		0.179 0.188 0.179 0.181	94 94 91			92	100
	102 🛫	0,192 20187	96 ° 94	95 Q	4 04	91	104
Wheat (grain)	249	0.208 0.207	\$04 ×	2014 2004	مُ 113	98	106
	\$ 414 A	0.977 	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	5 ³ 89 5	97	85	104
~Ģ	560	0.1697	2 79 2 2		89	87	94
		0.207 0.207 0.209	2 114 193 ~ 2104 ~	م م لائم س	100	97	114
	103 °°	04.31 - 154	~~ 76 ~ V 73 v	77	69	84	91
Rape (seed)	345	0.19% 0.19%	100 95	98	88	98	100
	Q 417 C	60781 0.195	91 97	94	85	93	101
	3 58 ~	0.172 0.178	86 89	88	79	81	108

Table 6.1- 5: Storage stability data and concurrent recovery data for BCS-CR60082



		Residue Level in Stored Samples			Day 0	Average %	Mean
Commodity	Storage Period (days)	mg/kg	% of nominal spiking level	Average % recovery	Normalized % Recovery ^a	of Fresh Concurrent Recoveries	Corrected Recovery ^b
	0	0.197 0.176 0.180	98 88 90	92	100	76 Å	
	6	0.159 0.119 0.145	80 60 72	71	70 70	76	
	34	0.178 0.174 0.134	89 87 67	81	88 C 2 3 3 4 5 5 5 5 5 5 5 5 5 5 5 5 5	Q 81 0 3	
Orange (fruit)	106	0.190 0.172 0.185	95 °* 86 293 *		Q 99 0	84 54	
	254	0.186 0.174 0.185		\$ 91 \$ 91 \$ \$			908
	415	0 .149	83 2 71 71 7 74 7 74	V V			₹ 92
	559	0.194 0.19 0.219	97 599 1095				105
		0.198 0.209 0:209	2 99 @04 5 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			چ ^ک 96	106
Orange* (fruit)	10° - ×	€480 (k ○0.168 ○ 0.155	90 84 77		82 82	83	101
a Day-0 Normaliz	3150	0478 0212 0.208	89 0 106 1094		98 98	103	97





► ANIMAL MATRICES

Information on stability of residues is given in the hen and goat metabolism studies (see Table 6.1%).

During these studies, all samples and extracts were stored in a freezer at \leq -18°C or for a short tone in a refrigerator. All samples of milk, eggs, excreta, edible organs and tissues were extracted within several months after sample collection. Quantitative analysis by HPLC was performed either on the day of extraction or up to six days after the start of extraction.

A second conventional extraction of liver and kidney was performed within 9,20 months after collection to be used for enzymatic cleavage experiments. Analyses of these second conventional extracts of liver and kidney showed no indication of degradation of parent compound and metabolites in the profiles when comparing to the HPLC metabolite profiles obtained after the first extraction. The storage stability of parent compound and metabolites in goat and herefiver as well as in goat kidney was exemplarily demonstrated for all other matrices.

	8				
Sample	Storage	Initial analysis	Demonstrated	Dovument No.	C Reference
	temperature	after@ampley	storage stability		
	(°C)	collection 2			<u>I</u>
Hen Liver	≤-18°C	< 5 months	20 months 2	M-691665-07-1	°K CA 6.2.2/01
Hen Liver	≤ - 18°C	< C months 0	9 pronths	MG0166201-1&	, KCA 6.2.2/02
Goat Liver	≤-18°C s	Approx. 3 months	Approx. 13 months	QM-604281-01-P	KCA 6.2.3/01
Goat Kidney	≤-18°C ⊚	Approx. 3 months @	Approx. 14 months		
Goat Liver	≤-18°Č∜	Approx. 3 months	11 months	M-604286-01-1	KCA 6.2.3/02
	×.			& °~	

Table 6.1- 6:	Storage stability data	from Ayest	ock met	abolism	studies
---------------	------------------------	------------	---------	---------	---------

The longest storage periods for samples from animal esidue studies (feeding studies) are shown in Table 6.1-7.

C		
Table 6.1- 7:	Perfods of frozen storage (2-18%) of animal-based samples (between san	nnling
	Teribus of nozen georage (2 -10, 3) of addinat-based samples (between sam	ipning
, Q	and analysis) for matrices relevant to this docer 0	

Saw	ole material	SA nalvto	Longest storage	×	Study
Animal	Matrix	group*	(days)	Beport No.	Annex point Document No.
ruminant	milk	S A O	s≪ < 3,0, √	17-8001	6.4.2/01
	cream				M-604191-02-1
	whey 🏷	X			
	fat	A O			
		× Ay			
L.	kidney 🖉 🧳	A & B			
	liver N	A & B			
poultry	eggs A	Q'AS	<i>∝</i> ≪ 30	17-8002	6.4.1/01
		Ă	Ø		M-605909-01-1
Ô	musele	⇒ A			
	musete b	⊖ ^O A & C			

* Analytic group & comprises free restricues of BCS-CN88460 and its metabolites BCS-DC20298, BCS-CY26497, BCS-CY24813, BCS-DC20255 and BCS-CX9979

Analyte group & comprises the sum of BCS-CY24813 and its conjugate M19, the sum of BCS-DC20298 and its conjugate M20 Analyte group C comprises the sum of BCS-DC22055 and its conjugate M37



In the dairy ruminant and poultry feeding studies, the analyses were done within 30 days after sample collection. Therefore further storage stability data for the relevant residues of BCS-CN88460 in all animal matrices are not necessary.

In most of the cases, the time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours in the residue studies. If not the case, the maximum storage period of extracts was covered by stability experiments conducted in the course of the analytical methods validations

(2016; M-558986-01-1; 2017; M-599206 01-1; referenced in MCA Section 4 under Point 4.1.2 (e)), in the residue study 15-2066 (2017, M-599206 01-1; M-584388-02-1) or in the residue study 15-2069 (2017, M-584384-02-1; KCA 6.3.3). These stability experiments are summarized in the MCA Summary Section 4 and referenced under Point 4.1.2 (e) and also in Table 6.1-8.

	Stability of resid	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		× ~ ~	
Matrices	Compound	Extracts	Storage conditions &		Réference 🖑
	tested	Ô,		leastr 🔊	L A
Tomato (fruit)	BCS-CN88460	Extract A	$\mathcal{O}^{\pm} \mathcal{O} C \pm \mathcal{O} C$	105 hours	OM-558 996 -01-1
	BCS-CR60082	Final extract	10 ℃ ¥ 3 ℃	A05 hotos 🔬	KCA¥.1.2 method 014
Orange (fruit)	BCS-CN88460	Extract	4°C±3°C 0	149 hours	
	BCS-CR60082	Finafextrack	C ± ℃ ℃	149 hours	
Wheat (grain)	BCS-CN88460	Extract A	¥°C ± 3°C √	🕉 hours	
	BCS-CR60082	Final extract	10 0 ± 3 °C	82 hours	<i>"</i> ">
Wheat (straw)	BCS-CN88460	Extract A	46C ± 3 2C Q	79 hours	×
	BCS-CR60082 🔊	Final extract	$10 \degree C \pm 3 \degree C$	•79 hours	0
Rape (seed)	BCS-CN88469	Extract AS	4 °C ± 3 °C	S4 hours	
	BCS-CR60082	Final extract	$10\% C \pm 3\%$	54 bours	
Bean (dry seed)	BCS-CN88460	Extract A	C ± 3 C	77 hours	
	BCS-6760082	Final extract	510 °C ₩3 °C	Ø7 hours√	
Barley (grain)	BCS CN88400 ~	Extract	4 ×Q± 3 °C	81 hoppyrs	M-584388-02-1
	jõ 🔊 🧍	Final extract	$10^{\circ}C \pm 33C$	81 hours	KCA 6.3.1
Barley (straw)	BCS-C888460	Exmact A	v₄°c_∌,∘cs×	83 hours	study 15-2066
ľ.		Final extract	10 °Ç≇ 3 °C Õ⊂ 🐇	83 hours	
Barley (green	BCS-CN88460	JĚxtrac A O	$4 \circ C \pm 3 \circ Q$	81 hours	
material)		Finalextract	Ô [®] °C ±3 [®] C . ○ [♥]	81 hours	
Wheat (green	BCS-CN88460	Funal extract	$10 \% \pm 3 \%$	98.5 hours	M-584384-02-1
material)					KCA 6.3.2 study 15-2069
Hen egg	BCS-CX88460	Extract A	$\int C \pm 2 C$	23 days	M-599206-01-1
Cow milk 🔍	BCS-DC20298	Extract A	5 °C ± 3 °C	23 days	KCA 4.1.2
Cow muscle	BCS-CY26497	Extract A	5°C ± 3 °C	23 days	method 01511
Cow fat	BCS-CY24813	Extract A	$\sim 5^{\circ}C \pm 3^{\circ}C$	27 days	
Cow liver	BCS-DC22055	Extract A	$\bigcirc 5 \circ C \pm 3 \circ C$	21 days	
Cowkidney	BCS&CX99799	Atract A	$5 \degree C \pm 3 \degree C$	22 days	
Hen liver		Extract A	$5 \degree C \pm 3 \degree C$	26 days	
Cow kidney	BCS-DC20298	Final extracQ	$5 \degree C \pm 3 \degree C$	22 days	
(hydrolyse)	M20 5				
Cow liver	BCS-CY24®13 +	Final extract	$5 \degree C \pm 3 \degree C$	21 days	
(hydrolyse)	NOT9 O	pr			
Hen liver	BCS-26,22055	Final extract	$5 \degree C \pm 3 \degree C$	26 days	
(hydrolyse)	M3				
Ô					

 Table 6.1- 8:
 Stability of residues in extracts



Moreover, relevant information on the stability of residues in the final or any intermediate extracts can be derived from the fortification experiments performed during sample analysis. Every analytical batch contains at least one freshly fortified sample for concurrent recovery determination. The extracts of the fortified samples and of the study samples are handled and stored in parallel. If the recoveries in the fortified samples are within acceptable ranges, the stability of the sample extracts is considered as being sufficiently proven.

Acceptable recoveries measured concurrently with each set of samples ensured the integri sample extracts during the period of time between extraction and analysis.

CA 6.2 Metabolism, distribution and expression of resid

The chemical structure and nomenclature of the fungieride s∕**₿**((common spame: isoflucypram) are provided below. , Y

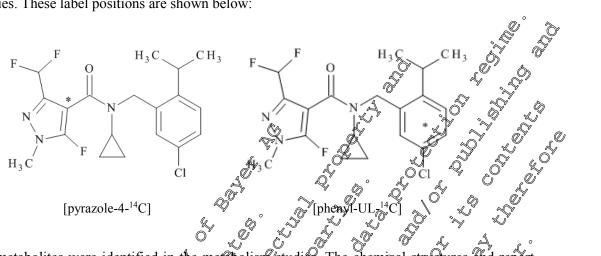
Chemical structure
Common name
Common name Sisoffacypram Signature Company experimental name Sisoffacypram Signature Company experimental name Sisoffacypram Signature Company experimental name Signature Co
HIDAC normal A Character A A A A A A A A A A A A A A A A A A A
Molecular weight 2 399.84 g/mol
Molecular weight 2 399.84 g/mol

Õ The metabolism of isoflucy pram was investigated in primary crops (tomatoes, wheat, soybean, oilseed are abready listed in this dossier, but will be submitted after are metabolic fate of isoflue pran has also been investigated in livestock (lactating goats and laying hers). rape) after post-emergence for application and in confined rotational crops. The representative rotational crops were wheat, Swiss chard and turnin which were studied at three plant back intervals. The metabolism of isoflucypram in primary cropp is further being investigated in potatoes after seed treatment. The potato metabolism studies are dready listed in this dossier, but will be submitted after finalization of the studies?

The metabolic fate hens).



As isoflucypram contains separate ring systems, two different radiolabels were used in all plant and animal studies. These label positions are shown below:



Numerous metabolites were identified in the metabolism studies. The chemical structures and report names used in the summaries are given at the end of this Section and in the List of Metabolites presented in Document N3. All residue values given in mg/kg refer to parent compound equivalents if not indicated otherwise.

Metabolism in plants

The metabolism of BCS-CN88460 in **tomato fruits** was investigated after two post-genergence spray applications, at a targeted single application rate of 75 g a s./ha. After tofiar application of [pyrazole-4-¹⁴C]isoflucypram or [phenyl-UIO¹⁴C]isoflucypram to tomatoes the TRK in fomato fruits was calculated based on the radioactivity in the surface wash solution and the fruit sample and amounted up to 0.170 mg a.s. equivalents/kg in total. Most of the radioactive residues up to 75% of the TRR) were recovered in the surface wash of togratoes. The only substance in the surface wash of togratoes the only substance in the surface wash of togratoes the only substance in the surface wash of the TRR.

The metabolism of BCS-CN88460 was investigated in wheat plants after two spray applications using a nominal application rate of 65 g a.s./hå each. The applications were performed at the growth stage of BBCH 30 (beginning of stern clongation) and BBCH 69 (end of flowering). After post-emergence spray application of (pyrazole 4-1⁴C)isoflueypran or [phenyl*UL-1⁴C] isoflueypram to wheat plants, TRR values in wheat straw and wheat hay were high (up to 16.031 mg/kg and 4.032 mg/kg, respectively) and the TBR values in grains were moderate and amounted up to 0.385 mg/kg. Parent compound was the math component tup to 64% of the TBR) in wheat hay and straw samples and the only component in wheat grain samples (up to 92% of the TRR). Metabolites in wheat hay and straw were detected in lower amounts (equal or below 10% of the TRR) and were formed predominantly by hydroxylation at the benzyl molety followed by hexose and malonic acid conjugation and to a lesser extend by additional demethylation. No label specific metabolism was observed in wheat.

The metabolism of BCS, N88460 was havestigated in **oilseed rape** plants after two foliar applications using a nominal application rate of 60 g a.s. the each. The applications were performed at the growth stage of BBCH 14 (thifoliolate on the 3rd up to 5th node unfolded) and BBCH 77 (70% of pods have reached final size). After post-emergence spray application of [pyrazole-4-¹⁴C] isoflucypram to oilseed rape, TRR values in oilseed rape intermediate harvest and mature plants were high and amounted up to 4.751 mg/kg and 4.076 mg/kg, respectively. The TRR values in oilseed rape forage and seeds were low and amounted up to 0.012 mg/kg and to 0.126 mg/kg, respectively. Parent compound BCS-CN88460 was the main component in intermediate harvest and mature plants (up to 88% of the TRR) and the only component in oilseed rape seeds (up to 74% of the TRR). The forage extract contained no residue above the limit of detection. Hexose and malonic acid conjugated metabolites after hydroxylation at the benzyl moiety were formed in oilseed



rape intermediate harvest and mature plants but were detected in low amounts (equal or below 5% of the TRR). No label specific metabolism was observed in oilseed rape.

The metabolism of BCS-CN88460 was investigated in **soybean** plants after three post-emergent Mant applications using a nominal application rate of 60 g a.s./ha each. The plants were applied at three different growth stages (BBCH 14, 51 and 84). After post-emergence spray application of [pyzzole-4-¹⁴C]isoflucypram or [phenyl-UL-¹⁴C]isoflucypram to soybean, TRR values in soybean straw were highest and amounted up to 17.715 mg/kg. The TRR in soybean forage and soybean hav were high and amounted up to 4.371 mg/kg and 4.679 mg/kg, respectively. The TRR values in seeds were low and amounted up to 0.035 mg/kg. Parent compound BCSGCN88460 was the main residue component in soybean straw (up to 70% of the TRR), and a major residue in soybean forage and hay Qup to 20% of the TRR). In soybean seeds parent compound was the only component (up to 77% of the FRR) BCS-CN88460 was moderately metabolised in soybean forage, hav and straw samples after thee post emergence applications. Besides parent compound, the following metabolites were odentified: BeS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, & BCS-CN88460-desfluoro-homoGSH, BCS-CN88460-desfluoro-mercapto-lactic acid-OH, BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc and BCS-CN88460-desfluoro-Cys-MA, accounting for op to 23% of the JRR. The main metabolic reaction observed was de-fluorination at position 5 of the pyrazole ring. Subsequently, conjugation with homoglutathione and degradation of the homoglutathione moiety followed by conjugation with malonic acid or degradation and desanation to mercapto factic acid group and hydroxylation of the benzyl moiety of of the propyl group. No tabel specific metabolism was observed in soybean. ju O O O O

Overall isoflucypram is moderately metabolized in primary crops and unchanged isoflucypram was the main or a major residue in all plants investigated. In human edible commodities (tomato fruit, soybean grain, rape seed and wheat grain) no metabolites were identified and parent represented the only residue. In general, no tabel specific metabolisation of the active substance was observed for all primary crops. Metabolites in sobbean feed items (straw forage, hay) were different from the metabolites found in feed items from rape (intermediate harves); mature plants) and wheat (hay, straw), involving metabolism in sobbean through GST (glutathione S-transferase).

Most important metabolisation in soybean occurred at the pyrazole ring: De-fluorination at position 5 of the pyrazole ring followed by conjugation with thomoglutathione resulted in metabolite BCS-CN88460-desfluoro homoGSH. Degradation of the homoglutathione moiety followed by conjugation with matoric acid or desamination to mercaptic acid group and hydroxylation at the benzyl moiety resulted in metabolites BCS-CN88460-desfluoro-Cys-MA, BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc. Furthermore, Clycositation was clearly Observed at the mercapto lactic acid group and formed metabolite BCS-CN88460 desfluoro-mercapto-lactic acid group and formed metabolite BCS-CN88460 desfluoro-m

In feed items from rape (intermediate harvest, mature plants) and wheat (hay, straw) parent compound represented the most prominent residue. In constrast to soybean - where the main metabolic route involved metabolism through GST at the pyrazole moiety - the most important metabolisation observed in rape and wheat was hydroxylation at the benzyl moiety followed by conjugation with hexose and malonic acid. In ylicat, hydroxylation at position 1 of the propyl group followed by hexose and malonic acid conjugation and to a minor extent demethylation of the pyrazole moiety formed the metabolites BCS-CN88460-propanol, BCS-CN88460-propanol-Glyc, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-desmethyl-propanol and BCS-CN88460-desmethyl-propanol-Gly-MA. In rape (intermediate tharvest, mature plants) metabolites were generally minor (<5% of TRR). Besides formation of BCS-CN88460-propanol-Glyc-MA also hydroxylation and conjugation at position 2 of the propyl group and of the phenyl moiety was observed forming the metabolites BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA also hydroxylation and conjugation at position 2 of the propyl group and of the phenyl moiety was observed forming the metabolites BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-hydroxyphenyl-Gluc-MA and BCS-CN88460-hydroxyphenyl-Glyc-MA.



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The primary crops represent three different crop categories (fruit, cereals and oilseeds) covering foliar application. Except for soybean, the general metabolic steps in the primary crop metabolism studies were very similar. The divergent metabolism observed for soybean is deemed specific to soybean, as this was not observed in rape - which pertains to the same metabolism crop group as soybean - and for $\sqrt{2}$ rape and wheat common metabolic reactions were observed. Therefore it is concluded that the nature of residues in primary crops after foliar application of isoflucypram is sufficiently understood and that no further studies are needed. Ŵ

In the following tables the distribution of parent compound and metabolites in the different plant watrices are shown. Generally, isoflucypram forms the main or a major residue in all crops

Table 6.2-1: TRR values and d after two foliar tree	estribution of parent compound	and metapolites in tomato truits
Reference		M-597481-01-1
Radiolabel		M-597481-01-1 phenyl-4/L-14C tomato fruits 78 and 78 96 &
Sample	pyražole-4-1 ⁴ C tomato fruits two foliar 79 and 89 168 0.170	tomato fruits
Type of application Single application rate [g a.s./ha]	two foliar y	78 and 78 ~
Single application rate [g a.s./ha]	79 and 89	
Total application rate [g a.s./ha]	79 and 89 57 5 0 168 0 5	5 <u>5</u> <u>5</u> <u>6</u> <u>6</u>
TRR [mg/kg]	0,170 0,170	Q 0.095 O
Compound 6	S Wof TRR	0.095 0 0.095 0 0.0
Isoflucypram	96 × 9	5 7% of PRR 5 59.2
Total identified		<u>لارم</u> مُح
Total characterised 2 L	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	1.5
Total extracted	× 299.8 5	99.8
Post extraction Wilds (DES)	V 6 92 2 5	[%] 0.2
Total		100.0
Single application rate [g a.s./ha]		

Table 6.2- 1:	TRR values and distribution	n of parent comp	ound and	metabo	lites in	tomato	fruits
	after two foliar treatments	with isoffucypram	í "	K)	-C	"M	~~``



Table 6.2- 2:	TRR values and distribution of parent compound and metabolites in wheat matrices
	after two foliar treatments with isoflucypram

Reference	Ν	1-604361-02	-1	Ν	1-604358-02-	1 🖉
Radiolabel	ľ	yrazole-4-14	С	p	henyl-UL-14	
Type of application		two foliar			∋two foliar	
Single application rate [g a.s./ha]		69 and 67		Ĩ	64 and 66	
Total application rate [g a.s./ha]		136		A	130	\$\$.0
RAC	hay*	straw	grains	hay*	straw	*ygrains
TRR [mg/kg]	4.032	15.536 "	0.385	3.040	16-031	0.284
Compound	% of TRR	% of TRA	% of TRR	% of TRR	So of TRO	% of TRR
Isoflucypram	50.0	64.0	92:Q	° 54.7	62.1	0 92.4
M18	2.4	Q 3.7	~	<u>ر</u> 0.8%	2.3	à "Q"
M41	2.5	k 209°	×	v ₁ 2.7	Ø 19	≪"
M21	10.3	0 [*] 8.7	Č Ø	~ 7.5	D5.0	4
M01	0.7	× 1.7×		A 997	0.95	× ~ ~
M06	Å			\$`` <u>`</u> ~	ð d	
Total identified	Q66.0	\$.0	92.9	<u>ک</u> 66.3	<u>2</u> .6	92.7
Total characterised	29.5	َُ≫18.1	Ý ~	<u></u> 3009°	<u>م</u> 20.5 م	?
Not analysed	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$	Â	<u>ک</u> 1.6	0.5	2.1	0.8
Total extracted	°∼y95.8	98.7	L 93/8	96.7 🔇	\$5.2	93.5
Post extraction solids (PES)	& 40 [°]	<i>√</i> 1.3 (6.4	× ,39	4.8	6.5
Accountability	100.0	~ 100c0	100.0≮	¥ 0 00.0	100.0 🖉	100.0





	matrices arter two	foliar treatments with i	sonucypram							
Reference	M-60	9378-01-1	M-609380-01-1	Ø						
Radiolabel	pyraz	cole-4- ¹⁴ C	phenyl-UL- ¹⁴ C	N 6						
Type of application	tw	o foliar	two@oliar							
Single application	64	and 62	6 Wand 63							
rate [g a.s./ha]	04	pyrazole-4- ¹⁴ C phenyl-UL- ¹⁴ C two foliar twoQbliar 64 and 62 69 and 63 126 126 tate forage# mature plants seeds inter- harvest# forage# mature 1 0.012 4.076 0.099 2.295 0.008 3.934 0.1266 f % of % o								
Total application rate [g a.s./ha]		126	126 ×							
	inter-		inter-							
RAC		Seeds	harvest*	e e						
TRR [mg/kg]		(1)h ²	3.295 0.008Q 3.634	0.126						
Compound	TRR TRR	TREV JRR	TRR TRR	ŢŔŔ						
Isoflucypram	81.9	- 88.1 🗸 71.00	4 .1 4 .1 3 2.0	₹\$73.6¢°						
M23	2.3	- 0.7								
M22	2.2	- 0	5 10 x 5 4 6							
M21	2.8	S & 0.6 & +S	2.2 J 2 2.5							
M24	3.1	- 1.0 *	3.8 G- 5 3.1 ×	/						
Total identified	92.3	- 91,3 571.0	949 84.4	73.6						
Total characterised	6.8 5	× 6.0 0 22.3	2.6 D.6	19.8						
Not analysed	0,4 %-	- 0.2 0								
Total extracted	69 ()			93.5						
PES	<u></u>		\$0.3 a 22.7 3.8	6.5						
Accountability		0 @100.0 109.0	100.0 0 100.0 100.0	100.0						
# Oilseed rape for age M23: BCS-CN8846(M21: BCS-CN8846(waSharvested 40 da Aydroxyphenyl-Glu -propanol-GlyCMA	ys after the first applicat c-MA M22 M24	ion S BCS-CN98460-2-propanol-Glyc- BCS-CN988460-hydroxyphenyl-G	MA lyc-MA						

Table 6.2- 3:	TRR values and distribution of parent compound and metabolites in oilseed rape
	matrices after two foliar treatments with isoflucypram



pyrazo three 59, 57	373-01-1 ble-4- ¹⁴ C c foliar 7 and 65 81 straw 17.715 % of TRR @	Seeds 5 0 0 0 0 0 0 0 0 0 0 0 0 0	forage* (3.936) % %	M-6093 phenyl- three 54,%6 17 hay [#] 1.397	UL- ¹⁴ C foliar and 66 6 5 8 9 7 8 .527 Q	
three 59, 57 1 hay [#] 4.679 % of	e foliar 7 and 65 81 81 17.715 % of	seeds 0,935	3.936 % %	three 54,96 a 54,96 a 17 hay [#] 1.397	foliar and 66 6 Supaw 8.527 2	× × × × × × × × × × × × × × × × × × ×
59, 57 1 hay [#] 4.679 % of	7 and 65 81 \$traw 17.715 % of	seeds 0,935	3.936 % %	54,96 a 54,96 a 17 hay [#] 1.397	and 66	× × × × × × × × × × × × × × × × × × ×
1 hay [#] 4.679 % of	81 straw 17.715 % of	seeds 0,935	3.936 % %	hay [#] 1.397	6 59 guaw 2 8.527 Q	× × × × × × × × × × × × × × × × × × ×
hay [#] 4.679 % of	straw 17.715 % of	seeds 0,935	3.936 % %	hay [#] 1.397	ayaw 2 8.527-Q	9 seeds 0.615
4.679 % of	17.715 % of	0,035	3.936 % %	1.397	8.527Q	0.675
% of	% of	→% of	% &	N N N N N N N N N N N N N N N N N N N		
				≈% of A	· · · · ·	
		TRR	TRR .	© TRR	°%&f èR	% of © TRR©
10.4	64.5	© 76.6	S 192	\$10 .3	ð 70.2 (69.8
15.2	Q.9	<u> </u>	J	0 17.6	2.1	A
7.8	4.8	ð "Ú	2 0.2	7.8	O _{2.8}	
3.2	L 1.94	~	0 17.0	>~2.8	لي الحي	\$ ²
11.2	\$3.0	2	Ø.7	10.7 گ) <u>– 28</u>	O
164	⁶ 4.6°	y V	~8.2	<u> </u>	4.3	<u> </u>
	in 8208	0 6.6	\$ [™] 72,2 [™]	600	ల్ 84.గి	69.8
29:Ľ	12.8	8L	22,8	23.6	r 10,3	
	<u>ک</u> 0.9	11,0	لاي 1.7€	J 165	1.0	
© 5.7		12.3	3,49	~ ~ 3.1	4 .1	30.2
	N N V			¥100.0ð	100.0	100.0
) 7 3	$\begin{array}{c c} & & & & \\ \hline 0 & & & & \\ \hline 7 & & & \\ 7 & & & \\ \hline 7 & & & \\ \hline 7 & & & \\ 7 & & \\ 7 & & & \\ 7 & &$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

Table 6.2- 4:	TRR values and distribution of parent compound and metabolites in soybean matrices
	after three foliar treatments with isoflucypram

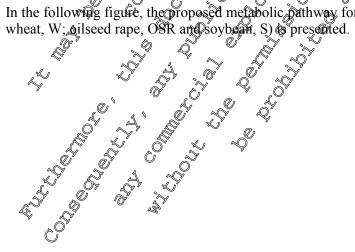
* Soybean forage was harvested 6 days after the first application

* Soybean hay was harvested 38 days after the second application @ M48: BCS CNISS (200 days)

soybean hay was harvestee 38 days after the second application M48: BCS-CN88460-desthuoro-mercapto-lactic acid-propyl-OH-Glyc M44: BCS-CN88460-desthuoro-mercapto-lactic acid-OH M46: BCS-CN88460-desthuoro-mercapto-lactic acid-OH M47: BCS-CN88460-desthuoro-mercapto-lactic acid-OH M47: BCS-CN88460-desthuoro-mercapto-lactic acid-OH M45: BCS-CN88460-desthuoro-fys-MA

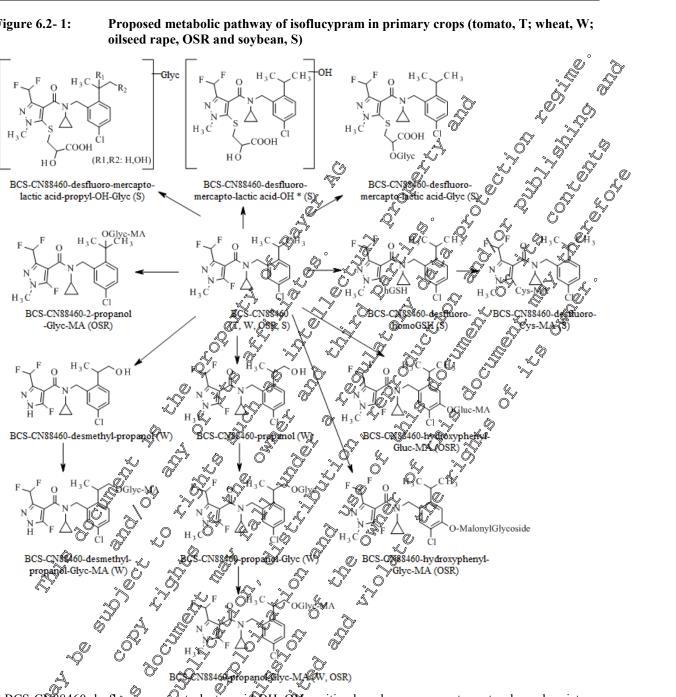
Ô Based on the result of the metabolism studie on primary gops, only parent compound was proposed as residue definition foodata collection and measured in the residue trials presented under Point 6.3.

In the following figure, theoroposed metabolic pathway for isoflucypram in primary crops (tomato, T;





Proposed metabolic pathway of isoflucypram in primary crops (tomato, T; wheat, W; Figure 6.2-1: oilseed rape, OSR and soybean, S)



* BCS-CE88460-desfluero-mercapto-lactic acidooH : QP position based on mass spectrometry: benzyl moiety. , Ç

K, Nature of the residues after processing

Isoflucypramovas stable under all tested processing conditions.

Ŵ

Based on these results, only patent compound was proposed as residue definition for data collection and measured in the processing studies presented in this MCA Summary under Point 6.5.3.



Metabolism in livestock

The metabolism of isoflucypram in livestock animals has been studied in laying hens and lactating goats.

The TRR-values and even transfer factors for eggs and edible tissues in laying hens after dosing with [phenyl-UL-14C]isoflucypram or [pyrazole-4-14C]isoflucypram were very low with respect to the dose level and the dosing period of 14 days. This indicates that test compound related radioactivity does not accumulate during the time of feeding. The evaluations of the TRR-values should however consider the fact that an exaggerated dose level of up to 18 mg a.s./kg feed/day was administered. Furthermore the fact that the entire radioactivity was detected in the excreta and the relatively high TRR in kideey and liver at sacrifice approx. 6 hours after the last administration revealed that the test compound related residues are further metabolised and finally eliminated from the ben's bodies. In fat isoflucypram represented the major residue with an amount of up to 0,010 mg/kg. In eggs and log muscle isoflucypram was detected in low amounts, only. While in those muscle and liver, unchanged isoflucypram was not found. Isoflucypram was merabolised most extensively i liver. The main metabolic reactions represented demethylation, hydroxylation followed by ordation to carboxylic acid. Further metabolic reactions included conjugation with gluckronic acid.

The TRR-values and the transfer factors in milk, organs and tissues in lactating goats after dosing with [phenyl-UL-14C]isoflucypram or [pyrazolez4,14C]isoflucypram were very low compared to the dose level of up to 45 mg a.s./kg feed/day and a dosing period of five days. The highest TRR galue was detected for liver and was caused by the short time period of six hours between last dosing and sacrifice. It indicates the significance of this organ for metabolism. The elimination of radioactivity was mainly faecal and less than 10% of the dose was eliminated with urine, which was reflected by the low TRR-value for kidney. This exerction behaviour was similar to the findings in the ADME studies with rats. The TRR-values in the respective evening and morning milk samples showed a diurnal pattern as they declined slightly prior to the delivery of the next dose for most days. A continuous increase was observed before a tesidue plateen-level was reached at day three after the first administration. Isoffecypram was the main residue in fat. Isoffucypram was intensively metabolised in liver and kidney, where which anged parent compound was any present in minor amounts. In milk and muscle unchanged patent compound was detected in low amounts but represented a major residue for both matrices. The main metabolism involves demethylation, bydrox lation followed by oxidation to carboxylic acid, and conjugation with shucuropic acid?

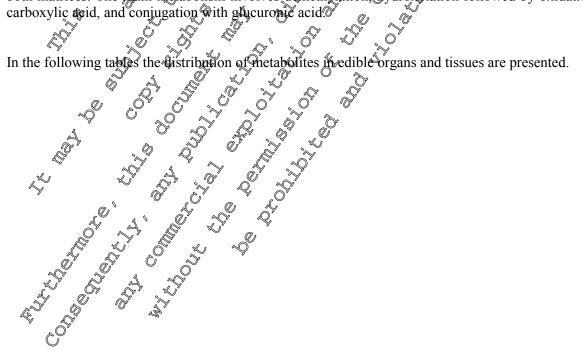




Table 6.2- 5:	TRR values	and distribution	on of parent co	ompound and	metabolites in	laying hens aft	er opsing with	isoflucypram		egine oud
Report			M-601665-01-1			e ³	<u> </u>			
кероп	Eggs	Leg Muscle	Thorax	Fat	Liver	Faggs	Leg Muscle	2601667-01- Thorax		Liver
	2889	Leg musere	Muscle	1 40		0 60		Muscle	Por all'	Liver
TRR [mg/kg]=	0.050	0.029	0.018	0.042	0.370	0.050	.0.3929 × C	0.017	0.0432	Gr 373
Dosing	14 x 1.0 mg/k	g body weight	•			14 x 1.0 mg/s	g body weight		T AOT	
	% TRR	% TRR	% TRR	% TRR	COPRR 6	TRR >	%. TRR	TRR A	% TRR	% TRR
Isoflucypram	3.7	2.3		23.¢Ç		6.4	ð <u>2</u> .9	U.	N K 204	
M36					<u>6</u> 5.4		4.1	-0° 7	- U.J.	9.2
M37				···· ۳	<u>s</u>	₹\$3.0	3.8			10.8
M38			:	\$ _ {- -	2.5	8.0		~~ [*]	Chior in	3.0
M07	5.2	15.0	17.9	05.1	6.9	B	14.2	Q1 223	~~59	5.6
M26				·	¢	A	as as	eller		1.2
M11		12.1	12.0	······································	5-21 5-21	do de	AP9.9	JUC 20.20	7.9	21.9
M06	22.3	29.3	D ^O 20.9	. J. 10.1	a <u>a-19</u> °	22.0	\$ 25.8	0 309	8.0	2.7
M12	3.4	9.1	11.0	A.S.	1.9	· O ^{LL} 7.2	\$6.6	8.6	3.0	5.8
M01	35.0	5.3	0.0 j.5.0	11.9	1.7*	\$3.9	2.5	4.3	6.5	1.7
Total identified	69.6	73.5	67.6	0 55.5	<u>}</u>	079.2	£ 7.9.8	76.3	51.5	62.0
Total characterised	23.7	19.3	je ^C 243*	37.1 7.30	45.6 100.0 0 0 0 0 0 0 0 0 0 0 0 0 0	13.6	~£ [°] ≥13.5	16.1	40.3	37.9
PES	6.6	3. Yu	₹ 8.2	7.30	\$9.1	«MD 7.2«	6.7	7.6	8.2	0.1
Total	100.0	100.0	100.0	±00.0	100.0	100.0	100.0	100.0	100.0	100.0
M36: BCS-CN M37: BCS-CN M38: BCS-CN M07: BCS-CN M26: BCS-CN M11: BCS-CN M12: BCS-CN M01: BCS-CN	69.6 23.7 6.6 100.0 188460-desmeth 1	1,2-propand yl-propanol-N- yl-2-propand yl-1,2-propand l-SA wcarboxylwa yl-propanol lic and COTUTION	iol-NGRUCA concA N-Gluc20 iol 20 cid 20 c	at i of tat	20 BIDD V					

- M37:
- M38: M07:
- M26:
- M11:
- M06 :
- M12:
- M01:



Report			M-604281-01-1		ng goats after dosing with isoflucypram					
(cport	Milk	Muscle	Fat	Liver	Kidney	h Milk	Musche	Liver	Kidney	
[RR [mg/kg]=	0.015	0.036	0.104	0.717	0.189	0.013	0.6M	0.348	0.1.83	
Dosing			0 mg/kg body w	veight	0,3	é° d		g body weight ~		
0	% TRR	% TRR	% TRR	% TRR	% TRR 2	KTRR N	% TRR	STRR O	% TRR	
soflucypram	33.4	22.3	58.7	3.5	C ^S 129	33.9	21.5	5.3	10 ¹¹ , 15	
A50				, O Y	6 3 5 8	2 ² 0°	2].5 	121	V,	
/120				~QP3.8				\$ \$\$3.0	4.0	
/125					×3.6	<u></u>	<u> </u>	a		
A10				V 1.6		Kraft-		A .3	4.2	
/19 (isomer 1)			1 <u>-</u>	13.1		2.3	C A	108.8	<u>~</u> ° 3.6	
A19 (isomer 2)		4.8	🌾	1 3C	0.7.0	<u>e</u> 9 26	106.5	5.8 5.8 5.5		
A11			Rein 32	\$0.9	4.2 °				3.6	
406		4.4	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.23		<u>√</u> € 6.7	0	<u> </u>		
<u>/12</u>		<u>8.</u>	3.3 20 ² 20 ²	5.8 * 1 5.8	18.0		9.0	7.2	6.8	
401		10.2	20	5.8			Ś 2		2.5	
102 Total identified	20.3	(7.7			<u>4.2</u>	5.80 \$ 50.4	14.2	2.8 47.2	1.4	
Otal Identified Total characterised	33.7	× 0/./	81.5 C 400	26.6	65.4 1 76		64.0 36.1	47.2	42.4	
PES	43.1	23.00		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			1	8.2	2.1	
Total	1.5	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			100.00	× 200.0	n.q. 100.0	100.0	100.0	
	100.0		100.01	400.0	Or Indelas		100.0	100.0	100.0	
450 BCS-CN884 420 BCS-CN884	160-N-methyl-pyra	zoje-carboxyko a	end and he is	0 ₇ × 0 ₁	w ^e	K ^C				
420 BCS-CN884 425 BCS-CN884	160-propened Office	A A	CUPP. ADL.		; ^{***} . 1°)»				
410 BCS-CN884	160-lactic acid	9.		ju or	L at ju					
119 BCS-CN884	160-propanol-Gluc	A (isomer)	10× 1		ð					
119 BCS-CN884	160-propanol-Glue	A (isomer 2)	e str	. C. V	1. La					
111 BCS-CN884	160-desmethyl-cart	boxyfic acid			~					
106 BCS-CN884	160-desmethyl-proj	panol Outer	1 0- × 10							
II2 BCS-CN884 I01 BCS-CN884	160-carboxync acio		,*	, 102						
101 BCS-CN884	160 - Digramon al	Pr Ch	e ^E X	aller						
102 DC5-C1100-		TOH BE	the to	v						
72		Ċ,×,	° P							
The second secon			10 ^C							
A (TOF JUE		JF							
A.		i la								



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The metabolism in hens (poultry) and goat (ruminant) is similar with some minor varieties and includes:

- 1) hydroxylation of isoflucypram to isoflucypram-propanol, isoflucypram-2-propanol or isoflucypram-1.2-propandiol
- 2) further oxidation to isoflucypram-carboxylic acid or to a lactic acid group
- 3) conjugation of isoflucypram-propanol, isoflucypram-2-propanol or isoflucypram-1,2-propandiot with glucuronic acid or sulfate
- 4) demethylation of the pyrazole moiety and conjugation with glucuronic acid after demethylation
- 5) cleavage of the phenyl moiety in combination with cleavage of the coclopropyl ring
- 6) dehydration after hydroxylation of the propyl group, followed by conjugation with glucubonic acid

Based on the results of the metabolism studies of livestock several compounds, were proposed as residue definition for data collection and measured in the feeding studies presented under Point 6.4.

- Isoflucypram parent compound and in metabolites M01, M02, M06, M17 and M12 were individually determined in milk, eggs and all tissues
- Additionally, the sum of M02 and its conjugate M20, and the sum of M01 and its conjugate • M19 were determined in cow liver and kidney. C
- Moreover, the sum of M06 and its conjugate M37 was determined in her live •

The metabolic pathway in laying hen, lactating goat and rat sevaluated to be similar since, generally, Ő the same metabolic steps are involved and the same metabolites are found.

In measone pairway in raying nen, jærating goat att rat (Sevahtared to be singlar since, generally, the same metabolic steps are involved and the same metab



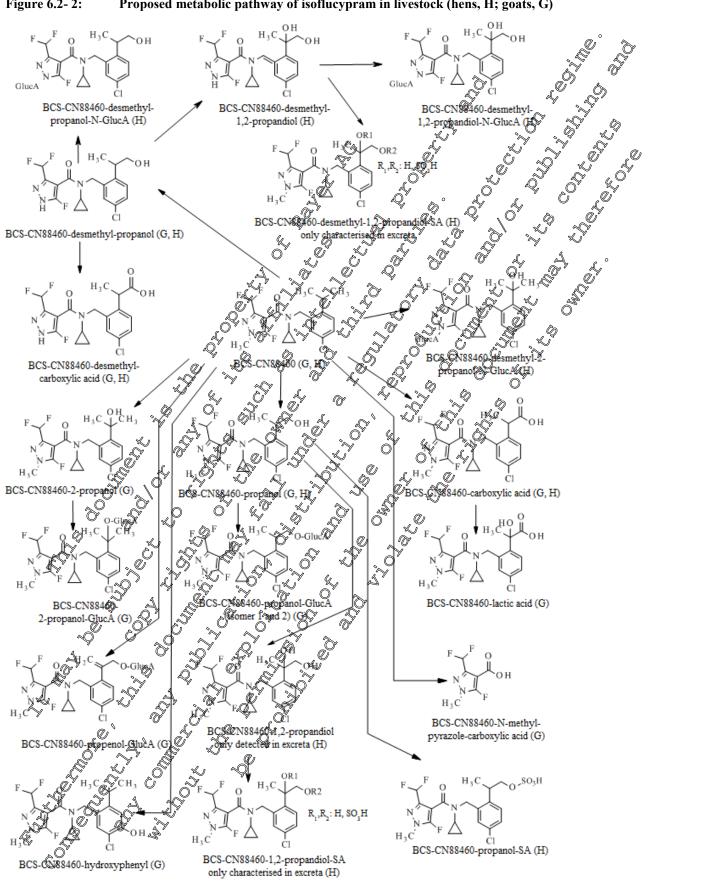


Figure 6.2-2: Proposed metabolic pathway of isoflucypram in livestock (hens, H; goats, G)



As the exact chemical structures of various metabolites could not be clarified in rats, some of the identified metabolites in livestock animals were not exactly observed in rats. Isoflucypram-2-propanol-GlucA is found in amount of 13% of the TRR in the liver of goats, but was not exactly detected in rat. Isoflucypram-propenol-GlucA is found in minor amounts in kidney and urine is the goats, but was not detected at all in rats. Isoflucypram-hydroxyphenyl was only detected in of the phenyl ring were detected in the rat.

N-glucuronic acid conjugates and conjugates with SA-group were only detected in hers. Conjugates with SA-group were only present in minor amounts, and mainly in excreta.

The general metabolic reactions for conjugation with glucuronic active and sulphonic active were also observed in the metabolism study with rats and could be verified by enzymatic cleavage of the conjugates to their specific aglycons. Hydroxylation and demetylation leading to the specific aglycons were observed in the metabolic pathway of the rate

All other metabolites including metabolites detected in fish were also detected in fie rat.

Metabolism in rotational crops

In the two confined rotational crop studies applied with an application rate of 198 - 202 g/ha of pyrazole and phenyl labelled isoflucypram, the residues of isoflucypram in rotational crops planted at all intervals were less than 0.08 mg/kg except in wheat hay and wheat straw of the pyrazole labelled confined rotational crop study where the content of isoflucypram was 0.014-0.220 mg/kg and 0.131-0.340 mg/kg, respectively. The TERs in the different taw agricultural commodities (RACs) were generally low, increased slightly from the 0^{st} to the 2^{nd} rotation and stayed stable or declined to lower values in the 3^{rd} rotation. The TRRs in the RACs of the phenyl labelled study were lower as the TRRs found in the study with the pyrazole label.

In the confined rotational crop study with isofticyprain labelled in the pyrazole mojety, unchanged parent compound was only detected in wheat forage. Swiss chard and tuthip leaves with amounts of equal or less than 7.0% (0.003 mg/kg) of the TRR. Up to thirteer pyrazole derivative metabolites were identified. As the TRR values of the confined study was generally low, none of the identified metabolites accounted for more than 0.022 mg/kg and none of the upknown compounds accounted for more than 0.022 mg/kg and none of the upknown compounds accounted for more than 0.021 mg/kg.

The main metabolic reactions were the cleavage of the parent compound to BCS-CN88460-N-methylcyclopropyl-pyrazoe-carboxamide (named as BCS-CR60082) and following conjugation of BCS-CR60082 with alarine (with or vithout defluorination) or the hydroxylation and defluoronation of BCS-CR60082 followed by conjugation with cysteine or glutathione. Other metabolic reactions were demethylation, hydroxylation, dearnination or defluorination of BCS-CR60082, followed by conjugation with glucose, lactic acid, acetic acid, cysteine or glutathione. The glutathione group was afterwards degraded to mercapio alcohol with an additional conjugation with malonic acid.

In the confined rotational crop study with is thucypram labelled in the phenyl mojety, unchanged parent compound was only detected in when forage, wheat hay and Swiss chard with amounts of equal or less than 17.0% (0.004 mg/kg) of the TRR. Due to very low TRR values in the confined study, no further metabolities were identified in the conventional extracts as none of the unknown compounds was larger than 0.009 mg/kg. No label specific metabolities were detected in the CRC study with the phenyl label.

Isoflue pramobelled in the pyrazole moiety lead to higher residues than isoflue pram labelled in the pherod moiety. This indicates that cleavage of the molecule more likely happens in soil, followed by uptake and subsequent conjugation in the plant.

In the following tables the percent of TRR values of parent compound and metabolites in the different samples are summarised.



M-595694-	DAT	TRR	PC	M49	M66	M62	M62	M52	M54	M69	M56	M69	Moz	M55	M57	M68	Total	Total) ŽES	Total
02-1		[mg/kg]				- i1	- i2			- i1		- i2 🦔	C. E				ident.	chat #	4	Ober
											9	6 TRIC	<i>*</i>		-C.F		Ő	Ch o	09	
wheat	62	0.041	7.0	9.2	22.4				9.3		4.0	LO-3.8	2.8		۲		60,6	324	7.1	100.0
forage	175	0.078	1.4	7.3	25.6		4.2	3.9	8.7		ø.4	10.2		~ () .)}			€ 76.6	A A	. 20	100.0
	335	0.072		4.3	15.4		3.2	2.0	6.3		O 1.8	\$ 7	^	2.1	4.5	÷	46.2	¢45.8 م	8.1	100.0
wheat hay	101	0.114		2.2	12.2	7.7			5.2		2.9	Ø9.0	, NO	1_6@	4.2	$\sqrt{2}$	£5.9	40. C	3.9	100.0
	233	0.220		1.1	13.9	3.0	5.8	5.7	6.5	<u> </u>	<u>}</u>	3.20	4.8	<u>~</u> 2.5	3.2	2.0	54.0	. A1.6	A.S	100.0
	387	0.187		2.3	7.9	2.9	3.8	7.0	48	3,3%	1.9	8.4	2.20 **	1.1	\$.6	_116 ^C	47.7 (37.7 🖉	02.1	100.0
wheat straw	139	0.131		7.0	2.6	2.3	3.5	2.6	\$ 6.6		3.7	11.9		P P	≫ 5.5		A\$7.7	32.	6.4	100.0
	286	0.247		2.8	9.1	3.6	3.4	5.0	5.5	ô"		5.9	, °,	J 1.1	3.80		ॐ 44.0	MG1.6	4.5	100.0
	427	0.340		5.8	2.8	3.2	3.3	5.6	×290	2.2	2.0	X8.6	1.0	1.6	∋ 2.9	14	45.1×	<i>5</i> 0.7 گ	4.2	100.0
wheat grain	139	0.004*						·	Ĵ>	S.	ł	∿'			₂		na.	n.a.	n.a.	100.0
	286	0.011			7.7			J.		»		A To	13.4	10	Â		¹ 21.2	\$ \$9.3	19.6	100.0
	427	0.016				A.	1		. <u>,</u> ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		⁰ 0 ⁵⁰	<i>.</i>	o O	· «			70	85.2	14.8	100.0
Swiss chard	56	0.031	6.0	18.9		e [%]			Ş21.2		^	/ ,	<u></u>			C ^y	0.ET	23.1	2.8	100.0
(im)	177	0.062	0.5	9.0	136	• 6.8		29A	6.3	5.2	<u> </u>	_	5 1.2	<u> </u>	and	ô	56.4	38.9	4.7	100.0
	330	0.056	0.8	7.3	$0^{2.3}$		1.6	\$23.0	<u>8</u> 4°	^	/	0.5	s_16	0.6	0		51.3	43.1	5.6	100.0
Swiss chard	62	0.026	4.6	19.¢	^	<u>م</u> ا ا	, È	34.2	<u>© 22.9</u>	<u> </u>	- A	·		. 6	{		81.1	14.9	4.0	100.0
(m)	189	0.062		3.8	18 B	12.2	,	10.4	6.2	Jube 2.5	<u> </u>	Ç	1.2	Jr	_ Q		44.7	49.5	5.8	100.0
	342	0.052	A.V.	4.0	2.8	N.		≥ 21.1	€ .7	. AN	×	0 [%]	K6 ^b		Ö		43.9	48.5	7.6	100.0
turnip roots	79	0.006*				ý		9 -2	»	<u>رژ</u>	_à C		5				n.a.	n.a.	n.a.	100.0
	212	0.006*			36-	ĺ	°	- <u>-</u>	<u> </u>		J.P		C	»			n.a.	n.a.	n.a.	100.0
	356	0.006*			^ر (NO.		s 4	je-			© ^y	_@				n.a.	n.a.	n.a.	100.0
turnip	79	0.018	4.8	1\$A	1	×	13:0	7.7		819	AND.		5.9	4.6	12.3		92.3		7.7	100.0
leaves	212	0.031		گ 12.7	8 ,1	6.tC	» <u>4.6</u>	1 .4	19.9		2.9	_ <i>@_</i>	7.2		7.4		73.3	19.7	6.9	100.0
	356	0.026	¥	9.4.0)≶4.7		2:8	2.9	Φ3.9	- A	5.0	<u>س</u>	5.8	1.8	3.8		55.4	36.9	7.7	100.0

- M66:
- M62- i2:
- M54:
- cyclopropyl-pyrazole-carboxamide Glyc (isomer 2); desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide OH-GSIG desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-more desfluoro-cycloprop O-byrazole desfluoro-N-methyl-cyclopropyl-pyrazote-carboxamide-OH-GSI6 desfluoro-cyclopropyl-pyrazote-carboxamide-Ala; M56:
- M67:
- desfluoro-N-methyl-cyclopropyl-pyrazele carboxamide mercapito cilyc-MA; M57:
- DAT: days after treatment, im: immeture; m: mature; n.a.: normalysed a second s
- # Total characterised based opextraction or chromatophaphic beneficiour.

- N-methyl-cyclopropyl-pyrazole-carboxamide (BCS-CR60082);
- M62-i1: cyclopropyl-pyrazole-carboxamide-Glyc (isomer 1);
 - desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-Cys;
- M69-i1: cyclopropyl-pyrazole-carboxamide-OH-lactic acid (isomer 1);
- M69- i2: cvclopropyl-pyrazole-carboxamide-OH-lactic acid (isomer 2):
 - desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-desamino-Cys;
 - cyclopropyl-pyrazole-carboxamide-acetic acid
- M55: M68:

M52:



	a.s./ha		parent compound an		10"		OT TI		Орт
4-595695-01-1	DAT	TRR [mg/kg]	РС	Total ident.	Dotal cl	har.#	PES .	Total	
				1	K % TF		¢		
wheat forage	62	0.023	17.0	17.		77.9	5.C	1000	
	175	0.018	12.2	<u>12.</u>		3081.3 . C	06.5		ð
1 . 1	335	0.015	5.2	5.		84.9	· 9.9	100.04	IJ.
wheat hay	101	0.039	1.1					0004 00	
	233	0.062				291.8 30		<u>S</u> C100.0	
1. s. s. f. of us	387	0.036	 Ø,	¥ 0, <u>-</u>		88.4	0.0 k 11.7		
wheat straw	139 286	0.051 0.070	, pe	×¢¢ ×		88.62 90.5	9.6	0 100.0	
			`\` \\\$\${\}	<u>}</u> - _	-		9.8	100.0	
heat and	427	0.055 0.001*				90,70 00.a			
vheat grain	139 286	0.001*					th.a.	100.0 100.0	
	427	0.004		<u> </u>		na co	n.a.	100.0	
wiss chard (im)	56	0.029	102 202.8	0 (2.			1) 11 ^{11 n.a.}	100.0	
wiss chard (iiii)	177	0.016	A 0 2 0 20		×	A Part (M	3.6	100.0	
	330	\$ \$.020				96.2	3.8	100.0	
Swiss chard (m)	62	0.020	× 6.1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		× .6	0 5.0	100.0	
wiss church (iii)	189	0.016				96.6	3.4	100.0	
	342	0.025	× \$			25,6	4.4	100.0	
urnip roots	79	0.003	1 d B a		n of	n.a	n.a.	100.0	
	212	0.003*	a line	Or n.			n.a.	100.0	
	356	@.0.003* _4		"Or a		n.a	n.a.	100.0	
urnip leaves	79	0.00408	0 ²		a K	n.a	n.a.	100.0	
F	212	0.006*	NU	K ² , ¹ n.	n Ø	n.a	n.a.	100.0	
	356 1	0.006* 20		in in	2	n.a	n.a.	100.0	
C (parent compoun DAT: days after trea TRR values were of Total characterised	d): BCS-CN88460; tment; im: immatur letermined by LSC based on extractor art the CTU end art the CTU end art the CTU end	e; m: wature; n.a.: no measurement followi for chromatographia class control of the control of t	t analysed by the second secon	and werenot extracted du	e to low residue	levels.			



The following metabolic reactions were observed:

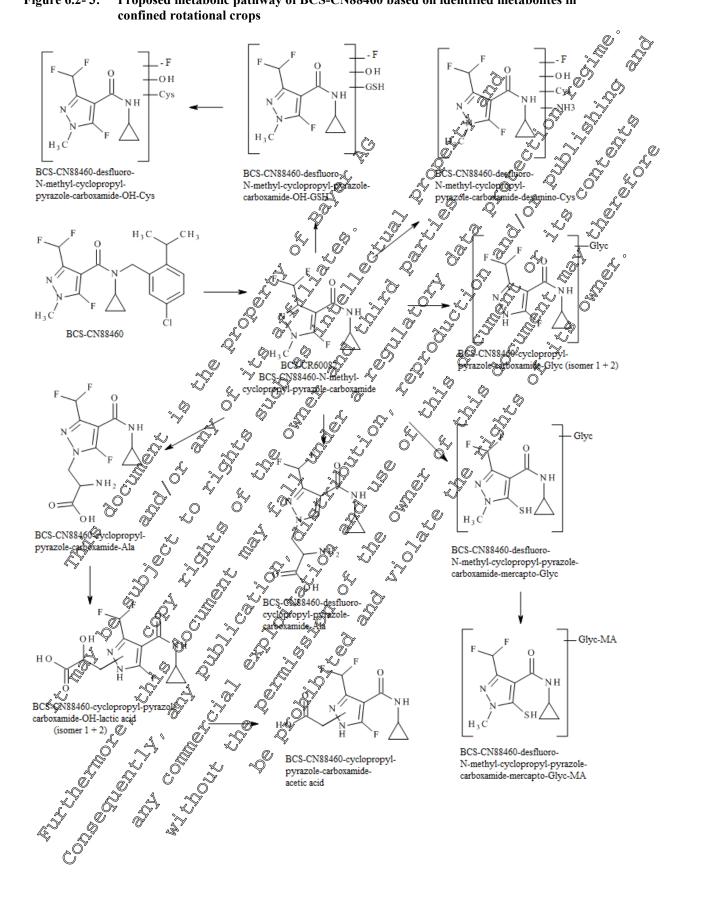
- cleavage of the parent compound leading to BCS-CN88460-N-methyl-cyclopropyl-• pyrazole-carboxamide (BCS-CR60082)
- conjugation of BCS-CR60082 with alanine, lactic acid or acetic acid with gr with out • defluoronation of the pyrazole ring Ő
- demethylation of BCS-CR60082 followed by conjugation with glucose •
- hydroxylation, deamination and defluoronation of BCS-CR60082 followed by conjugation • with cysteine or glutathione
- defluoronation of BCS-CR60082 followed by conjugation with glucose and glutathione • and degradation of the glutathione group to mercapto atcohol, additional conjugation w malonic acid

Based on these results, parent compound and its metabolite M42 were proposed as residue definition

Based on the identified metabolites the metabolity of BCS-CN84400 in confined plational crops is adequately understood and the following infetabolic pathway is proposed.



Proposed metabolic pathway of BCS-CN88460 based on identified metabolites in **Figure 6.2-3:** confined rotational crops





CA 6.2.1 Metabolism, distribution and expression of residues in plants

The metabolism of isoflucypram in primary crops has been investigated after foliar treatment in tomatoes (fruits), wheat (cereals), oilseed rape and soybean (oilseed) using isoflucypram effer labelled in the phenyl or in the pyrazole moiety as shown in the table below. The metabolism of isoflucypram is further being investigated in potatoes (root crop) after seed/tuber treatment. The potato metabolism studies are already listed in this dossier, but will be submitted after finalization of the studies.

Table 6.2.1-1	: Overvie	w over available plant metaboli	studies
Crop group	Сгор	Application	Target application Reference
fruits	tomato	foliar application, pyrazele-label	2 x 7 g a.s./ha M-59@485-01@
fruits	tomato	foliar application, pkpnyl-lakel	2 2 75 g & M 2597481 -01-1
cereals	wheat	foliar application, pyrazote-label	2 x 65 ga.s./ha M-604561-02-4 °
cereals	wheat	foliar application, phenyl-label	∑ 2 x63 g a s9ĥa ≪ M-604358 92-1
oilseed	oilseed rape	foliar application, pyrazole label	2 x 60 g a.s./ha y x 609378-01-1
oilseed	oilseed rape	foliar application, phenyl-label	2 x 60 g a.s. da M-609380-01-1
oilseed	soybean	foliar application, pyrazolectabel	3 4 60 g 8./ha M-609373-01-1
oilseed	soybean	to far application phenyl-label	√ x 60 g a.s./ba ♀ 4.609376-01-1
root crops	potato 🔬	tuber deatment, pyrazele-label	Will be filed subsequently after finalization
root crops	potato 🎇	tuker treament, phenyl-habel	Fof the studies 7 5 7

Table 6.2.1- 1:	Overview over available plant metabolism studies
	over view over available plant metabolich staates

expression residues distribution and in formatoes (foliar spray Metabolism, application) Ô

 $[pyrazole^{2}]^{4}C]$ and $[phenyl-UL-^{14}C]BCS-$ Metabolism_b studies[®] in tomatoesoweresconducted with CN88460%

Table 6.2.1- 2:	Øvervie	wover avai	lable tomato	metabolism studies
			o. ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	- *

Plant	Application	BBCH Code	Reference
tomato	two foliar pray applications, 2,375 g r./ha	BBCH 14-15	M-597485-01-1
	porazole@abelled	and	
	isoflucypram 🔍 📣 🖉	BBCH 85-86	
tomato 🖉	two foliar spray application 2×16 g as that	BBCH 14-15	M-597481-01-1
	phenyl-laberled	and	
L. L.	isoflucypram	BBCH 85-87	

Summary of metabolism in tomatoes (foliar spray application)

The metabolism observe in tomatoes after foliar application of [pyrazole-4-14C] and [phenyl-UL-14C] BCS-CN\$8460 Forresponds well between the two labels. Most of the radioactive residues were recovered in the surface wash of tomatoes. Parent compound was the main compound. No relevant metabolisation of isoflucypram occurs in tomato fruits after foliar treatment.



Report: Title:	KCA 6.2.1/01; (2017; M-597485-01-1) Metabolism of [pyrazole-4-14C]BCS-CN88460 in tomato
Report No.:	EnSa-16-0959
Document No.:	M-597485-01-1 OECD Test Guideline No. 501
Guideline(s):	OECD Test Guideline No. 501
	Commission Regulation (EU) No 283/2013 in accordance with Regulation (EC) No 1107/2009 US EPA OCSPP Test Guideline No. 860.1300
~	JAP FAMIC-ACIS Notification 12 Nousan 8147
Guideline deviation(s):	
GLP/GEP:	yes The second s

Executive Summary ~

The metabolism of BCS-CN88460 in tomato truits was investigated after two post-emergence spray applications. The test compound, [pyrazole-Q¹⁴C]BCS-CN88460 was formulated as an EC200 and applied to two tomato plants at growth stages BBCH 14 245 (four or five leaves unfolded) and BBCH 85 - 86 (50-60 % of ripe fruits), i.e. a total of two applications per plant. The total actual application rate was 27.97 mg a.s., corresponding to an application rate of 168 g a.s./ha based on a plant density of 12,000 tomato plants/ha. m

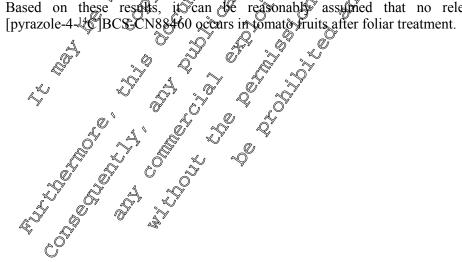
Tomato fruits were harvested at the end of the fruit ripening period (BBCH 87, 89). After surface washing with dichloromethane, tomato fruits were hoppogenised and sufficiently extracted by conventional methods with a mixture of acetonitrile/water.

The TRR in tomato fruits was cabulated based on the radioactivity in the surface wash solution and the fruit sample and amounted to 0.170 mg a sequivalents by in total. The largest portion of the TRR was detected in the surface wash solution (0.1250ng/kg, 73.6%) of the TRR. The fruit extract and post-extraction solids (PES) among ted to 0.045 mg/kg 26.1% of the ORR) and < 0.001 mg/kg (0.2% of the TRR), respectively

Parent compound was the main compound in the tomato fruit sample and amounted to 0.165 mg/kg, 96.7% of the TRR (sum of surface wash solution and extracts). Only four very minor metabolites (total 0.007@mg/kg, single compound \$0.003~mg/kg) were detected in the surface wash solution and tomato frant extracts. Ż R \bigcirc

Parent compound was identified in an isolated fraction of the surface wash solution by spectroscopic methods and confirmed in extract of fruits by HPLC co-chromatography with the reference compound.

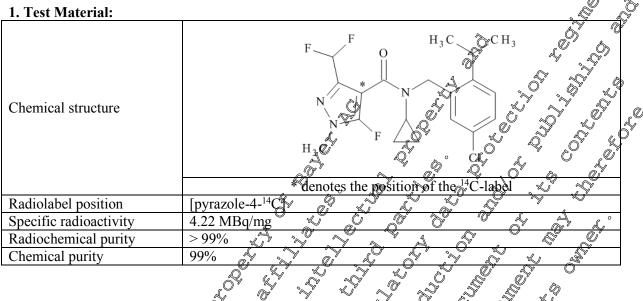
Based on these research, it can be reasonably assumed that no relevant metabolisation of





I. Materials and Methods

A. Materials



Formulation of the test compound

Stock solutions were prepared by dissolving of the test compound in acetonitrue. The identity of the test compound in the stock solution was confirmed by spectroscopic methods (LC-MS/MS and ¹H-NMR). Adequate parts of the stock solution were transferred into glass vials and evaporated to dryness. The formulation concentrate was prepared by combining the test compound with a corresponding amount of the EC 200 Blank formulation. The formulation concentrate was homogenised using a vortex mixed. Afterwards the formulation was calluted with water by stirring or swirling in order to obtain the ready-to-use application solutions.

- 2. Soil: Einheitserde T', plk/CaCh) = 5.8/15 vol.% clave $\sqrt{2}$
- 3. Plant: Tomato, variety "Philona", representative for fruiting crops

B. Study Design

1. Experimental conditions:

Two tomato plants *Oycopersicon lycopersicuno* variety: Philona) were cultivated under natural temperature and light conditions in the vegetation area of the test facility. Plants were irrigated as needed to maintain the optimal prowth conditions. Each plant was grown in its own planting container (30 L pots). The containers were filled with white moor peat and "Einheitserde T" and marked with the name of the test compound, study number and radioactivity symbol.

The application conditions simplified two spray applications each with an intended application rate of 75 g a.s./ha. The first treatment was performed at growth stage BBCH 14 - 15 (four or five leaves unfolded). The plants were reated with 100 mL of the application solutions. At the first application 55.66 MBq of the labelled test compound were applied to two tomato plants, corresponding to 79.14 g as ha. At the second application (performed at BBCH 85 – 86; 50-60% of ripe fruits) 62.35 MBq of the labelled test compound were applied to two tomato plants, corresponding to 88.65 g a.s./ha.

Taking into the account the amount of radioactivity found in the rinsing solution of the sprayer equipment, a total amount of 118.01 MBq (27.97 mg) was applied onto the two tomato plants. This resulted in a total mean application rate of 168 g a.s./ha based on a plant density of 12,000 tomato plants/ha.



2. Sampling:

Tomato fruits were collected at BBCH 87 - 89, 14 days after the second treatment, weighed and subdivided into two aliquots.

For investigation of the metabolic pathway, a subset of fruits was washed by dipping the fruits into a° dichloromethane bath. Afterwards the fruits were diced and homogenised. Afterwards the approx. \leq -18 °C until extraction.

C. Analytical Procedures

1. Extraction:

After surface washing with dichloromethane, the tomato fruits sample was conventionally extracted three times with mixtures of acetonitrile/water (8/2; v/v) using a high speed blender. The combined extracts were subjected to a clean-up step using an SPE RP 18 cartridge and rinsed with acetonitrile/water (8:2, v/v) and methanol/dichloromethane (1:1, Jv). The surface wash solution and the SPE percolate and rinse were concentrated and analysed by IPLC

The TRR value of the fruit sample was calculated by summing up the radioactivity in the surface wash, the extract and the post extraction solids (PES) based on the weight of the sample used and the specific radioactivity.

2. Identification and characterisation:

Parent compound and metabolites were countified in the surface wash solution and in the conventional extract of tomato fruits by HPLC analysis based on teversed phase chromatography (RP 18) with an acidic water/acetonitrile/THF gradients

Parent compound was identified by spectroscopic methods in the surface wash and by co-chromatography with reference compound in the extract. The peaks in the individual HPLC profiles of the extracts were numbered in ascending order according to appearance in the chromatogram Corresponding peaks in the HPLC profiles were designated with the same number. Unidentified metabolites were designated with "unknown" and numbered in ascending order. Corresponding unidentified metabolites in the different HPLC profiles were designated with the same number.

Table 6.2.1-3: List of reference compound	
Report name/ retention/pure in HPLC and remarks	Chemical Structure
Parent compound (BCS CN88460) (BCS CN88460) (arrited and arrived arriv	$F \qquad F \qquad H_3C \qquad CH_3$ $N \qquad H_3C \qquad CH_3$ $H_3C \qquad Cl$



3. Storage stability:

Extraction and quantification of four trace metabolites and parent compound were finished within six month. Hence, no further stability investigations were conducted.

II. Results and Discussion

The metabolism of [pyrazole-4-¹⁴C]BCS-CN88460 in tomatoes was investigated after two sprays applications.

The TRR value of the tomato fruit sample was calculated by summing up the radioactivity determined in the surface wash solution, the extract and the post extraction solid (PES) based on the weight of the sample used for extraction and the specific radioactivity of the test compound. The TRR for the fruit sample was low considering the application rate and amounted to 0.170 mg/kgQ

Table 6.2.1- 4:	TRR value in tomato fruits :	after foliar applic	ation of pyrazo	de-4- ¹⁴ COBCS-CON8846€	,

Matrix	Timing and Application Growth stage PHI* ppm (mga.s. equiv./kg)
Tomato fruits 15 a	o foliar spray applications at BBCH 4- and BBCH 85-86 al application rate 168 ga a.s./hc

* PHI: preharvest interval (corresponds to days after last deatmen (DAT at the start of darvest sampling)

For tomato fruits, the main portion of the radioactivity (0.125 mg/kg, 73.6% of the TRR) was detected in the surface wash solution Residues in the tomato fruit sample were efficiently extracted with conventional methods using acetomtrile/water (82; v/v) and amounted to 261% (0.045 mg/kg) of the TRR. The post extraction solids amounted to 0.2% (0.001 mg/kg) of the TRR, only. There were no losses during the sample preparation and no radioactivity was observed in the distillate of the concentration procedures.

Ro		
Table 6.2.4- 3:	Distribution of radioactivition the extract of the comato fruits after two foliar	
1 abie 0.2.3- 3.	Districtution we radioactivity and the extraction the contacto in this arter two ionar	
	applications of [pythzole-4-14C]BCS-CN88460	
sQ"	appression pression pression - 4 - C press - C press - C pression - 2 - C press - C	
le la		

k∕~"			
	Sample $\mathcal{L}' \sim \mathcal{O}' \ll \mathcal{I}'$	🔬 🎝tomato) fruits
		0° _{>>} 0.1	.70
		> % OF TRR	mg/kg
Ą	Surface wast solution	073.6	0.125
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Conventional extract	26.1	0.045
A	Losses (distillate)	~~~	
A A A A A A A A A A A A A A A A A A A	Total extracted	y 99.8	0.170
.~	Postextraction solids (PES)	0.2	<0.001
$\sim$	Accountability 2	100.0	0.170

Besides parent compound (0.165 mg/kg, 96.7% of the TRR), only four very minor metabolites ( $\leq 0.003 \text{ mg/kg}$ ) were detected in the surface wash solution and tomato fruit extracts.

The TRE and the distribution of parent and metabolites in tomato fruits are shown in Table 6.2.1-6 below



# Table 6.2.1- 6:Distribution of parent compound and metabolites in the extracts of<br/>tomato fruits after two foliar applications of [pyrazole-4-14C]BCS-CN88460

Sample	tomate	o fruits	l l
TRR [mg/kg] =		0.170	
Compound (BCS-CN88460)	% TRR	mg/kg	
BCS-CN88460 (parent compound)	96.7	0.965	
Total identified	96.7	0.165	
unknown 1	0.3	0.001	
unknown 2	0.5 1.6 0.2 1.0	0.003	
unknown 3	0.2	َ <0.00€	
unknown 2 unknown 3 unknown 4	1.0	0.602	
	° 3.1 ×	<b>0</b> :007 ~	
Analysed extract(s)	× 99	0.176	L A
Extracts not analysed		, st	
	×99.8	~0.170 °€	
Post extraction solids (PES)	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	© <0.001	
Accountability 🔗 🛷 🗡	× 300.0 S	<b>6</b> ,170 5	
ÂŤI. Conclus			- ~y _~y
🗸 🔬 All. Conclus	ions 🗸 💦	, ⁶ 9	

The metabolism of the fungicide isoflucipram (BCS-CN88460) was investigated in tomatoes after two post-emergence spray applications. The application fate amounted to 168 g a.s. ba. The test compound was ¹⁴C-labelled at the pyrazore-4-position

The TRR level in tomatoes was 0/170 mg/kg. The redioactive residues were efficiently recovered by surface wash with dichloromethane. (73.6%, 0.125 mg/kg of the TRR) and conventional extraction with acetonitrite water mixtures. In the tal, 99.8% TRR was recovered from the tomatoes.

Parent compound was the only major component in tomatoes (96.7%, 0.165 mg/kg of the TRR).

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Therefore, it can be reasonably assumed that no relevant metabolisation of [pyrazole-4-14C] BCS-CN88460 occurs in tomato fruits after folian treatment.

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<i>a</i> ,	
Domonto N	
Report:	K (A 6.2.1) (2; (20) 7; M-597481-01-1
Title:	Metabolism of othenyl-CL-14CBCS-CN88460 in tomato
Report No.	EnSa-06-0960
Document No.:	M-507481-01-1
Guideline(s):	V OLED Test Guide me No. 501
V	Commission Regulation (EC) No 283/2013 in accordance with Regulation (EC) No
	1107/2009 ~~ ~~
ŐY	US CARA OCSPP Test Guideline No. 860.1300
Į.	JAP FAMIC-ACIS Notification 12 Nousan 8147
Guideline deviation	(YS): @one (A)
GLP/GEP:	yes of
GLP/GPP:	
Č ^O	Executive Summary

The metabolism of BCS-CN88460 in tomato fruits was investigated after two post-emergence spray applications. The test compound, [phenyl-UL-¹⁴C]BCS-CN88460, was formulated as an EC 200 and



applied to two tomato plants at growth stages BBCH 14 - 15 (four or five leaves unfolded) and BBCH 85 - 87 (50-70 % of ripe fruits), i.e. a total of two applications per plant. The total actual application rate was 26.02 mg a.s., corresponding to an application rate of 156 g a.s./ha based on a plant density of 12,000 tomato plants/ha.

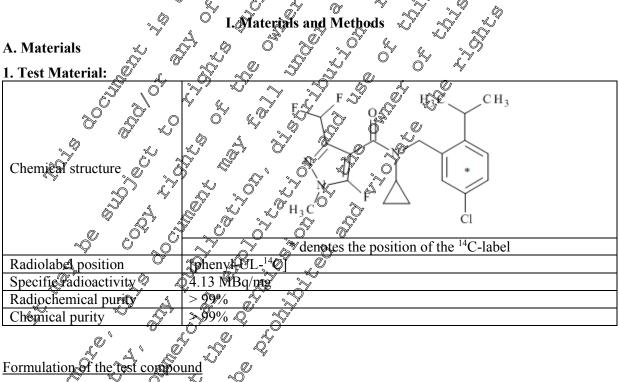
Tomato fruits were harvested at the end of the fruit ripening period (BBCH 87 -89). After surface washing with dichloromethane, tomato fruits were homogenised and sufficiently extracted by conventional methods with a mixture of acetonitrile/water.

The TRR in tomato fruits was calculated based on the radioactivity in the surface wash solution and the fruit sample and amounted to 0.095 mg a.s. equivalents/kg in total to he largest portion of the TRR was detected in the surface wash solution (0.071 mg/kg, 74.6% of the TRR). The fruit extract and post-extraction solids (PES) amounted to 0.024 mg/kg (25.1% of the TRR) and 0.001 mg/kg (0.2%) of the TRR), respectively.

Parent compound was the main compound in the tomato fruit sample and amounted to 0.094 mg/kg, 98.2% of the TRR (sum of surface wash solution and extracts). Only two very minor metabolites (total 0.002 mg/kg, single compound  $\leq 0.001 \text{ mg/kg}$ ) were detected in the surface wash solution and tomato fruit extracts.

Parent compound was identified in extract of fruits by HPLC co-chroniatography with reference compound.

Based on these results, it can be reasonably assumed that no relevant metabolisation of [phenyl-UL-¹⁴C]BCS-CN88460 occurs in tomato fruits after foliar treatment.



Stock solutions were prepared by dissolving of the test compound in acetonitrile. The identity of the test compound in the stock solution was confirmed by spectroscopic methods (LC-MS/MS and ¹H-NMR). Adequate parts of the stock solution were transferred into glass vials and evaporated to drapess. The formulation concentrate was prepared by combining the test compound with a corresponding amount of the EC 200 blank formulation. The formulation concentrate was homogenised using a vortex mixer. Afterwards, the formulation was diluted with water by stirring or swirling in order to obtain the ready-to-use application solutions.



- "Einheitserde T", pH (CaCl₂) = 5.8, 15 vol.% clay 2. Soil:
- 3. Plant: Tomato, variety "Philona", representative for fruiting crops

#### **B. Study Design**

#### **1. Experimental conditions:**

Two tomato plants (Lycopersicon lycopersicum, variety: Philona) were cultivated ander atural temperature and light conditions in the vegetation area of the test facility. Plants were irrigated as needed to maintain the optimal growth conditions. Each plant was grown in its own planting container (30 L pots). The containers were filled with white moor peat, "Einfeitserde T" and marked with the name of the test compound, study number and radioactivity symbol

The application conditions simulated two spray applications each with an intended application rate of 75 g a.s./ha. The first treatment was performed at growth stage BBCH 14°- 15 Prour of five Leaves unfolded). The plants were treated with 100 mL of the application solutions. At the first application 53.99 MBq of the labelled test compound were applied to two tomato plants, corresponding to 78.4 g a.s./ha. At the second application (performed at BBCH 85) - 80 50-70% of Tipe dutits) 53.5 MBq of the labelled test compound were applied to two tomato plants, corresponding to 77.7 g a.s./ha.

Taking into the account the amount of radioactivity found in the finsing solution of the sprayer equipment, a total amount of 107.49 MBq (26.02 mg) was applied onto the two tomato plants. This resulted in a total mean application rate of 156.1 g a.s./ha/based on a plant density of 12,000 tomato plants/ha.

#### 2. Sampling:

Adays after the second treatment, weighed and Tomato fruits were collected at BCFR subdivided into two aliquots. **K** 

For investigation of the metabolic pathway, a subset of Fuits was hed by dipping the fruits into a dichloromethana both Affective the full of the full dichloromethane bath. Afterwards the fruits were dired and homogenised. Aliquots were stored at approx. ≤ № 8 °C until extraction.

#### C. Analytical Proceed

#### 1. Extraction:

After surface washing with dich promethane, the toppato fruit sample was conventionally extracted three times with mixtures of acetonipile/water (8/2; v/v) using a high speed blender. The combined extracts were subjected to a clean-up step using an SPE RP 18 cartridge and rinsed with acetonitrile/water (8,2, v/x) and  $\mathcal{F}HF/methanol/(1:1, v/v)$ . The surface wash solution and the SPE percolate and rinse were conceptrated and analysed by HPLC.

The TRR value of the fruit ample was acculated by summing up the radioactivity in the surface wash, the expact and the post extraction solids (PES) based on the weight of the sample used and the specific radioactivity.

- rost



#### 2. Identification and characterisation:

Parent compound and metabolites were quantified in the surface wash solution and in the conventional extract of tomato fruits by HPLC analysis based on reversed phase chromatography (RP 18) withan acidic water/acetonitrile/THF gradient.

Parent compound was identified by co-chromatography with the reference compound. The weaks on the individual HPLC profiles of the extracts were numbered in ascenting order according to appearance in the chromatogram. Corresponding peaks in the HPLC profiles were designated with the same number. Unidentified metabolites were designated with "unknown" and numbered in ascending order. Corresponding unidentified metabolites in the different HPLC porfiles were designated with the same number.

Table 6.2.1- 7:	List of reference compound
-----------------	----------------------------

<b>Report name</b> / retention time in HPLC and remarks	Chemical name (IUPAC)
Parent compound (BCS CN88460)	N-(5-chbro-2- isopropylbenzyl)-N- cyclopropyl-3- (difluoromethyl) filuoroff- methyls H-pyrazole-4- carboxamide H 3C H 4C H 3 H 4C H 3 H 5 H 5 H 5 H 5 H 5 H 5 H 5 H 5
3. Storage stability:	

Extraction an Quantification of four tracemetabolites and parent compound were finished within six month. Hence, no further stabilit investigations were conducted.

Results and Discussion

[phony The metabolism of N88460 in tomatoes was investigated after two spray C⁻¹ applications.

The TRR value of the tong to fund same was calculated by summing up the radioactivity determined in the surface wash solution, the extract and the post extraction solids (PES) based on the weight of the sample used for extraction and the specific radioactivity of the test compound. The TRR for the fruit sample was low considering the application rate and amounted to 0.095 mg/kg.

#### TRR value in tomato fruits after foliar application of [phenyl-UL-¹⁴C]BCS-CN88460 Table 6.2.1- &

Mateix		Growth stage at harvest	PHI* (days)	ppm (mg a.s. equiv./kg)
Tomato frants	OT wo for an treatments at BBCH 14-15 and BBCH 85-87 Total application rate: 156 g a.s./ha	BBCH 87 - 89	14	0.095

* PHI: preharvest interval (corresponds to days after last treatment (DAT) at the start of harvest/sampling)



For tomato fruits, the main portion of the radioactivity (0.071 mg/kg, 74.6% of the TRR) was detected in the surface wash solution. Residues in the tomato fruit sample were efficiently extracted with conventional methods using acetonitrile/water (8/2; v/v) and amounted to 25.1% (0.024 mg/kg) of the TRR. The post extraction solids amounted to 0.2% (< 0.001 mg/kg) of the TRR, only. There were no %losses during the sample preparation and no radioactivity was observed in the distillate of the concentration procedures. 

The distribution of the radioactive residues is shown in the following table.

Table 6.2.1- 9:	Distribution of radioac applications of [phenyl			foliar	
	Sample		tomato fruits		-
	TRR [mg/kg]	49	0.095	K ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	

Sample     Office (matc) (parts)       TRR [mg/kg]     0.095       Surface wash solution     74.6       Conventional extract     25.1       Losses (distillate)     74.6       Total extracted     25.1       V     92.8
Surface wash solution
Conventional extract Losses (distillate)
Losses (distillate)
Post extraction solids (PES) (0.2 Color Color
Accountability of the 100.0 of 0,095 of a

Ô

0 Besides parent compound (0094 mg/kg 98.2% of the TRR, only two very minor metabolites (≤0.001 mg/kg) were detected in the surface wash solution and tomato fruit extracts?

The TRR and the distribution of parent and metabolites in tomato fruits are shown in the following table.

Table 6.2.1- 10:	Distribution of parent compound and me	tabolites in th	e extracts of t	omato fruits after
e		]BCS-CN884	60	
		, <b>tomat</b> o	o fruits	
E.	IRK mg/kgy≢	n 11	)95	
	Compound (BCSCN88460)	TRR 🖏	mg/kg	
	BCS-(N88460 (parent compound)	98.2	0.094	
~Q	$\mathbf{T} (\mathbf{O}^{\mathbf{v}}) (\mathbf{O}^{$	98.2	0.094	
Å	unknown	0.8	0.001	
Ø,	unknown 2 2 W	0.7	< 0.001	
	unknown 2 unknown 2 Total characterised Analysed extracts	1.5	0.002	
<i>S</i> [™]	Analysed extract(s)	99.8	0.095	
a C	Extracts not analysed			
	Total extracted	99.8	0.095	
, i i i i i i i i i i i i i i i i i i i	Post extraction solids (PES)	0.2	< 0.001	
S P	Accountability	100.0	0.095	
	Accountability			'
Č,				



#### **III.** Conclusions

The metabolism of the fungicide isoflucypram (BCS-CN88460) was investigated in tomatoes after two post-emergence spray applications. The application rate amounted to 156 g a.s./ha. The test compound was ¹⁴C-labelled in the phenyl-moiety.

The TRR level in tomatoes was 0.095 mg/kg. The radioactive residues were efficiently receivered by surface wash with dichloromethane (74.6%, 0.071 mg/kg of the TRR) and conventional extraction with acetonitrile/water mixtures. In total, 99.8% TRR was recovered from the tomatoes.

Parent compound was the only major component in tomatoes (98.2%, 0.494 mg/kg of the TRR).

Therefore, it can be reasonably assumed that no relevant metholisation BCS-CN88460 occurs in tomato fruits after foliar treatment.

Metabolism, distribution and expression of residues in wheat (Coliar spray application),

Metabolism studies in spring wheat after foliar application were conducted with ole-4-14 @ and [phenyl-UL-¹⁴C]BCS-CN88460.

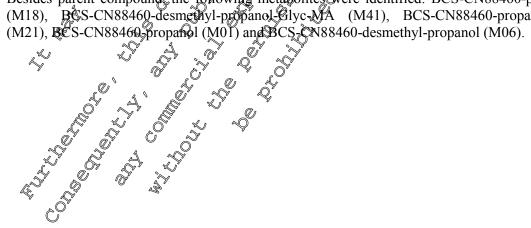
Table 6.2.1- 11:	Overview ove	r avai	lable@	vheat m	etabolis	m studie	s õ	
		Q,	Ro	10	×	Ň	Õ	C

Plant	Application Application ate BBCh Code Reference
wheat	two foliar spray applications, 2,565 g a.s./ha BBGH 30 MC604361-02-1
	pyrazole-labelled y later where the second sec
	Isonucypram
wheat	two foliar spray applications. 2 x 6 g a s to a by BBCH/30 M-604358-02-1 and m BBCH/30 M-604358-02-1
	phenyl-labelfed at a grant of and and a grant of and
	isoflucypram

## Summary of metabolismon wheat (foldar spray application)

The metabolism studies in wheat after foliar application. Parent compound BCS-CN88460 was the main residue component in wheat hay and straw and the only component in wheat grains. BCS-CN88460 was moderately metabolised in wheat after two post-emergence applications. The main metabolic reactions were hydroxylation in position 1 of the propyl group followed by conjugation with hexos and malonic acid and to a lesser extent demethylation of the pyrazole moiet

Besides parent compound the tollowing metabolites overe identified: BCS-CN88460-propanol-Glyc (M18), BCS-CN88460-desmethyl-propanol-Glyc-MA (M41), BCS-CN88460-propanol-Glyc-MA





Report:	KCA 6.2.1/03; M.; 2018; M-604361-02-1
Title:	Amendment no.1 to final report - Metabolism of [pyrazole-4-14C] BCS-CN88460 in
	wheat plants
Report No.:	S14-01087 M-604361-02-1
Document No.:	M-604361-02-1
Guideline(s):	OECD Test Guideline No. 501
	OECD Test Guideline No. 501 Commission Regulation (EU) No 283/2013 in accordance with Regulation (EC) No 1107/2009
	1107/2009
	US EPA OCSPP Test Guideline No. 860.1300
	JAP FAMIC-ACIS Notification 12 Neusan 8147
Guideline deviation(s):	none
GLP/GEP:	none ve of the second s

Executive Summary

The metabolism of BCS-CN88460 was investigated in wheat plants after two spray applications. For each of the two foliar applications the test item [prrazol@4-14C]BCS-CN88460 was formulated as an aqueous EC 50 using a nominal application rate of 65 g,a.s./ho each, the applications were performed at the growth stage of BBCH 30 (beginning of stem congation) and BBCH 69 (and of flowering). The actual application rates corresponded to 69 and 67 g as./ha for the first and second application, respectively resulting in a total application rate of 136 g a.s./ha

Wheat hay was harvested at BBCH 69,1 day prior to the second application, wheat straw and grains were harvested at maturity (BBCH 89). The total radioactive residues (TRR) in wheat straw and hay were high and amounted to 15.536 mg corkg and 4.030 mg corkg. Expectively. The TRR in wheat grains was moderate and amounted to 0,385 mg corkg.

Homogenised plant material from RACs was conventionally extracted with a mixture of acetonitrile/water (8/2, v/v). The extraction rates after conventional extraction of wheat hay, straw and grains were high and amounted to 95.8% (3.864 mg/eq/kg) of the TRR for hay, 94.0% (14.604 mg/eq/kg) of the TRR for straw and 93.6% (0.360 mg/eq/kg) of the TRR for grain. The post extraction solids (PES) of all RACs remaining after conventional extraction amounted to  $\leq 6.4\%$  of TRR.

Solids after conventional extraction of straw were exhaustively extracted using microwave assistance with a mixture of acet of trile/water/formic acid (50/50,4; v/v/v) releasing further 4.7% (0.727 mg eq/kg) of RR. 4

Residues in the conventional stracts were analysed and mantified by HPLC. The parent compound and metabolites were either identified by co-chomatography with the reference compound or by spectroscopic analysis in solated fractions of wheat straw. Additionally, the metabolite pattern and retention times of the current and the wheat metabolism study with the phenyl label were compared.

The parent substance BCS-CN88460 represented he most prominent residue component in all RACs accounting for 50.0% of TRR (2016 ng eq/kg) in wheat hay, 64.0% of TRR (9.933 mg eq/kg) in wheat straw and 92.0% of TRR (0.354 mg eq/kg) in wheat grains. Besides parent compound no other metabolite was detected in the extract of grains. In wheat straw five metabolites were identified besides parent compound: BCS-CN88460-propanol-Glyc (M18), BCS-CN88460-desmethyl-propanol-Glyc-MA (M41), BCS-CN88460-propanol-Glyc-MA (M21), BCS-CN88460-propanol (M01) and BCS-CN88460-desmethyl-propanol (M06) accounting for 3.7, 2.9, 6.7, 1.7 and 1.1% of the TRR, corresponding to 0.561, 0.448, 1.042, 0.267 and 0.171 mg eq/kg, respectively. BCS-CN88460-propanol-Glyc-MA and BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA and BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA and BCS-CN88460-propanol were also identified in wheat hay and amounted to 2.4, 2.5, 10.3 and 0.7% of the TRR, corresponding to 0.096, 0.103, 0.414 and 0.029 mg eq/kg, respectively.



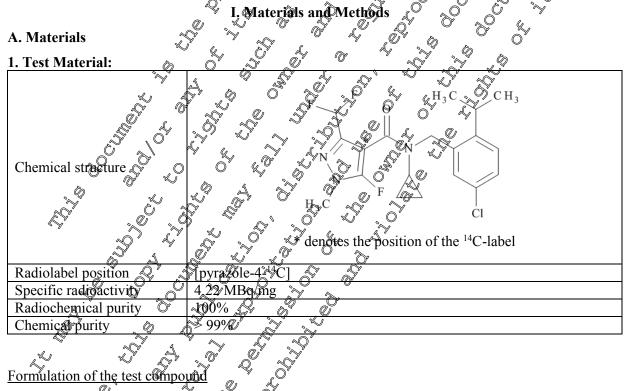
Overall, identification rates were sufficient and amounted to 80.0% of TRR for straw, 66.0% of TRR for hay and 92.0% of TRR for grains. Unknown metabolites were characterised in the extracts by their chromatographic behavior, individually accounting for equal to or less than 3.1% of the TRR.

Comparison of metabolic profiles with those of a parallel study with [phenyl-UL-¹⁴C]BCS-CN\$8460 revealed a high correspondence and no label specific metabolite could be observed for the both labels.

More conjugates may be present among the characterised unknown metabolites in the chromatograms. Therefore, acid hydrolysis (1 M HCl, 100 °C, 1 h) of the conventional extracts of wheat bay and straw were conducted in order to analyse for hydrolysable conjugates. Major hydrolysis products detected in the acidic hydrolysates besides parent compound were the aglycons BCS-CN88460-desmethylpropanol and BCS-CN88460-propanol. Identification rates after hydrolytic treatment increased. Based on these results it can be concluded that a significant amount of residues in the conventional extracts of hay and straw consists of conjugates of BCS-CN88460-desmethyl propanol and BCS-CN88460propanol.

As metabolic reactions, hydroxylation of the propy group followed by conjugation with hexose and malonic acid and the demethylation of the pyrazole moiety were observed.

Based on these results, the degradation behavior of [pyracole-44 C]BCS-CN88460 in wheat is adequately understood and a pathway jeproposed.



The test compound was formulated as an EC 50 for the experiment. The active substance [pyrazole-4-¹⁴C]BCS-CN88460 was desolved in accionitrile. For each spray dilution, adequate parts of the stock solution were transferred into special glass vials and evaporated to dryness. Blank formulation was added and the mixtures were homogenised using a magnetic stirrer. The sample was then adjusted with water to a final volume of 100 mL of the spray dilution and homogenised by stirring.

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#### 2. Soil:

	Soil chara	acteristics		
Туре	TOC	pH (CaCl ₂ )	CEC	
Sandy loam	2.1%	7.23	15.5 meg/100 g	~ '0'
			S S	

#### 3. Plant: wheat, variety "KADRILJ", representative for cereals

#### B. Study Design

#### 1. Experimental conditions:

The experiment was conducted with wheat plants based on a plant density of 5,000,000 wheat plants per hectare. A planting container with a surface area of 1 m² was used corresponding to the rate of 500 grains per m². The plants were applied at two different growth stages (BBCH 30 and 69). At both growth stages the target application rate was 65 g/ha. The planting container was folled with sardy loam soil "CUPF_soil". The plants were cultivated in the glass-roofed greenhouse of the test facility. The plants were grown similar to natural temperature and light conditions, but protected from rainfall. The plants were watered by pouring water onto the coil in the planting cultainers.

The wheat plants were treated with 100 mL of the aqueous spray effutions using a controlled track sprayer with a flat fan nozzle. At the 1st application 29.1 JBq of the labelled jest compound were applied, corresponding to 6.9 mg a.s. At the 2nd application 28.4 MBq of the test compound were applied, corresponding to 6.7 mg a.s. The total actual treatment rate was 69 and 67 g a.s./ha for the 1st and 2nd application, respectively. The seed density was 500 grains/m². After spray application onto the wheat plants of the planting container, the spray device and the protective pastic foil around the planting container with acetonitrile water (8/2; 50). The actual amount applied was calculated by subtracting the losses from the radioactivity in the original application solution.

#### 2. Sampling:

At growth stage BBCH 69 the RAC has and a BBCH 89 the RACs straw and grains were harvested. Plant samples were collected by cutting approximately 12 cm above the soil level. Plants sampled at hay stage were dried in a hood for 4 days. The total weight of each sample was determined. The samples were homogenised with liquid hitrogen using a high speed blender. The sample materials were stored in a preezer ( $\leq -1$  % C). Alrquots of the homogenates were extracted conventionally. The final TRR values of the samples were determined by summing up the radioactivity measured in the conventional extracts and in the remaining solids.

# C. Analytical Procedures

### 1. Extraction:

# Conventional estraction procedure and sample clean up:

Aliquots of the homogenised samples of wheat hay, straw and grains were conventionally extracted three times with a mixture of acetonitrile/water (8/2; v/v) using a high speed blender. After each extractron step, the extracts were filtered by suction and the solids were rinsed with a small amount of the solvent paxture ased for extraction. The solids were dried, homogenised aliquots subjected to compusition

The expects were combined and subjected to a clean-up step using a SPE RP 18 cartridge, which was rinsed with methanol and water and conditioned with acetonitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitrile/water (8/2; v/v). The percolate and the rinse were combined. Less polar fractions on the



cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v). Volume and radioactivity of this fraction was also determined. Each combined percolate/rinse solution obtained from SPE purification was mixed with emulsifier and evaporated to the aqueous remainder. The final conventional extracts were then analysed by HPLC with the general profiling method. All theat samples and extracts were stored in a freezer ( $\leq -18$  °C).

#### Exhaustive extraction and corresponding clean-up:

Solids from the conventional extraction of wheat straw were exhaustively extracted two times with acetonitrile/water/formic acid (50/50/1; v/v/v) under microwave assistance at increased temperature (0 to 5 min increase to 120 °C, 5 to 20 min at 120 °C, 800 W). The microwave extracts were cooled down at room temperature, combined and concentrated by rotary evaporation. Anquots of the extracts were centrifuged and separated into supernatant and pellet, which was dissolved in acetonitrile/water. Both extracts were further analysed HPLC.

#### Hydrolysis of the conventional extracts from wheat hay and straw

Hydrolysis experiments in acidic medium were conducted with conventional extract of wheat hay and straw, to further characterise the residues. Aliquits of the conventional concentrated purified extract of wheat hay and straw were incubated with  $\frac{4}{3}$  M HCl and  $\frac{5}{6}$  actionitrite at 100 °C for 1 hour and afterwards centrifuged. For wheat straw, the superplatant was removed and the pellet was dissolved in acetonitrile/water (1/1; v/v) whereas no pellet was formed during processing of wheat hay. Aliquots of the extracts were used for further HPLC analysis with the general profiling method. All wheat samples and extracts were stored in a freezer (2-18 °C).

The radioactivity in liquid samples was determined by liquid scattillation counting (LSC). Solid samples were combusted. The  $CO_2$  produced by combustion was absorbed in a  $CO_2$  absorbent/ scintillation cocktail mixture and the radioactivity was measured by LSC.

Conventional and microwave stracts were analysed by HPLC based on reversed phase chromatography using an ocidic water/aeetomyile/THF gradient.

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## 2. Identification and characterisation

For identification of radioactive ingredients in conventional extract from wheat straw, selected major radiosignals were isolated by HPLC fractionation. Additional fractions were prepared by hydrolysis of isolated fractions by addition of HCl. The structures were identified by spectroscopic methods. Purity of isolated fractions before and after spectroscopic analysis was sufficient and each fraction was used as radiolabelled reference compound

Metabolic profiles of all BACs were compared, as analysed by HPLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the wheat metabolism study with the phenyl label. Parent compound was identified in wheat grains extract by TLC and HPLC co-chromatography with non-radiolabelled and radiolabelled reference compound BCS-CN88460. Metabolic profiles of wheat hay and straw before and after hydrolysis were compared with corresponding profiles of the wheat pretabolism study with the phenyl label, as analysed by HPLC.

Major metabolites and hydrolytic cleavage products from conventional extract of wheat straw in isolated fractions were identified by spectroscopic analysis. Metabolites in the conventional extract of wheat straw overe confirmed by co-chromatography with the identified compounds. Unknown metabolites were characterised based on their extraction and chromatographic behavior.



<b>Report name</b> / other names/codes	Chemical Name (IUPAC)	Structure 🦉 🎅
Parent compound BCS-CN88460 Radiolabeled reference: S_PY_1_1000 Non-radiolabeled reference: BCS-CN88460-01-02	N-(5-chloro-2-isopropylbenzyl)-N- cyclopropyl-3-(difluoromethyl)-5- fluoro-1-methyl-1H-pyrazole-4- carboxamide	F F H ₃ C C H ₃ Ø N A N O F G G G G G G G G G G G G G G G G G G

#### Table 6.2.1- 12:List of reference compounds

#### 3. Storage stability:

All extraction experiments with wheat have stray and wain and the first PPLC, analyses were performed within one month after harvest of the wheat plant raw material. The stability of the stored extract of wheat hay, straw and grains was demonstrated by re-analysis of the extract by HPLC after 21, 14 and 15 months of storage.

A second analysis of wheat straw and grains was needed for analytical reasons and performed after 4 and 13 months of storage of the respective plant material after harvest. The storage stability of these samples could be demonstrated

It was therefore concluded that the residues in the samples were sufficiently stable during the experimental period of the study and that the chromatograms represented the metabolic pattern in the samples at harvest.

#### 6 II Results and Discussion

The metabolism of pyrazole  $4^{-14}$ CJBCS-CN88460 in wheat was investigated after two spray applications. Wheat plants were treated with [pyrazole  $4^{-14}$ CJBCS-CN88460 formulated as an EC 50 at BBCH 30 (beginning of stem elongation) and BBCF 69 (end of flowering). The actual single target application, rate corresponded to 69 and 67 g a.s./ha for the tirst and second spray application, respectively which was slightly above the anticipated maximum application rate (2 x 65 g a.s./ha). The total application rate amounted to 136 g ac/ha.

The TRR values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solids. The residue levels are shown in ppm or mg active substance equivalents per kg sample material mg a.s.equiv./kg or simplified mg eq/kg). The TRR in wheat hay and straw were high and amounted to 4.032 mg eq/kg and 15.536 mg eq/kg, respectively. The wheat grains showed a moderate TRR of 0.385 mg eq/kg.

,×Q	s s	<u></u>	S "O"		J.		
Table 6.2.1-13:	ŤRR	walues	in whea	t matrices	after	foliar application of	
1001001201 100		10	Gama			ional appneation of	
	pvr	azole-4	E-,™C B@	8-CN8846	0		
. ()		Å	¥ !~~	<u> </u>			

Matrix Timeng and Application	PHI (days)*	ppm (=mg eq/kg)
Wheat hav 1 spray application at BBCH 30,	27	4.032
Wheat straw 2 spray applications at BBCH 30 and BBCH 69,	17	15.536
Wheat grains 69 and 67 g a.s./ha (136 g a.s./ha total)	17	0.385

* PHI: preharvest interval (corresponds to days after last treatment (DAT) at harvest/sampling)



Wheat hay was conventionally extracted three times with acetonitrile/water mixtures releasing 95.8% of the TRR (3.864 mg eq/kg). After purification and concentration steps 95.4% of the TRR (3.846 mg eq/kg) were analysed. Losses during sample clean up were 0.4% (0.018 mg eq/kg) of the TRR.

Wheat straw was conventionally extracted three times with acetonitrile/water mixtures releasing 94.0% of the TRR (14.604 mg eq/kg). After purification and concentration steps 93.5% of the TRR (14.521 mg eq/kg) were analysed. For wheat straw samples, a microwave extraction was performed. With this exhaustive method about 4.7% (0.727 mg eq/kg) of the TRR were extracted additionally. Finally, the residue level in the solids of wheat straw was 1.3% of the TRR (0.206 mg k/kg) Dosses during sample clean up of straw samples were 0.083 mg corkg.

Wheat grains were conventionally extracted three times with acetoaitrile/water mixtures releasing 93.6% of the TRR (0.360 mg eq/kg). Based on the down amount of radioactivity (0.002 mg/kg) and high matrix load the third extract was not combined. After purification and concentration steps 92.0% of the TRR (0.354 mg eq/kg) were analysed. Losses during sample clean up were 0.006 mg eq/kg

Table 6.2.1- 14:	Distribution of radioactivity in	the extracts of	wheat ma	trices after	r two foliar
	applications of [pyraz0]e-4-14	BCS-@N88460			(j. 1

	n di			0' */	N N	õ
	o [©] γ ha	aty of	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	aw 🖉	g Øgra	ins
	% YRR	🕅 mg eq kg	% TRR	n@eq/kg	%;\$RR_*	ýmg eq/kg
TRR		<b>4</b> 032		K 15.58		0.385
Conventional Extraction 🔗	95.8	3.864	¢94.0 ¢	14,604	° 93.6×	0.360
Analysed extracts	95.4	3.846	© 93.5 [™]	Å.521	<b>92</b> .0	0.354
Losses (not analysed) [#]		\$9018 L	Q.5 [\]	£ 0.085	1.6	0.006
Microwave Extraction 🔬 🛛 🦧	₽ <del>.</del> @	õ S	Q4.7 🐇	0.727	<i>б</i> у	
Analysed extracts		5	لي ⁷ 4.7 ⁰	0.727 🎝		
Total extracted	≥~ ⁹ 95.8√S	<b>3.864</b> _~Ç	98,7	£ 15.3 <b>30</b>	93.6	0.360
Post extraction solids (RES)	42	<b>0.168</b>	À.3	0.206	6.4	0.025
Accountability	100.0 🧏	4.032	<b>∂</b> 100.€	<b>\$5.536</b>	100.0	0.385
#1 1 1			N.V.	SK /		

# losses during clean up, concentration, centrifugation, etc.

In the conventional extract from wheat hay 66.0% of the TRR (2.659 mg eq/kg) were identified in total. The parent compound was the major component representing 50.0% of the TRR (2.016 mg eg/kg), whereas the metabolites BCS-CN88460-propanol-Glyc, BCS-CN88460-desmethylpropanol-Glyč-MA, BCS N88460-propanol-Glyc-MA and BCS-CN88460-propanol represented 2.4, 2.5, 10.3 and 0.7% of the TRR corresponding to 0,096, 0.103, 0.414 and 0.029 mg eq/kg, respectively. In the conventional wiract from wheat straw 77 % of the TRR (11.969 mg eq/kg) were identified in totak. The parent compound was the major component representing 62.9% of the TRR (9.761 mg eq/kg), where as the metabolites BCS-CN88460-propanol-Glyc, BCS-CN88460-desmethylpropanol-Glyce MA, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-desmethyl-propanol and BCS-CN884@-propanol represented 2.5 2.9, 6.7, 0.7 and 1.4% of the TRR corresponding to 0.383, 0.448, 1.042, 0.116 and 0219 mg eq/kg respectively.

K.

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In the exhaustive extract of wheat straw 3.0% of the TRR (0.453 mg eq/kg) were further identified. consisting parent compound and metabolites BCS-CN88460-propanol-Glyc, BCS-CN88460deamethyl propanol and BCS-CN88460-propanol representing 1.1, 1.2, 0.4 and 0.3% of the TRR corresponding to 0.172, 0.178, 0.055, 0.048 mg eq/kg, respectively. In total, 80.0% (12.422 mg eq/kg) of the **PRR** were identified in the conventional and exhaustive extracts of wheat straw.

Conventional extract from wheat grains contained only parent compound representing 92.0% of the TRR corresponding to 0.354 mg eq/kg.

⁻⁻ not performed



The TRR and the distribution of parent and metabolites in wheat matrices are shown in the following table.

#### Distribution of parent compound and metabolites in the extracts of wheat matrices after two foliar applications of [pyrazole-4-14C]BCS-CN88460 Table 6.2.1-15:

after two foliar applications of [pyrazole-4-14C]BCS-CN88460								
	wh	eat hay	whe	at straw	wheat grains			
TRR [mg eq/kg] =	4	1.032	1	\$536	∞ 0.38\$° ≪			
Conventional extract		Ø		1	2			
Report name	% TRR	mg eq/kg	% TARK	mg eq/kg	% TRR	mg 🚓 kg 🦾		
BCS-CN88460 (parent compound)	50.0	2.016	62.9	9.761	92.Q	63354 &		
BCS-CN88460-propanol-Glyc (M18)	2.4	0.096	Q2.5	• 0.3 <b>8</b> 3	n.d.	Ön.d. 🖉		
BCS-CN88460-desmethyl-propanol-Glyc-MA	Q [°]	0.103	່ຳທີ່	0.448	n.d.	h n d		
(M41)						4 11. <b>a</b> .		
BCS-CN88460-propanol-Glyc-MA (M21)	\$√10.3 °	0.414	6.7	×1.042	n.d.Y	n.d.		
BCS-CN88460-propanol (M01)	0.2	00029	@ ⁷ 1.4 ~	0.21 <b>9</b>	nd.	n.d. n.d. n.d.		
BCS-CN88460-desmethyl-propanol (M06)	sn@t.	n.d.	0.7	0,016	-n.u.	n.d		
Subtotal identified	66.0	× 2.65	72,1	∖ <b>, 1</b> 9.969 ≪	92.0	0.354		
Unknown 88 🖉 🦿	n.d		<b>0</b> .6	× 0.086	n d.	On.d.		
Unknown 2	1.5	190952	0.2	0.029	®n″∂	n.d.		
Unknown 32	ÎM .	0.044	0.	0.963	Sn.d. ≪	n.d.		
Unknown 33	©1.7	0.065	0,05		11.u. 1/	n.u.		
Unknown 34	♥ 0.9~>>	0,036	Q1.5	© 0.239	fx.d.	n.d.		
Unknown 35	0.6	0.026	¥*0.9 ©	0.138	@.d.	n.d.		
Unknown 36	Ø.1	@0.046 ~>	n d,×	∘_n:d.	n.d.	n.d.		
Unknown 66	Q 0.8 1	0.032	×0,2	~~~0.034~~	n.d.	n.d.		
Unknown 37	₹ 1 <u>,8</u> 0°	0071	n.d.	n.d.	n.d.	n.d.		
Unknown 38	16	<b>3</b> €%066 C	0.5%		n.d.	n.d.		
Unknown 39	J¥.1	5.0.042	1.0	0.149	n.d.	n.d.		
Unknown 40			Q.2	@0.030	n.d.	n.d.		
Unknown 66 Unknown 37 Unknown 38 Unknown 39 Unknown 40 Unknown 40 Unknown 50 Unknown 50 Unknown 42 Unknown 43 Unknown 43 Unknown 52 Unknown 52 Unknown 52 Unknown 55 Unknown 55		0:051	Ø0.1 🔬	0.018	n.d.	n.d.		
Unknown 3 0 0 0 0 40	K.U	0.039	n.d.	n.d.	n.d.	n.d.		
Unknown 23 of s		\$ 0.037 \$ 0.037 0 140	n.e.	n.d.	n.d.	n.d.		
Unknown 5 Q		0.09	702.d.	n.d.	n.d.	n.d.		
Unknown			×1.4	0.210	n.d.	n.d.		
Unknown 42		0.127~~ v 0.059	1.3 1.1	0.204 0.168	n.d.	n.d.		
Unknown 42 J J J J J J J J J J J J J J J J J J	$0.6^{\circ}$	0.039	n.d.	n.d.	n.d.	n.d. n.d.		
Unknown 44	0.0	0.624 6.021	0.7	0.104	n.d.	n.d.		
Unknown 45		0.050	0.7	0.104	n.d. n.d.	n.d.		
Unknown 52	0.0 	0.050 D n.d.	0.8	0.127	n.d.	n.d.		
Unknown 52	p n d	n.d.	0.2	0.038	n.d.	n.d.		
Unknown 25, Unknown 25, Unknown 25,	n°d	n.d.	0.5	0.074	n.d.	n.d.		
Unknown 55		n.d.	0.3	0.047	n.d.	n.d.		
Unktown 59	$\approx n d$	n.d.	0.5	0.047	n.d.	n.d.		
Unknown 61	n d	n.d.	0.7	0.110	n.d.	n.d.		
Unknown 62	n d	n.d.	0.9	0.136	n.d.	n.d.		
Unknown 102	n d	n.d.	0.3	0.054	n.d.	n.d.		
Unknown $10\%$	n.d.	n.d.	0.3	0.054	n.d.	n.d.		
Unknown A S & S	n.d.	n.d.	0.2	0.032	n.d.	n.d.		
Unknows 14	n.d.	n.d.	0.2	0.032	n.d.	n.d.		
Unknown 67 5 5	n.d.	n.d.	0.5	0.071	n.d.	n.d.		
Subtotal characterised	29.5	1.187	16.4	2.552	n.d.	n.d.		
Unknown 44 Unknown 52 Unknown 52 Unknown 53 Unknown 55 Unknown 61 Unknown 61 Unknown 102 Unknown 102 Unknown 67 Unknown 67 Unknown 67				co	ntinued c	on next page		



#### Table 6.2.1-15 continued

	whea	ıt hay	wheat	straw	wheat grains, °		
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg		mg eq/kg	
Exhaustive extract *						X V	
BCS-CN88460 (parent compound)			1.1	0072	(	U &-	
BCS-CN88460-propanol-Glyc (M18)			1.2	9.178	4		
BCS-CN88460-desmethyl-propanol (M06)			0.4	0.055	~~		
BCS-CN88460-propanol (M01)			0,3	0.048	<u>م</u> °		
Subtotal identified		Ô	360	0.453	$\sim$		
Unknown 40		ᅠ ~~	0.1	0.018		~~	
Unknown 43	Æ		° [%] 0.2	0.026	2	\$ - v	
Unknown 3	"Q"_		<u>م</u> 0.5		~~~	e o	
Unknown 7			°∛ _@02	<u>6</u> .024	Å		
Unknown 41	%		∞_0.1	0.021	~ ~?		
Unknown 45	Å Ö	° , °	🔊 0.4	0.059	°~~	≪v	
Unknown 50	Φ″ <u></u> @	~	a 0,1		al	<u> </u>	
Subtotal characterised	1 ~~~-~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Ŭ 4	1.8	0.276		r "	
Total identified	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	× 2.6 <del>5</del> 9	80.0		92.0	<b>(0</b> .354	
Total characterised	2925	<b>1,187</b> م	⁰ ⁷ 18.2	2.827	\$	0	
Analysed extract(s)	& <i>D</i> 5.4	~℃3.846		15248	Ø 92.Q	0.354	
Not analysed / Losses	)° ° 0.4	× 0.018		0.083	\$¢	0.006	
Total extracted	<u>ک</u> 95 ک	3.864	_098.7	015.330	<b>\$93.6</b>	0.360	
Post extraction solids (PES)	Ø 42	@.168	Q [×] 1.3	0206	🔬 6.4	0.025	
Accountability	⊘100.0	^{4.032}	V* 100,0	15.536	0 100.0	0.385	
* Given as sum of supernatant and dissolved per	llet a	Ø N		×2 0	'n		

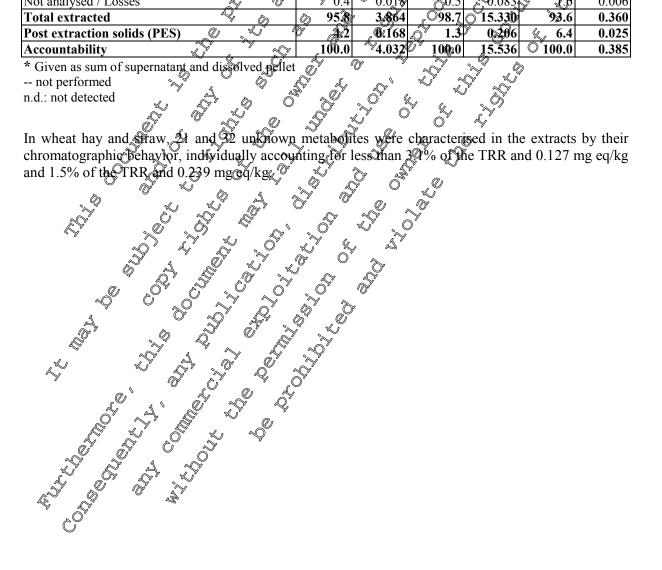




Table 6.2.1- 16:	Summary of characterisation and identification of radioactive residues in wheat
	matrices after two foliar applications of [pyrazole-4-14C]BCS-CN88460

	whea	ıt hay	wheat	straw	wheat	grains
TRR [mg eq/kg] =		4.032		15.536		19,385
Compound	% TRR	mg eq/kg	% TRR	mg eð kg	% TRR	mg eq/kg
BCS-CN88460 (parent compound)	50.0	2.016	64.0	9.933	92.6	0354
BCS-CN88460-propanol-Glyc (M18)	2.4	0.096	3.7	0.561	Ş	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
BCS-CN88460-desmethyl-propanol-Glyc-MA (M41)	2.5	0.103	2,0	0.448		
BCS-CN88460-propanol-Glyc-MA (M21)	10.3	ੰ	Q6.7	1.042	,°, \$	W
BCS-CN88460-propanol (M01)	0,7	0.029	0°1.7	0.267	Q,	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
BCS-CN88460-desmethyl-propanol (M06)	A		Ž 1,1	0.071	L,	õ "Q
Total identified	∞66.0	2.659	<b>80</b> .0	12,422	O 9200	0254
Number of unknown peaks	k, B	l° S	ي مي 3.	27 2	· · · · · · · · · · · · · · · · · · ·	- 🗸
Largest unknown peak	O JA	<u>8</u> .119	× 1,50	r 0 <i>2</i> 39	_م	1
Total characterised	<u>ू</u> @9.5	<b>©1.187</b>	2 18.2	2.827	O' L	° 67
Analysed extract(s)	95.4	3.8006	, 98.2	015.248	92.0	Ø.354
Not analysed / Losses	e a a a a a a a a a a a a a a a a a a a	0,018	× 0.5	0.083	Q 1.6	0.006
Total extracted	×95.8	3.864	୦ <u>୬</u> ୫7	15.330	93.6	0.360
Post extraction solids (PES)	4.2	0.168	⁰ 1.3	0.206	°~_6.4	0.025
Accountability	or 1009	4:032	100.0	7 15,536	<b>100.0 %</b>	0.385
je v je	 			<u></u>	0	

More conjugates may be present among the characterised unknown metabolities in the chromatograms. Therefore, acid hydrolysis (1 MHCl, 100 °C 1 h) of the conventional extracts of wheat hay and straw were conducted in order to analyse for hydrolysable conjugates.

In hydrolysed extract of wheat hay 90.5% of the TRR (3.640 mg(eq/kg) were analysed. The parent compound was the major component representing 44.4% of the WRR (1.791 mg eq/kg), whereas the metabolites BCS-CN88460 proparol-GW, BCS-CN88460 proparol-Glyc-MA, BCS-CN88460 proparol and BCS-CN88460 desmethyl-proparol represented 0.8, 0.9, 22.3 and 6.9% of the TRR corresponding to 0.031, 0.036, 0.901 and 0.27% mg eq/kg, respectively.

In hydrólysed extract of wheat straw 92.5% of the TRR (14.372 mg eq/kg) were analysed. The parent compound was the major component representing 67 %% of the TRR (10.397 mg eq/kg), whereas the metabolites BCS-CN88460-propanol-Glyc, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol and BCS-CN88460 desmethyl-propanol represented 0.2, 0.3, 10.5 and 3.6% of the TRR corresponding to 0.024, 0.056, 1,625 and 0.564 mg eq/kg, respectively. In contrast to hydrolysis of the hay extract, a pellet was formed during hydrolysis of the straw extract. Therefore values of analysed residues are given as sum of supernation and chosoly deplet.

Identification rates after hydrolytic treatment increased for wheat hay from 66.0% of the TRR (2.659 mg eq/kg) before hydrolysis to 75.3% of the TRR (3.035 mg eq/kg) after hydrolysis and for wheat straw from 77.1% of the TRR (11.969 mg eq/kg) before hydrolysis to 81.6% of the TRR (12.666 mg eq/kg) after hydrolysis. Two major metabolites were formed after acidic hydrolysis as a result of deconjugation of residues: BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol. BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol. BCS-CN88460-desmethyl-propanol and the TRR (0.277 mg eq/kg) and 3.6% of the TRR (0.564 mg eq/kg) in conventional extract from wheat straw. Metabolite BCS-CN88460-propanol was detected in hydrolysed extract from wheat hay and straw accounting for 22.3% of the TRR (0.901 mg eq/kg) and 10.5% of the TRR (1.625 mg eq/kg), respectively.

Based on these results it can be concluded that a significant amount of residues in the conventional extracts of hay and straw consists of conjugates of BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol. A comparison of the distribution of parent compound and metabolites in the conventional wheat hay and straw extracts before and after hydrolysis is given in the table below.



Analogous hydrolysis experiments were performed in the parallel study with the phenyl-label showing good accordance with the current study.

extracts of whea	at matric	es before	and after	r hydroly	sis (1 M I	HCI, 100	°C, 1 h)	57 07
	wheat hay					wheat	straw	
	conve	ntional	conve	ntional	conve	ntional	S Conven	wonal 🖉
		ract		ract	<i>s</i> ext		¢ extr	
	before h	ydrolysis	after	drolysis*	before h	ydrolysi	afterdyd	lrolysis*
Report name	% TRR	mg eq/kg	TRR	mg eq/kg	TRR	mg eqQkg	%QRR	Qng C Qq/kg
BCS-CN88460 (parent compound)	50.0	2.016	🄊 44.4	1.791	<i>Q</i> 62.9	¢9.761 (	67.0	10.397
BCS-CN88460-propanol-Glyc (M18)	2.4	0.69%	0.8	0.031	2.5	°0.383	×9.2	~ <b>0</b> 24
BCS-CN88460-desmethyl-propanol- Glyc-MA (M41)	2.5	Ø⁄103	A -	n d	وبچ ر	Q448	°≫n.d.	n.d.
BCS-CN88460-propanol-Glyc-MA (M21)	10.3	0.414	<b>.</b> 9	0.036	A 6.7	C 1.042	Q 3	00056
BCS-CN88460-propanol (M01) BCS-CN88460-desmethyl-propanol	Ø.7	<u>\$0,029</u>	22.3	¢0.90£	۲´ کې	0319	≪10.5	£1.625
(M06)	Sm.d.	n.d	× S	0,277	©0.7	£0.116	^م ر کې کې	0.564
Total identified	Q ⁷ 66.0	2,659	~75.3	3.035	o [₩] 77,	/ 11.969	× <b>81.6</b>	12.666
Total characterised	29.5	<b>A</b> 187	چې 15.0	⁽⁾⁾ 0.605	· 16.4	2552	<b>ر 11.0</b>	1.706
* values are given as sum of superna	tant and a	lissolved	nollat da	ring kar	alveis of	wheat hay	Sytract 1	no nellet

#### Distribution of radioactive residues of parent compound and metabolites in the Table 6.2.1-17:

- messolved pe * values are given as sum of supernatant and dissolved pellet; during word of wheat have xtract, no pellet was formed n.d.: not detected

The metabolism of BCS CN88460 in wheat was investigated after two coliar applications at growth stages BBCH 10 and BBCH 69. The when plants were treated with [pyrazole-4-14C]BCS-CN88460 formulated as an EC 50 at a single application rate of 60 and 60 g a.s and for the first and second spray application arespectively, corresponding to a total application rate of 136 g a.s/ha. Wheat hay was harvested at BBCH 69. day prior to the second application, wheat straw and grains were harvested at ô maturity (BBCH 89) Š  $\langle \gamma \rangle$ 

Residues in wheat grains were agnificantly lower than these in wheat hay and straw. The extraction rates of hay, straw and grains were bigh. Overall identification rates in wheat hay, straw and grain were sufficient In al RACC parent compound BCS-CN88460 was the main residue component and the only component in wheat grains. Besides garent compound, other metabolites were identified in wheat straw and hay: BCS-CN88460-propanol-Clyc (M18), BCS-CN88460-desmethyl-propanol-Glyc-MAS (M41), BCS-CN88460-propande Glyc MA (M21), BCS-CN88460-propanol (M01) and BCS-CN88460-desmethyl-propanal (M06).

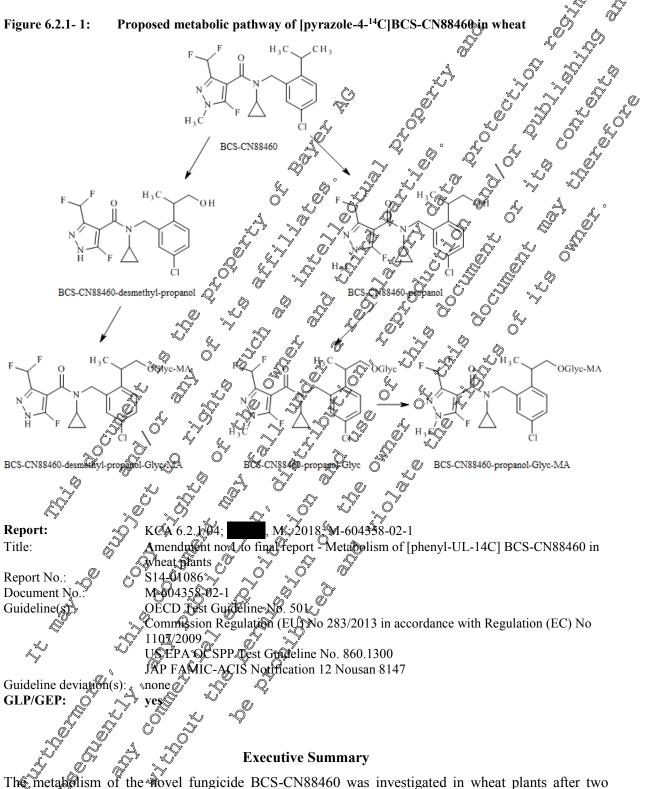
The results in the present study are in good agreement with the results with the phenyl-label. No label specific metabolites were observed Acid Ovdrolysis of the conventional extracts of wheat hay and wheat straw showed cleavage of the identified conjugates to the aglycons BCS-CN88460-propanol and BCS-QN884694 despothyl-propand and the presence of further conjugates of the aforementioned aglycons

The test compound pyrazole-4-14C]BCS-CN88460 was moderately metabolised in wheat after two post emergence applications. The main metabolic reactions observed were:

- hydroxylation in position 1 of the propyl group followed by conjugation with hexose and malonic acid
- demethylation of the pyrazole moiety



Based on these results, the degradation behavior of [pyrazole-4-¹⁴C]BCS-CN88460 in wheat is adequately understood.



The metabolism of the novel fungicide BCS-CN88460 was investigated in wheat plants after two applications. For each of the two foliar applications the test item [phenyl-UL-¹⁴C]BCS-CN88460 was formulated as an aqueous EC 50 using a nominal application rate of 65 g a.s./ha each. The applications were performed at the growth stage of BBCH 30 (beginning of stem elongation) and BBCH 69 (end of



flowering). The actual application rate corresponded to 64 and 66 g a.s./ha for the first and second application, respectively resulting in a total application rate of 130 g a.s./ha.

Wheat hay was harvested at BBCH 69, 1 day prior to the second application, wheat straw and goins were harvested at maturity (BBCH 89). The total radioactive residues (TRR) in wheat straw and hay were high and amounted to 16.031 mg eq/kg and 3.040 mg eq/kg, respectively. The TRR is wheat grains was moderate and amounted to 0.284 mg eq/kg.

Homogenised plant material from RACs was conventionally extracted with a mixture of acetonitrile/water (8/2, v/v). The extraction rates after conventional extraction of wheat hay, straw and grains were high and amounted to 96.7% (2.940 mg ea/kg) of the TRR for hay, 95.2% (3.264 mg eq/kg) of the TRR for straw and 93.5% (0.266 mg eq/kg) of the TRR for grains. The post extraction solids (PES) of all RACs remaining after conventional extraction amounted to  $\leq 65\%$  of RR.

Residues in the conventional extracts were analysed and quantified by HPLQ. The parent compound was identified by co-chromatography with the reference compound and membolities were assigned by comparison of the metabolite pattern and reference compound and membolities were assigned by study with pyrazole label.

The parent substance BCS-CN88460 represented the most prominent residue component in all RACs accounting for 54.7% of TRR (1.661 mg eq/kg) in wheat hay, 621% of TRR (9.954 mg eq/kg) in wheat straw and 92.7% of TRR (0.264 mg eq/kg) in wheat grains. Besides parent compound no other metabolite was detected in the extract of grains. In wheat straw five metabolites were identified besides parent compound: BCS-CN88460-propanol-Glyc (M08), BCS-CN88460-desmethyl-propanol-Glyc-MA (M41), BCS-CN88460-propanol-Glyc-MA (M21), BCS-CN88460-propanol-Glyc-MA (M21), BCS-CN88460-propanol-Glyc-MA (M21), BCS-CN88460-desmethyl-propanol-Glyc-MA (M21), BCS-CN88460-desmethyl-propano

Overall, identification rates were sufficient and amounted to 72.6% of TRK for straw, 66.3% of TRR for hay and 92.5% of FRR for grains. In wheat hay and straw, 23 and 39 unknown metabolites were characterised in the extracts by their chromatographic behavior, individually accounting for less than 3.1% of the TRR and 0.095 mg earkg and 2.1% of the TRR and 0.345 mg ea/kg.

Comparison of metabolic profiles with those of a parallel study with [pyrazole-4-14C]BCS-CN88460 revealed a high correspondence and no label specific metabolite could be observed for the both labels.

More conjugates might be present among the characterised unknown metabollites in the chromatograms. Therefore, acid hydrólysis (1 M fICl, 190 °C, 1 h) of the conventional extracts of wheat hay and straw was conducted in order to analyse for hydrolysable conjugates. Major hydrolysis products detected in the acidic hydrolysates besides parent compound were BCS-CN88460-desmethyl-propanol (M06) and BCS-CN88460 propartiel (M04). Identification rates after hydrolytic treatment increased. Based on these results it can be concluded that a significant amount of residues in the conventional extracts of hav and straw consists of conjugates of BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol. Analogous hydrolysis experiments were performed in the parallel study with the pyrazque-label showing good accordance with the current study.

Storage stability was demonstrated for residues in wheat hay and straw by extraction and comparison of extracts for up to 30 months.

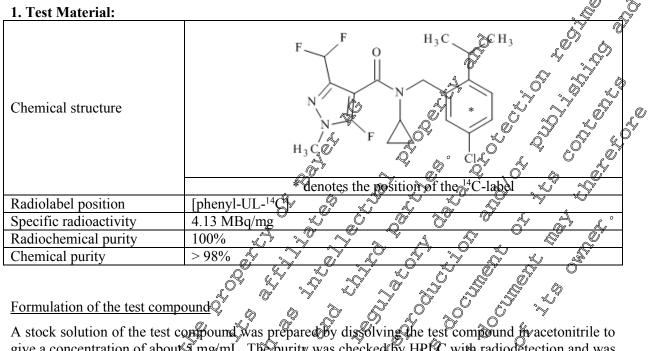
As metabolic cactions, hydroxylation of the propyl group followed by conjugation with hexose and maloric acid and the demethylation of the pyrazole moiety were observed.

Based or these results, the degradation behavior of [phenyl-UL-¹⁴C]BCS-CN88460 in wheat is adequately understood and a pathway is proposed.



#### I. Materials and Methods

#### A. Materials



give a concentration of about mg/mL. The purity was checked by HPLC with radiodetection and was 100%. The test compound was formulated as an EC 50 for the experiment. The active substance [phenyl-UL-¹⁴C]BCS-CN88460 was dissolved in acctonitrite. For each spray dilution, adequate parts of the stock solution were transferred into special glass vials and evaporated to dryness. Blank formulation was added and the mixtures cere homogenised using a magnetic stirrer. The sample was then adjusted with water to a final volume of 100 mL of the stray dilution and homogenised by stirring.

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2. Soil: 🔊	N	×° (			
R ^a		6	Soil char	cteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteristics pteris	
, i l	Type 1		TOC V	≪pH (Ca℃l ₂ )	CEC
	andy to an	n se a	2.1%	23	15.5 meq/100 g
2. Soil:				entative for cereals	
3. Plant: 🕰	wheat, varie	ety "KADR	ÆJ", represe	entative for cereals	
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### **B. Study Design**

#### **1. Experimental conditions:**

The experiment was conducted with wheat plants based on a plant density of 5,000,000 wheat mants per hectare. A planting container with a surface area of 1 m² was used corresponding to the rate of 5000 grains per m². The plants were applied at two different growth stages (BRCH 30 and 69). The experiment was conducted, representing the intended application type for BCS-CN88460, The formulated test compound was applied to the wheat plants at a target rate of 2 x 65 g a.s. (ha. The garget) rate corresponds to the anticipated maximum application rates for the use type. The planting container was filled with sandy loam soil "CUPF_soil". The plants were cultivated in the glass-rooted greenhouse of the test facility. The plants were grown similar to natural temperature and light of conditions, but protected from rainfall. The plants were watered by pouring water onto the soppin the planting containers.

The wheat plants were treated with 100 mL of the aqueous spray dilutions as a spray using a controlled track sprayer with a flat fan nozzie. At the 1st application 263 MBG of the labelled test compound were applied, corresponding to 6.4 mg as. At the  $2^{n}$  application 2% MBq were applied, corresponding to 6.6 mg a.s. The total actual treatment rate was 64 and 66 g a.s./ha. The seed definity was 500 grains/m². Calculations for losses during application are taken into account: After spraying the spray dilution onto the wheat plants of the planting container, the spray defice and the protective plastic foil around the planting container were wised with accountine (8/2 v/v). The actual amount applied was calculated by subtracting the losses from the radioactivity in the original application solution.

#### 2. Sampling:

At growth stage BBCH 69 th RAC hay an at BBCH 82 the RACs straw and grains were harvested. Plant samples were collected by conting approximately 4-2 cm above the soil level. Plants sampled at hay stage were dried in a flue for 4 days. The total weight of each sample was determined. The samples were homogenised with liquid nitrogen using a brigh speed blender. The sample materials were stored in a freezer ( $\leq 38$  °C) Aliquots of the homogenates were extracted conventionally. The final TRR values of the samples were determined by summing up the radioactivity measured in the Ky OF LY OF LY Y OF LY OF LY Z OF LY OF LY And same conventional extracts and in the remaining solves.

## C. Analytical Procedures

### 1. Extraction:

## Conventional extraction procedure and sample clean up

Aliquots of the homogenised samples of wheat hay straw and grains were extracted three times with a mixture of acetonitrile/water (8/2; y/v) using a high speed blender. After each extraction step, the extracts were filtered by suction and the solids were rinsed with a small amount of the solvent mixture used for extraction. The solids were dried, hopogenised aliquots subjected to combustion.

The extracts were combined and subjected to a clean-up step using a SPE RP 18 cartridge, which was rinsed with wethand and water and conditioned with acetonitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitrie/water (8/2; v/v). The percolate and the rinse were combined. Less polar fractions on the cartridge were cluted by ringing the cartridge with methanol/tetrahydrofurane (1/1; v/v). Volume and radioactivity of this fraction was also determined. Each combined percolate/rinse solution obtained from SPE purification was mixed with emulsifier and evaporated to the aqueous remainder. The final conventional extracts were analysed by HPLC. All wheat samples and extracts were stored in a freezer  $(\leq -18 \, ^{\circ}\mathrm{C}).$ 



#### Hydrolysis of the conventional extracts from wheat hay and straw:

Hydrolysis experiments in acidic medium were conducted with conventional extracts of wheat hay and straw, to further characterise the residues. Aliquots of the conventional concentrated purified extract of wheat hay and straw were incubated with 1 M HCl and 5% acetonitrile at 100 °C for 1 hour and afterwards centrifuged. For wheat straw, the supernatant was removed and the pellet was dissolved in acetonitrile/water (1/1; v/v) whereas no pellet was formed during processing of wheat hay. Aliquots of the extracts were analysed by HPLC.

The radioactivity in liquid samples was determined by liquid scintillation counting (LSG). Solutions samples were combusted. The CO₂ produced by combustion was absorbed in a CO₂ absorbent/ scintillation cocktail mixture and the radioactivity was measured by LSC.

Parent compound and metabolites were quantified in the extracts by HPLC with radiodefection based on reversed phase chromatography using an acidic water/acetonitrile/TFF gradent.

#### 2. Identification and characterisation:

Metabolic profiles of all RACs were compared as analysed by HPLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the wheat metabolism study with the pyractile label in which the major metabolities were identified spectroscopically. Parent compound was identified in wheat grains extract by TLC and HPLC co-chromatography with non-radiolabeled and radiotabelled reference compound BCS-CN88460. Metabolic profiles of wheat hay and straw before and after hydrofysis were compared with corresponding profiles of the wheat metabolism study with the pyrazole label as analysed by HPLC.

Unknown metabolites were characteriser based on their extraction and chromatographic behavior.

## Table 6.2.1- 18: List of reference compound

	@?			$\bigcirc$	0 ~	1
Report name / other names/codes		Chemical Nat	me (IUPAQ)			Structure
Parent componed BCS-CN88460 Radiolaboled refer S_PH_1000 Non-radiolabeled BCS-CN88460-01	ence:	isopropylben Cyclopropyl- (difluoromet methyl-111-p carboxamide	izðð-N- 3- hyl)-5-fluoro yrazole-4-5	-1- ×	H ₃ C	$ \begin{array}{c}                                     $

#### 3. Storage stability:

All extraction experiments with wheat hay and straw and the first HPLC analyses were performed within one month after harvest of the wheat plant raw material. The stability of the stored extract of wheat hay, straw and grains was depronstrated by re-analysis of the extract by HPLC after 30, 28 and 15 months of torage

A second analysis of wheat storw and grains was needed for analytical reasons and performed after 30 months of storage of the respective plant material after harvest. The storage stability of these samples could be deprioustrated.

It was therefore concluded, that the residues in the samples were sufficiently stable during the experimental period of the study and that the chromatograms represented the metabolic pattern in the samples at harvest.



#### **II. Results and Discussion**

The metabolism of [phenyl-UL-¹⁴C]BCS-CN88460 in wheat was investigated after two spray applications. Wheat plants were treated with [phenyl-UL- 14 C]BCS-CN88460 formulated as an E@50 at BBCH 30 (beginning of stem elongation) and BBCH 69 (end of flowering). The actual single farget application rate corresponded to 64 and 66 g a.s./ha for the first and second spray application, respectively which was slightly above the anticipated maximum application rate. The total application rate amounted to 130 g a.s./ha.

The TRR values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solid. The residued evels are shown in prim or org active substance equivalents per kg sample material (mg a.s.equiv Ag or simplified mg gq/kg). The TRR in wheat hay and straw were high and amounted to 3.040 mg eq/kg and 16.03 mg eq/k respectively. The wheat grains showed a moderate **TRR** of 0.284 mg eq/bg.

Table 6.2.1- 19:	TRR values in wh	neat matrices af	ker folige	application	@phenyl-U	JL-14C BCS	al a
	CN88460		ř "V	× 4	<i>Q</i> ¹		Ň

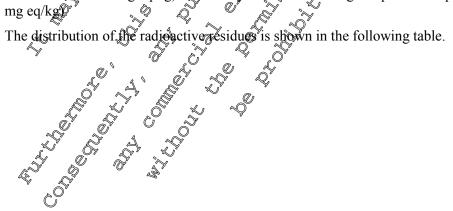
Matrix	Timing and Application PHI days)* (=mg eq/kg)
Wheat hay	1 spray application at BBCH 30, 64 g a.s./ha
Wheat straw	2 spray applications at BBCH 30 and BBCH 60 16.031
Wheat grains	64 and 66 g ars /ha (18) g a s (ha total)

* PHI: preharvest interval (corresponds to days after last treatment (DAT) at harvest/sampling)

0 Wheat hay was conventionally expracted three times with acetonitrile/water mixtures releasing 96.7% of the TRR (2.940 mg eq/kg). After purification and concentration steps 96.2% of the TRR (2.925 mg eq/kg) were andysed Dosses during sample clean up were 0.5% of TRR (0.015 mg eq/kg).

Wheat stray was conventionally extracted three times with accontrile/water mixtures releasing 95.2% of the TRR (15,264 mg eq/kg) After purification and concentration steps 93.1% of the TRR (14.922 big eq/kg) were analoged. Losses during sample bean up of straw samples were 2.1% of TRR (0.342 mg eq/kg).

Wheat grains were conventionally extracted three times with acetonitrile/water mixtures releasing 93.5% of the TRR (0,266 mg eq/kg). Based on the low amount of radioactivity (0.001 mg/kg) and high matrix had the third extract was not combined. After purification and concentration steps 92.7% of the TRR (0.264 mg eq/kg) were analysed. Losses during sample clean up were 0.8% of TRR (0.002 mg eq/kg@ Ô





Sample	hay		str	aw	grains 🖉 🤶		
	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg oq/kg	
TRR		3.040		16.031	) )	0.284	
Conventional Extraction	96.7	2.940	95.2	15.264	93.5	\$ <b>.0</b> , <b>2</b> 66	
Analysed extracts	96.2	2.925	93.1	14,922	87.7	S0.264	
Losses (not analysed) [#]	0.5	0.015	م 2.1	0.342	× 0.8	`≫` 0.062	
Total extracted	96.7	2.940	<b>%</b> 95.2	15.264	<u> </u>	<b>0,2</b> 66	
Post extraction solids (PES)	3.3	0.099	4.8	0.767	×	6 ⁵⁰ .019	
Accountability	100.0	3:040	100.9	r6.03 <u>۴</u>			

Table 6.2.1- 20:	Distribution of radioactivity in the extracts of wheat matrices after two foliar
	applications of [phenyl-UL-14C]BCS-CN88460

0 Ø In the conventional extract from wheat hay 66.3% of the TRR 2.015 mg eg/kg) were identified in total. The parent compound was the major component representing 54,7% of the RR (1.661 mg eq/kg), whereas the metabolites BCS-CN88460-ptopan@-Glyc, BCS-CN88460-despethylpropanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA and BCS-CN88460-propanol@epresented 0.8, 2.7, 7.5 and 0.7% of the TRR corresponding to 0.023, 0.081, 0,229 and 0.021 prig eq. (5), respectively.

In the conventional extract from wheat straw \$2.6% of the PRR (14,640 mg eq/kg) were identified in total. The parent compound was the major component representing 92.1% of the TRR (9.954 mg eq/kg), whereas the metaboliter BCS-CN88460-propanol-Gyc, BCS-CN88460-desmethylpropanol-Glyc-MA, BCSCN88460-propanol-Glyc-MA, BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol represented 2.3, 1,95.0, 63 and 8.9% of the TRR corresponding to 0.373, 0.306, 0.808, 0.052 and 0.147 mg eq/kg, respectively.  $\bigcirc$  $\bigcirc$ 

The conventional stract from wheat grains contained only parent compound representing 92.7% of the TRR corresponding to 0.264 mg eq/kg. The compound was identified by co-chromatography using

HPLC and TLC The TRR and the distribution of parent and metabolites in wheat matrices are shown in the following table.



# Table 6.2.1- 21:Distribution of parent compound and metabolites in the extracts of wheat matrices<br/>after two foliar applications of [phenyl-UL-14C]BCS-CN88460

						<u> </u>
	whea	t hay	wheat straw		wheat	grains
$\Gamma RR [mg eq/kg] =$		3.040		16,031	,	0.284
Compound	% TRR	mg eq/kg	% TRR	mg@q/kg	% TR <b>R</b>	mg eg kg
BCS-CN88460 (parent compound)	54.7	1.661	62.1	9.954	<b>9</b> 2.7	0.264
BCS-CN88460-propanol-Glyc (M18)	0.8	0.023		0.373	S. On.d.	Ø n.d.
BCS-CN88460-desmethyl-propanol-Glyc-MA		Ĉa	, C	,		Y S
(M41)	2.7	0.081	Ø.9	0.306	Ç na	″ (0%.d. ≪∫
BCS-CN88460-propanol-Glyc-MA (M21)	7 🔊	0.229		0.808	j.d.	Nn.do
BCS-CN88460-propanol (M01)	<u>1</u> .7	0.021	Q 0.9	0,047	" n.d.	C n.C
BCS-CN88460-desmethyl-propanol (M06)	n.d.	n.d.	× Ø3	Q052	0° n.d	@.d.
Fotal identified	66.3	· 2.005	× 72.6	.@11.640	\$2.7	<b>9.264</b>
Unknown 2 (	) _ WI	\$0,020	S 0.4	0,009		« n.d.
Unknown 72 .4	×1.2	@,0.035	n.d.		n.d.	r fyd.
Unknown 74	_~~~ 0 <i>Z</i>	× 0.022	And	n.d.	, n.d.	n.d.
Unknown 28	n 🔊		03	× 0.048	, ^{sh} h.d.	n.d.
Unknown 29	Qa.d.	and n d	K nài	AS950	n.d.	n.d.
Unknown 30	°∛n d	n.d		× 0 115	S n.d.	n.d.
Unknown 31	ô n ô		0 0 4	0 0 0 59	M.d.	n.d.
Unknown 32	D [*] \$.5	0.046	$\hat{Q}$ 07	0004	∬ n.d.	n.d.
	. 0.9	0.02	U ^V . @4	0.057	$\bigcirc n.d.$	n.d.
Unknown 34 6 0 A	0.9	0.028	~Qn d	°∑ n d	n.d.	n.d.
Unknown 35	S of	40018	, ≪ ^v n.d. n.d≰		n.d.	n.d.
$\Box n k n own 36 \qquad \checkmark \qquad $		\$0.034	∽ §a.d.	°∼n.d.	n.d.	n.d.
Unknown 37	1.1	0.03	$\bigcirc 0.8$	√y0.126	n.d.	n.d.
Unknown 77		0.040 0.040	0.0 کې n.d		n.d.	n.d.
$\operatorname{Unknown} 38 \qquad $	y Nn d	Nn d		0.063	n.d.	n.d.
	× 1.0	A 0 034	0.4	0.067	n.d.	n.d.
Unknown 79	°∼ n da	n d	∞ 0.2	0.038	n.d.	n.d.
Unknown 200 S			0.5	0.050	n.d.	n.d.
	$\hat{O}$ 0 7	× 0.000	n.d.	n.d.	n.d.	n.d.
Unknown 64	1 %	0.092	n.d.	n.d.	n.d.	n.d.
Unknown of the second s		0.097 20.07	1.5	0.248	n.d.	n.d.
Unknown 23	- 0.9 & d	Q nd	1.5	0.248	n.d.	n.d.
Unknown 5 0 0 0 0 0	Sec. 0.7	0 022	n.d.	n.d.	n.d.	n.d.
		0.022	1.0	0.162	n.d.	n.d.
		0.095	0.6	0.102	n.d.	n.d.
	× 1.0	0.033	2.1	0.104		
	× 3.0	0.090	2.1	0.343	n.d.	n.d.
Unknown 42		0.037	0.4		n.d.	n.d.
Unknown 43	1.0	0.032	0.3	0.054	n.d.	n.d.
Unknown 33 Unknown 34 Unknown 35 Unknown 36 Unknown 37 Unknown 37 Unknown 38 Unknown 39 Unknown 79 Unknown 40 Unknown 40 Unknown 40 Unknown 5 Unknown 7 Unknown 7 Unknown 7 Unknown 7 Unknown 7 Unknown 7 Unknown 7 Unknown 7 Unknown 42 Unknown 43				cont	inued on n	ext page



#### Table 6.2.1-21: continued

	whe	at hay	whea	nt straw	wheat	t grains 。
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg er/kg
Unknown 45	n.d.	n.d.	0.3	0.054	n.d.	n.d
Unknown 84	n.d.	n.d.	0.2	0.040	🔊 n.d.	nd. nd. nd. nd. nd. nd. nd. nd.
Unknown 46	n.d.	n.d.	0.2	0.034	n.d.	🧳 🚬 Qr.d.
Unknown 47	n.d.	n.d.	0.2	0.036	n.d.	🖓 🚕 n.d.
Unknown 48	n.d.	n.d.	0.4	04060	nad	ຸ ິ n.ຢ
Unknown 50	n.d.	n.d.,	<b>O</b> 0.2	Ø.036	pr.d.	n.et , , , , , , , , , , , , , , , , , , ,
Unknown 51	n.d.	n.d.	♥ 0.3	<b>Q</b> 0.050	© n.d.	n.d.
Unknown 52	n.d.	p.d.	0.2	0.035 گ	n.d.	n.d.
Unknown 53	n.d.	a.d.	0.2	<b>₽`@</b> 031	A nd.	aça.
Unknown 54	n.d.	🖓 n.d.	0.2	<u>گ</u> 0.032	N.d.	n.d.
Unknown 55	n.d.	🕵 næd.	్ల ని0.4	_≪″ 0. <b>060</b>	n.đ.	√ √ n.d.
Unknown 57	n.d.	Oʻ _{so} nd.	<u>کی</u> 0.4	S 2070	or n.d.	A. n.d.
Unknown 58	n.d	, 🔊 n.d.	0.4	0.058	🔉 🖗.d.	g.d.
Unknown 61	n d.	n?d	Ø.4	0.06	🗶 n.d,	n.d.
Unknown 11	<b>2</b> 1.0	رتم ( <u>مر</u> م) 0,030	^م رح 0.5	© 04085	or not	n.d.
Unknown 12	_Õ [♥] n.d.	🖌 🔍 🖓 n.d.	Q.8	9.121	S. J.d.	<u>م</u> n.d.
Unknown 62	n.d.	n.d.	9.5	0.08	n.d.	n.d.
Unknown 63	n.d.	The state	0.5	030\$4	"O n.d.	″ n.d.
Unknown 13	🎽 🦄 n.d	" h.d.	0.3 🎸	0.048	o n.d.	n.d.
Unknown 14	× 20	¢0.068	y 0.6	×0.103	n.d.	n.d.
Total characterised 🔬 🕺	9 30.0	0.910	_20.5	3.281	🔊 n.d.	n.d.
Analysed extract(s)	96.2	2925	ູ 0ິ [≫] 93.≵	14.922	6 92.7	0.264
Not analysed / Losses 🔊 🔗	<u>65</u>	Q0.015	9.9	0.342	0.8	0.002
Total extracted 🖉 🔬	<u>\$</u> 99.7	2.240	ý <b>95</b> .2	15.264	93.5	0.266
Post extraction solids (PRS)	د∑ <u>3.3</u> ∉	<b>)</b> () () () () () () () () () () () () ()	్ల 4.8	Ø <b>\$76</b> 7	6.5	0.019
Accountability	<u> </u>	3.040 🕺	> 100,0	16.031	100.0	0.284
n.d. not detected 🛷 🐇			¥ O	× Ø		

In wheat hay and straw, 23 and 39 Onknown metabolities were characterised in the extracts, individually accounting for less than 34% of the TRB and 0.095 mg eq/kg and 2.1% of the TRR and 0.345 mg eq/kg.



Table 6.2.1- 22:	Summary of characterisation and identification of radioactive residues in wheat
	matrices after two foliar applications of [phenyl-UL- ¹⁴ C]BCS-CN88460

	whea	ıt hay	wheat	straw	wheat	grains
TRR $[mg eq/kg] =$		3.040		16.031		0.284
Compound	% TRR	mg eq/kg	% TRR	mg 🏟 kg	% TRR	mg eq/kg
BCS-CN88460 (parent compound)	54.7	1.661	62.1	9.954	92.%	00264
BCS-CN88460-propanol-Glyc (M18)	0.8	0.023	2.3	ő.373 ر _ا	₫?d.	n.d.
BCS-CN88460-desmethyl-propanol-Glyc-MA (M41)	2.7	0.081	1.0	0.306	م م n.d. الم	nğ.
BCS-CN88460-propanol-Glyc-MA (M21)	7.5		.05.0	0.808	C ¢.	"n.d.
BCS-CN88460-propanol (M01)	04	0.021	0.9°0.9	0.147	Qn.d.	n.d
BCS-CN88460-desmethyl-propanol (M06)	d.d.	n.d.	$\dot{Q}$ 0.3	0.052	" n.d.	Ô ngế
Total identified	Q 66.3	2.015	<b>. D</b> .6	ÎN:640	° 92Ø	0264
Number of unknown peaks	k, d	3 5	چ کې	20 0		d. 🗸
Largest unknown peak	¢×_%ĭ	<del>0</del> .095ھ	2 Q	r 0 <i>2</i> 345	, n,	d °
Total characterised	<b>30.0</b>	0.916	20.5	3.281	O' d	ð. 🎢
Analysed extract(s)	96.2	2,005	93.1	014.92	92.7	Ø.264
Not analysed / Losses	, × .0,5	20,015	2 ×	) 0 <i>3</i> 42	0.8	0.002
Total extracted	96.7	2.940	95.2	15.264	S 93.5	0.266
Post extraction solids (PES)	3.3	0.099	<b>4.8</b>	0.767	° _∿ 6.5	0.019
Accountability	õ 1060	3,040	A 100.0	7 16,031	<b>% 100.0</b>	0.284
n.d. not detected	M	o 4		×2 .4	0 [°]	

More conjugates might be present among the characterised unknown metabolites in the chromatograms. Therefore, and hydrolysis (1 M HCl, 100 °CO1 h) of the conventional extracts of wheat hay and strawwere conducted in order to analyse for hydrolysable conjugates.

In hydrolysed extract of wheat hay 95.2% of the TRR (2893 mg eq/kg) were analysed. The parent compound was the major component representing 49.6% of the TRR (1.508 mg eq/kg), whereas the metabolites BCS-CN88460-propanol-Glyc, BCS-CN88460-propanol and BCS-CN88460-desmethyl-propanol represented 0.6, 21.1 and 6.7% of the TRR corresponding to 0.019, 0.642 and 0.204 mg eq/kg, respectively.

In hydrolysed extract of wheat straw 92.5% of the TRR (14.892 mg eq/kg) were analysed. The parent compound was the major component representing 60.8% of the TRR (9.751 mg eq/kg), whereas the metabolites BCS-CN88460 proparol-Glyc BCS-CN88460-desmethyl-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA, BCS-CN88460-desmethyl-propanol represented 0.3 0.3, 0.1, 02.7 are 4.0% of the TRR corresponding to 0.053, 0.054, 0.022, 2.046 and 0.644 mg eq/kg, respectively, in contrast to bydrolysis of the hay extract, a pellet was formed during hydrolysis of the straw extract. Therefore values of analysed residues are given as sum of supernatant and dissolved pellet.

Identification rates after hydrolytic treatment increased for wheat hay from 66.3% of the TRR (2.015 mg eq/kg) before hydrolysis to 78.0% of the TRR (2.373 mg eq/kg) after hydrolysis and for wheat straw from 72.6% of the TRR (11.640 mg eq/kg) before hydrolysis to 78.2% of the TRR (12.570 mg eq/kg) after hydrolysis. Wo major metabolites were formed after acidic hydrolysis as a result of deconjugation of residues: BCS-CN88460-desmethyl-propanol and BCS-CN88460-propanol. BCS-CN88460-desmethyl propanol in wheat hay accounted for 6.7% of the TRR (0.204 mg eq/kg) and 4.0% of the TRR (0.644 mg eq/kg) in the hydrolysed extract from wheat straw. Metabolite BCS-CN88460 propanol was detected in hydrolysed extract from wheat hay and straw accounting for 21.1% of the TRR (0.642 mg eq/kg) and 12.7% of the TRR (2.046 mg eq/kg), respectively.

Based on these results it can be concluded that a significant amount of residues in the conventional extracts of hay and straw consists of conjugates of BCS-CN88460-desmethyl-propanol (M06) and



BCS-CN88460-propanol (M01). A comparison of the distribution of parent compound and metabolites in the conventional wheat hay and straw extracts before and after hydrolysis is given in the table below.  $Q_{\mu}^{\circ}$ 

Analogous hydrolysis experiments were performed in the parallel study with the pyrazole label showing good accordance with the current study.

		ÿ		$\overline{\mathbf{O}}$	<u></u>		st i
	v	heat hay	Q.	5¥ 5	d,	t straw	
	conventiona extract before hydro	° ext	ntional race « trolysis*	eonver extr before de al-		conven vyextra after hyd	net V
Report name	% TRR	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	mg @q/kg		orysus ⊕mg eq/kgg	% TRR	næg ¢§/kg
BCS-CN88460 (parent compound)	<b>\$9</b> .7	661 <i>°</i> 49.6	1.500	62.1	9954	60.8	9.751
BCS-CN88460-propanol-Glyc (M18)		023 .08	0.0019	2.3 2.3	50.373	or og	0.053
BCS-CN88460-desmethyl-propanol-	^{Q°} , <u>5</u> 97, <i>b</i>	981 n.d.	on.d	) (49)	0,306	ر پر 0.3	0.054
BCS-CN88460-propanol-Glyc-XX (M21)	c, 7.5\$\$♥ 0.	229 n.d.	≪n.d.	5.0	ي 0.808	^{©°} 0.1	0.022
BCS-CN88460-propanol (MOR)	P`\$\$7`\$	921 21.1	<u>∖</u> 0.642	× 49	0.147	12.7	2.046
BCS-CN88460-desmethyl-propanel (M06)	©n.d.		0 204	ر 0.3	\$052 \$0052	4.0	0.644
Total identified	S 66 2 2.	805 38.0	2.373	◎ 72.6	∀11.640	78.2	12.570
Total characterised 🔊 🔗	30.0 ~0,	910 🔊 17.2		2025	3.281	14.3	2.262

# Table 6.2.1- 23:Distribution of radioactive residues of parent compound and metabolites in the<br/>extracts of wheat matrices before and after hydrolysis of M HCl, 100°C, 1 fb/

* values are giver as sum of supernatant and dissolved bellet; during hydrolyers of wheat hay extract, no pellet was formed.

a TII. Conclusions

The metabolism of BCS-CN88460 in wheat was investigated after two foliar applications at growth stages BBCH 30 and BBCH 59. The wheat plants were beated with [phenyl-UL-¹⁴C]BCS-CN88460 formulated as an ECO0 at a single application rate of 64 and 66 g a.s./ha for the first and second spray application, respectively, corresponding to a fotal application rate of 130 g a.s/ha. Wheat hay was harvested at BBCH 69.1 day prior to the second application, wheat straw and grains were harvested at maturity (BBCH 89).

Residues in wheat grains were significantly lower than those in wheat hay and straw. The extraction rates of hay, straw and grains were high. Overall, identification rates in wheat hay, straw and grain were sufficient. In all RAC parent compound BCS-CN88460 was the main residue component and the only component in wheat grains. Besides parent compound, other metabolites were identified in wheat straw and hay: BCS-CN88460-propanol-Glyc (M18), BCS-CN88460-desmethyl-propanol-Glyc-MA (M21), BCS-CN88460-propanol (M01) and BCS-CN88460-propanol (M06).

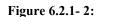
The results in the present study are in good agreement with the results with the pyrazole-label. No label specific metabolites were observed. Acid hydrolysis of the conventional extracts of wheat hay and wheat straw showed cleavage of the identified conjugates to the aglycons BCS-CN88460-propanol and BCS-CN88460-desmethyl-propanol and the presence of further conjugates of the aforementioned aglycons.



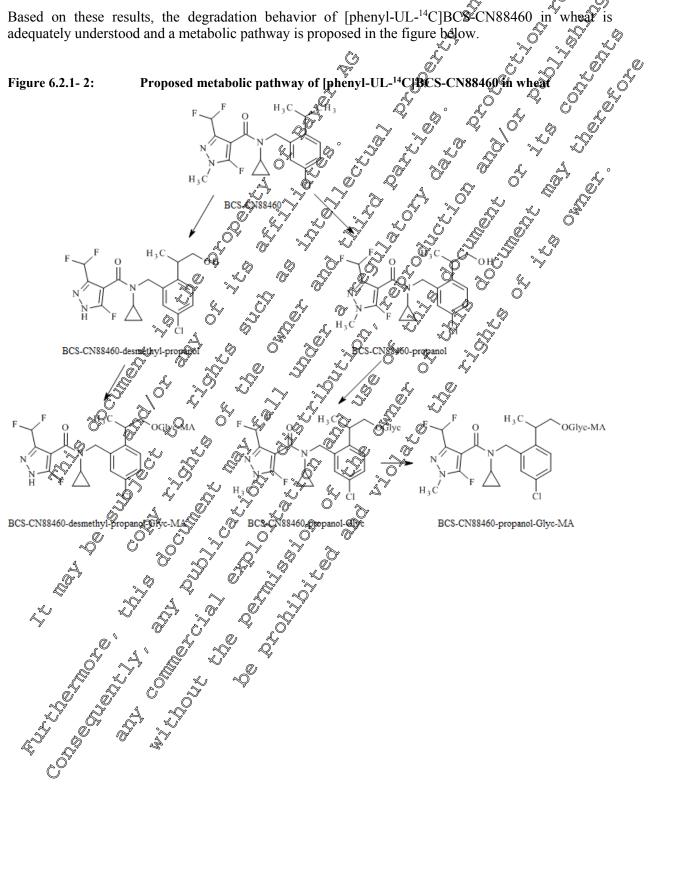
The test compound [phenyl-UL-14C]BCS-CN88460 was moderately metabolised in wheat after two post-emergence applications. The main metabolic reactions are listed below:

- hydroxylation in position 1 of the propyl group followed by conjugation with hexose and malonic acid
- demethylation of the pyrazole moiety

wheat^{s;} Based on these results, the degradation behavior of [phenyl-UL-¹⁴C]BCS-CN88460 in adequately understood and a metabolic pathway is proposed in the figure below.



Proposed metabolic pathway of [phenyl-UL-





#### Metabolism, distribution and expression of residues in potatoes (tuber treatment)

Metabolism studies in potatoes after tuber/seed treatment will be conducted with [pyrazole-4-¹⁴C] and [phenyl-UL-14C]BCS-CN88460. The studies are already listed in this dossier but will be field subsequently after finalization of the studies. L.

Table 6.2.1- 24:	<b>Overview</b>	over potatoes	metabolism	studies
	0.01.11011	over potatoes	metuoonom	staates

*	try after infanzation of the ste		ð		
Table 6.2.1	-	bes metabolism studies			
Plant	Application	Target application rate	BBCH_Code	Reference 🛇 🖉	
potato	tuber treatment, pyrazole-	Will be provided after	BBCH00	Will be provided	
	labelled isoflucypram	finalization of the study		after finalization@f	
ootato	tuber treatment, phenyl-	×	BBCH 00	Che study	
	labelled isoflucypram	L D	ý Ö		
		yrazole4 ¹⁴ C] <b>B</b> CS-CN88460			
Report:		Ŵ N	in Potato after S		
Title:	Metabolism of [n	yrazol 4-14C] BCS-CN98460	and Potatovafter 8	ed Treatment	
Report No.:	S17-01394.		y _0 - 7	de A o	
Document 1	No.:	A. F. C. Q		OT DT A	
Guideline(s	Will be provided	after finalization of the study.	A.Or		
Guideline d	leviation(s):			r de de	
GLP/GEP:	yes 🖉			ά ^γ .	
			S S		
	Q'		0.00	ŝ v	
Keport:	Match allers of the	hand II 14 me CE allog 14	Datation of a constraint	ad the astronome	
l Itle:	Metabonsm or p	nenyi-UL-"CABCS-CN88460	an Potato atterse	ed greatment	
keport No.:	SI/-01/392			Ĩ	
Jocument I		Dan Collingting of the own day		₩ Ĵ	
Juideline d	b). wyn de provided	anter manzanou or the study.		,	
GLF/GEF	yes to		oʻ 😽		
			s o		
	E a 4 4				
Metaboli	sm. distribution and ex	pression of Fesidues	in oilseed ra	pe (foliar sprav	
applicati	en) × ×		Ø		
PP					
Metabólisi	m studies in oilseed rape, we	re conducted with [pyrazol	$e-4-^{14}C$ and [p	henyl-UL- ¹⁴ C]BCS-	
CN88460.					
	Metabolism of [p S17-01394. No.: b): Will be provided leviation(s): Superior of p S17-64392 No.: b): Will be provided leviation(s): Superior of p Superior of p Supe				
Fable 6.2.1	- 25: Ovérwiew over availa	ble offseed fape morabolism	studies		
Plant	Application	Target application rate	<b>BBCH Code</b>	Reference	
oilseed	two foliar spray applications,	2 x 60 g a.s./na	BBCH 14	M-609378-01-1	
ape 🖉	pyrazole-habelled		and		
м. 	isoflucypram		BBCH 77		
oilseed	two foliar spray applications,	©2 x 60 g a.s./ha	BBCH 14	M-609380-01-1	
ape	phenys-labelled		and		
		$\cap^{\nu}$	DD GU FF		

BBCH 77

mar spras applications, 2 x ( phenyl-labelled isothucypram



#### Summary of metabolism in oilseed rape (foliar spray application)

The metabolite pattern corresponds well when comparing the two metabolism studies in oilseed rape after foliar application. Parent compound BCS-CN88460 was the main residue component in all R&Cs except in forage extract which contained no residue above the limit of detection. Parent compound was the only component in oilseed rape seeds. BCS-CN88460 was moderately metabolised in oilseed rape intermediate harvest and mature plants samples after two post-emergence applications. The man metabolic reactions were hydroxylation in position 1 or 2 of the propyl group of the phenyl ring followed by conjugation with hexose and malonic acid and hydroxylation in position 4 of the phenyl moiety followed by conjugation with hexose and malonic acid.

Besides parent compound, the following metabolites were identified BCS-CN88460-hydroxyphenyl-Gluc-MA (M23), BCS-CN88460-2-propanol-Glyc MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24).

Report:	
Title:	KCA 6.2.1/05; $2017$ Metabolism of [pyrazole 4-1/4C]-BCS-Cl 88460 moilsee@rape $\sqrt{2}$
Report No.:	S16-01038 @ , y @ , y @ , y
Document No.:	M-609378-01-Q ( , , , , , , , , , , , , , , , , , ,
Guideline(s):	OECD Test Guideling No. 501 V V S S
	Metabolism of [pyrazole-4-F4C] Asc S-Cix88460 moliseed rape S16-01038 M-609378-01-0 OECD Test Guideline No. 501 Commission Regulation (EU) No 283/2013 in acordance with Regulation (EC) No 1107/2009 US EPA OCSPP Test Guideline No. 860.1300 JAP FAMIQ-ACIS Notification 12 Nousan 8147
	No 1107/2009 2 0 2 0 2 0 4
	US EPS OCSPP Test Guideline No. 860.1306
	JAP FAMIC-ACIS Sotification 12 Nousan 8147
Guideline deviation(s):	none yes A g g g g g g g g g g g g g g g g g g
GLP/GEP:	
\$	
and the second se	yes A G A G A A A A A A
La	
	Executive Symmary

The metabolism of BCS-CN88460 was investigated in offseed rape plants after two foliar applications. For each of the two boliar applications the test item [pyrazole-4-¹⁴CIBCS-CN88460 was formulated as an aqueous EC 50 using a nominal application rate of 60 g a  $^{\circ}$ /ha each. The applications were performed at the growth stage of BBCH 14 (triblicate on the 3rd up to 5th node unfolded) and BBCH 77 (70% of pols have reached final size). The actual application rates corresponded to 64 and 62 g a.s./ha for the first and second application, respectively resulting in a total application rate of 126 g a.s./ha.

Oilseed rape intermediate harvest was harvested at BBCH 30, 2 days after the first application, forage at BBCH 55, 40 days after the first application, and mature plants and seeds were harvested at BBCH 89, 21 days after the second application. The total radioactive residues (TRR) in intermediate harvest and mature plants were high and amounted to 4.751 mg eq/kg and 4.076 mg eq/kg, respectively. The TRR in forage was low due to the increase of plant mass from first application at BBCH 14 until sampling of forage at BBCH 55 and amounted to 0.012 mg eq/kg. The TRR in seeds was low and application 0.099 mg eq/kg.

Homogenised plant material from RACs was conventionally extracted with a mixture of acetonitrile/water (8/2; vv). The extraction rates after conventional extraction of intermediate harvest, forage, mature plants and see as were high and amounted to 99.5% (4.730 mg eq/kg) of the TRR for intermediate barvest 85.4% (0.010 mg eq/kg) of the TRR for forage, 97.4% (3.970 mg eq/kg) of the TRR for mature plants and 71.0% (0.070 mg eq/kg) of the TRR for seeds.

Solids after conventional extraction of seeds were exhaustively extracted using microwave assistance with a mixture of acetonitrile/water/formic acid (50/50/1; v/v/v) releasing further 9.8% (0.010 mg eq/kg) of TRR. The post extraction solids of seeds after microwave extraction were subjected to consecutive enzyme digestion with cellulase and amylase, which released further 1.5% of the TRR



(0.002 mg eq/kg). Subsequent extraction under acidic conditions with HCl released 11.0% of the TRR (0.011 mg eq/kg). 8.1% of the TRR (0.008 mg eq/kg) of this extract were further characterised by partitioning with ethylacetate. In the unpolar ethylacetate fraction remained 5.4% (0.005 mg eq/kg) of the residues and 2.7% of TRR (0.003 mg eq/kg) remained in the water phase.

The post extraction solids after conventional and exhaustive extractions accounted for 0.5% of the TRR (0.022 mg eq/kg), 14.6% of the TRR (0.002 mg eq/kg), 2.6% of the TRR (0.106 mg eq/kg) and 6.7% of the TRR (0.006 mg eq/kg) for intermediate harvest, forage, mature plants, and seeds, respectively.

Residues in the conventional extracts were analysed and quantified by HPLC. The parent composed and metabolites were either identified by co-chromatography with the reference compound of by spectroscopic analysis in isolated fractions of intermediate harvest. Additionally, the metabolite pattern and retention times of the current and the offseed rape metabolism study with the phenyl lakel were compared.

The forage extract contained no residue above the limit of detection. Parent compound BCS-CN88460 represented the most prominent residue component in all RACs, accounting for \$1.9% of TRR (3.890 mg eq/kg) in intermediate harvest, \$8.1% of TRR (3.589 mg eq/kg) in mature plants and 7.6% of TRR (0.070 mg eq/kg) in seeds. Parent compound was the only component detected in the extract of seeds.

Besides parent compound four metabolites were identified in intermediate harvest and mature plants.

In intermediate harvest, BCS-CN88460 hydroxyphenyl-Gluc-MA (M23) BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460 propanol-Glyc-MA (M21) and BCS-CN88460 hydroxyphenyl-Glyc-MA (M24) accounted for 2.3 2.2, 2 and 3 1% or the TRK corresponding to 0,109, 0.106, 0.131 and 0.148 mg eq/kg, respectively.

In mature plants BCS-CN88460-hydroxyphenyl-Gruc-MA (MZ3), BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24) accounted for 0.7 0.9, 0 and 7.0% of the ORR corresponding to 0.027, 0.038, 0.025 and 0.040 mg eq/kg, respectively.

Overall, identification rates, were high and amounted to 2.3% if TRR for intermediate harvest, 91.3% of TRR for mature plants and 71.0% of TRR for seeds. In intermediate harvest, 22 unknown metabolites were characterised in the extracts, individually accounting for equal or less than 1.5% of the TRR and 0.072 mg eq/kg and 16 were characterised in mature plants, individually accounting for equal or less than 1.5% of the TRR and 0.054 mg eq/kg.

Comparison of metabolic profiles with those of a parallel study with [phenyl-UL-¹⁴C]BCS-CN88460 revealed a high correspondence and no label specific metabolite could be observed for the both labels.

Acid hydrolysis (1 N HOI, 100 °C, 10h) of the conventional extract of intermediate harvest was performed in order to analyse for hydrolysis the conjugates. Comparison of metabolic profiles before and after hydrolysis indicated cleavage of the identified conjugates BCS-CN88460-hydroxyphenyl-Gluc MA (M23), BCS-CN88460-2-prepanol Olyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24) to less polar compounds. Analogous hydrolysis experiments were performed in a parallel study with the phenyl-label showing good accordance with the current study.

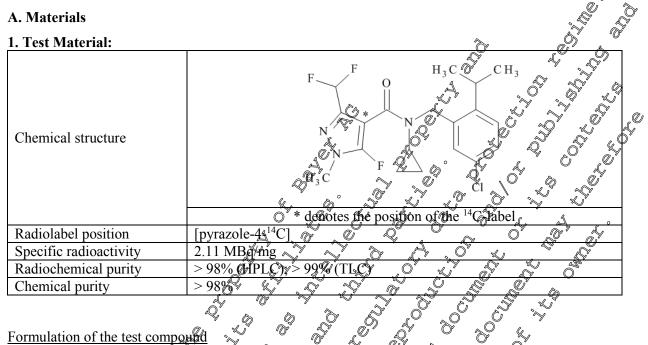
All convertional and explaustive extraction experiments of the raw agricultural commodities and the first HPLC analyses were performed within three months after harvest of the oilseed rape samples.

As metabolic reactions, hydroxylation in position 1 or 2 of the propyl group of the phenyl ring followed by conjugation with hexose and malonic acid and hydroxylation in position 4 of the phenyl moiety followed by conjugation with hexose and malonic acid were observed.

Based on these results, the degradation behavior of [pyrazole-4-¹⁴C]BCS-CN88460 in oilseed rape is adequately understood and a pathway is proposed.



#### I. Materials and Methods



The test compound was diluted as a 50.50 mixture of radiolabelled and non-radiolabelled test compound resulting in a calculated final specific activity for the test item of 2. 14 MBq/mg. A stock solution of the test compound was prepared by dissolving the test compound in actionitrile. The purity in the stock solution for both applications and the identity of the test compound in the application dilutions was checked by HPLC with radiodetection and was above 98%

The test comported was formulated as an EC 50 for the experiment and therefore [pyrazole-4-¹⁴C] BCS-CN88460 was dissolved in accionitrile. For each of the two spray dilutions, adequate parts of the stock solution were transferred into glass vials and evaporated to dryness. Blank formulation was added and the mixtures were knowed using a magnetic stirfer. The sample was then adjusted with water to a final volume of 100 mL of the spray dilution and omogenised by stirring.

2. Soil:		Soil chara	cteristics	
4 4	Type 🗞	AQOC S	[©] pH (CaCl ₂ )	CEC
	Sandy foam Q	©2.37%	7.48	20.9 meq/100 g
3. Plant:	oilseed rape, variety	² 2.379 ² ERRX, repro	esentative for oilse	eds



#### **B. Study Design**

#### **1. Experimental conditions:**

The experiment was conducted with oilseed rape plants (variety: JERRY) at the rate of 275 seeds per  $m^2$  in a planting container with a surface area of 1 m². The planting container was filled with sandy loam soil. The plants were cultivated in the glass-roofed greenhouse of the gest facility and were grown similar to natural temperature and light conditions, but protected from rainfall. They were watered by pouring onto the soil in the planting containers. The plants were applied at two different growth stages (BBCH 14 and 77). For both applications the target single application rate was 60 g a.s./ha. The target rate corresponds to the anticipated maximum application rate for the use type.

For each application, the plants were treated with 100 mL of the aqueous spray dilutions using a controlled track sprayer with a flat fan nozzle. To avoid contamination of the surrounding area by drift, the plants in the planting container were endosed with a foil housing. After spraying the spray dilution onto the oilseed rape plants in the planting container, the spray device and the protective plastic foil around the planting container were rinsed with acetopitrile/water (\$72; v/v). The actual amount applied was calculated by subtracting the losses from the adioactivity in the original application solution. At the 1st application 13.5 MBg of the labelled test compound were applied, corresponding to 6.4 mg a.s. At the  $2^{pq}$  application 3.1 MBq of the test compound were applied, corresponding to 6.2 mg a.s. The actual single treatment rates were 64 and 62 g a.s./hg corresponding to a total actual application rate of  $\frac{126}{26}$  g a sha.  $\frac{1}{2}$ 

#### 2. Sampling:

Two days after the first application (at BBCH 30), the RAC intermediate harvest and 40 days after the first application at BBCH \$5, the RAC forage was harvested. The RACs seeds and mature plant (= rest of plant including pods without seeds were harves at at BBCH \$9, 21 days after the 2nd application.

Intermediate harves forage and mature plants were sampled by cut-off of the plants 1-2 cm above the soil surface. Seeds were combined with the mature plant sample. 📎 Ø

The total weight of each sample was determined. The samples were homogenised with liquid nitrogen using a high speed blender. The sample materials were stored in a freezer ( $\leq$  -18 °C). Aliquots of the homogeneites were extracted. The actual TRR values of the samples were determined by summing up the radioactivity measured in the extracts and in the remaining solids.

# C. Analytical Proceedings

### Conventional extraction procedure and sample clean up:

For conventional extraction of obseed cape intermediate harvest, forage, mature plants and seeds, aliquots of the homogenized samples were extracted three times with a mixture of acetonitrile/water (8/2; v/v) using high speed hende After each extraction step, the extracts were filtered by suction and the solids were mosed with a small amount of the solvent mixture used for extraction. The solids were dried and aliquots were subjected to combustion.

The extracts were combined and subjected to a clean-up step using an SPE RP 18 cartridge, which was rinsed with methanot and water and conditioned with acetonitrile/water (8/2; v/v) beforehand. The flowshroug fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitric water (8/2;  $\sqrt[v]{v}$ ). The percolate and the rinse were combined. Less polar fractions on the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v).



Each combined percolate/rinse solution obtained from SPE purification was mixed with emulsifier and evaporated to the aqueous remainder. The final conventional extracts were analysed by HPLC with the general profiling method.  $Q_{\mu}^{\circ}$ 

#### Exhaustive extraction and corresponding clean-up:

Solids from the conventional extraction of oilseed rape seeds were exhaustively extracted two times with acetonitrile/water/formic acid (50/50/1; v/v/v) under microwave existince at increased temperature (0 to 5 min increase to 120 °C, 5 to 20 min at 120 °C, 800 W). The microwave extracts were cooled down at room temperature. After each extraction step, extract and solids were filtrated by suction and centrifuged and finally the extracts were companed.

Aliquots of the combined extract were subjected to a clean-up step using a SPE RP18 carridge which was rinsed with methanol and water beforehand. The flow-through fraction was collected and the cartridge was rinsed with acetonitrile/water (8/2;  $\sqrt{8}$ ). Less polar fractions on the cartridge were elured by rinsing the cartridge with methanol/tetrahydrofurane (1/1;  $\sqrt{8}$ ).

The flow-through fraction and the rinse obtained from SPE purplication were combined and mixed with emulsifier and evaporated to the aqueous remainder the final exhaustive extract was addived by HPLC with the general profiling method. The extract was stored in a freezer  $(2 - 18^{\circ}C)$ .

(1)

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#### Release of residues upon enzymatic digestion

Solids of oilseed rape seeds after extraction were further incubated with collulase in sodium acetate buffer (0.1 M) to release radioactive residues. The solids were autoclaved in buffer (121 °C, 2 bar vapor pressure) for 2 hours. After autoclaving the sample was cooled down at room temperature and the buffer was set to pHS by use of acetic acid. The solution was mixed with 100 mg cellulose, incubated for 24 hours in awater bath at 37 °C and centrifuged.

Solids of oilseed rape seeds remaining after callulas treatment were further incorated with amylase in sodium acetate buffer (0.1 M) to specifically release radioactor restrues previously assimilated to carbohydrates. The colids were autoclaved in buffer (121 °C, 2 bar vapour pressure) for 2 hours. After autoclaving the sample was cooled down to 20 °C and the buffer was set to pH 5 by use of acetic acid. The solution was mixed with 50.0 mg amylase (1.4 units/mg), incubated for 24 hours in a water bath at 37 °C and centrifuged.

Release of residues upor acidicextraction with HCl:

Solids of oilseed rapelseeds after enzymatic digestion with cellulase and amylase (approx. 5 g) were further extracted with HCL (5 M 30 mD) to release radioactive residues. After addition of the HCl solution, the mixture was incubated for 60 minutes at 920° Cunder microwave assistance.

Residues contained in the combined extracts obtained by acidic extraction were characterised by partitioning. Therefore, the complete extract was neuralized by addition of 10M NaOH and mixed with ethylacetate (1/1; v/v) in a separatory funnel and shaken by hand. Ethylacetate and water phase were separated. The water phase was again mixed with ethylacetate (1/1; v/v) in a separatory funnel and the procedure was repeated.

Hydrolysis of the convertional extracts from @lseed rape intermediate harvest:

Hydrolysis experiments in acidic medium ( N HCl) were conducted with concentrated conventional extract from intermediate barvest. Therefore, the final purified extract was mixed with 10 N HCl to obtain a concentration of approximately 1 N HCl and incubated 100 °C for 1 hour. Afterwards, the mixture was adjusted to pH 7 with 10 N NaOH and analysed by HPLC.

The redioactivity in liquid samples was determined by liquid scintillation counting (LSC). Solid samples were combusted. The  $CO_2$  produced by combustion was absorbed in a  $CO_2$  absorbent/ scintillation cocktail mixture and the radioactivity was measured by LSC.

Conventional and microwave extracts were analysed by HPLC with radiodetection based on reversed phase chromatography using an acidic water/acetonitrile/tetrahydrofurane gradient.

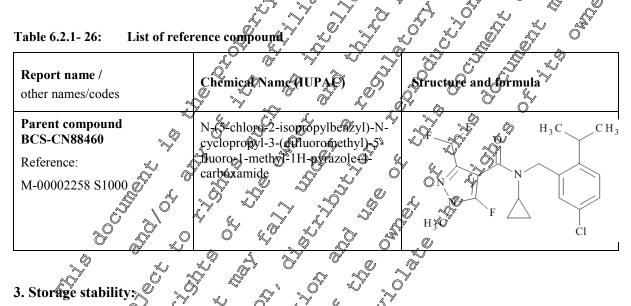


#### 2. Identification and characterisation:

For identification of radioactive ingredients in conventional extract from intermediate harvest, selected major radiosignals were isolated as fractions of elutent by HPLC fractionation. Isolated fractions were identified by spectroscopic analysis as following metabolites: BCS-CN88460 hydroxypherel-Glue-MA, BCS-CN88460-2-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA and BCS-CN88460-hydroxyphenyl-Glyc-MA.

Metabolic profiles of all RACs were compared, as analysed by HPLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the oilseed rape metabolism study with the phenyl label. Parent compound was identified in oilseed rape seeds, extract by TLC and HPLC co-chromatography with the test compound. Metabolic profiles of corresponding profiles of the oilseed rape metabolism study with the phenyl label, as analysed by HPLC.

Unknown metabolites were characterised based on their extraction and chromatographic behavior.



All conventional extraction experiments of the raw agricultural commodities were performed within two months after harvest of the object rape samples. The exhaustive extraction of seeds was performed within three months after harvest. All first quantitative analyses by HPLC were performed within two days after the sert of extraction.

It was therefore concluded, that the residues in the samples were sufficiently stable during the experimental period of the study and that the chromatograms represented the metabolic pattern in the samples at harvest.

### ⁷ II. Results and Discussion

The metabolism of [pyrazole-4⁴⁴C]BCS-CN88460 in oilseed rape was investigated after two spray applications.

Oilsee rape plants were freated with [pyrazole-4-¹⁴C]BCS-CN88460 formulated as an EC 50 at BBCH 14 Grifoliolate on the 3rd up to 5th node unfolded) and BBCH 77 (70% of pods have reached final size). The actual single application rate corresponded to 64 and 62 g a.s./ha which was slightly above the anticipated maximum application rate (2 x 60 g a.s./ha). The total application rate amounted to 126 g a.s./ha.



The TRR values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solids. The residue levels are shown in mg active substance equivalents per kg sample material (mg a.s.equiv./kg or simplified mg eq/kg).

TRR values in intermediate harvest and mature plants were high and amounted to 4.751 mg eq/kg and 4.076 mg eq/kg, respectively. The TRR in forage and seeds were low and amounted to 0.012 mg eq/kg and 0.099 mg eq/kg.

The high TRRs found for intermediate harvest and mature plants are due to harvest shortly after the first foliar application (PHI = 2 d) in case of intermediate harvest or due to sampling after two foliar applications in case of mature plants. For forage, the low TRR can be excribed to the increase of plant mass from the 1st foliar application at BBCH 14 to sampling 40 days after 1st application at BBCH 55.

Table 6.2.1- 27:	TRR values in oilseed rap	e matrice	es after	foliar	apphicat	ion _{po} f	[pyrazo	ole_4	C BCS-
	CN88460	×,	<u>Ô</u>	, N	×	K)		"N	- 20

ř _n ř .	
PHI (days)*	ppm (=mg eq(kg)
	Q Q.751
	0.012
O 21Ô	گُن 4.076
	0.099
	PHI (days)*

* PHI: preharvest interval (corresponds to days after last treatment (DAT) at harvest/sampling)

Intermediate harvest was conventionally extracted three times with acetonitrile/water mixtures releasing 99.5% of the TRR (4.730 mg eg/kg). Dosses during sample clean up accounted for 0.4% of the TRR (0.020 mg eg/kg). After concentration and purification steps 99.1% of the TRR (4.710 mg eq/kg) were analysed. The post extraction solids amounted to 0.5% (0.022 mg eq/kg) of the TRR, only.

Forage was conventionally extracted three times with acetonitrile/water mixtures releasing 85.4% of the TRR (0.010 mg eq/kg). No losses of RA occurred during sample clean up and 85.4% of the TRR (0.010 mg eq/kg) were analysed. The post extraction solities amounted to 14.6% of the TRR (0.002 mg eq/kg), only.

Mature plants were conventionally extracted three times with acetonitrile/water mixtures releasing 97.4% of the CRR (3.970 mg eq/kg). Losses of RA during sample clean up accounted for 0.2% of TRR and 0.006 mg eq/kg). After concentration and purification steps 97.3% of the TRR (3.964 mg eq/kg) were analysed. The post extraction solids contained 2.6% (0.106 mg eq/kg) of the TRR.

Seeds were conventionally extracted three times with acetonitrile/water mixtures releasing 71.0% of the TRR (0.070 mg eq/kg). No losses of RA occurred during sample clean up and 71.0% of the TRR (0.070 mg eq/kg) were analyzed. The post extraction solids after conventional extraction accounted for 29.0% of TRO (0.029 mg eq/kg).

The PES of seeds were subjected to exhaustive extraction under microwave support. This treatment released 8.8% of the TRR (0.010 mq eq/kg). Losses during sample clean up accounted for 2.2% of the TRR (0.002 mg eq/kg) and 7.6% of the TRR (0.008 mg eq/kg) were analysed by HPLC. Additionally, the solids remaining after exhaustive extraction were incubated consecutively with cellulase and amylase for release further residues. This digestion released 1.5% of the TRR (0.002 mg eq/kg).

Subsequent acidic extraction additionally released 11.0% of the TRR (0.011 mg eq/kg). Losses of RA during neutralization of the acidic extract accounted for 2.9% of TRR (0.003 mg eq/kg). The neutralized extract was further characterised by partitioning with ethylacetate. 5.4% of the TRR



(0.005 mg eq/kg) was detected within the ethylacetate fraction and 2.7% of the TRR (0.003 mg eq/kg) were detected within the water phase.

In total 93.3% of the TRR (0.093 mg eq/kg) was extracted from seeds. Total losses of RA accounted for 5.1% of the TRR (0.005 mg eq/kg). The post extraction solids amounted to 6.7% (0.006 mg eq/kg) of the TRR.

The distribution of the radioactive residues is shown in the following table.

applicat	ions of [p	yrazole-4-	¹⁴ C]BCS	CN88460	jo ^w -	Ň		8 4
	interm har	iediate vest	for	age	mature	e plants		eds
TRR $[mg eq/kg] =$		4.751	lu iča	• 0. <b>Q</b> Q2		<i>w</i> 4.078		0.099
Compound	% TRR	mg eq/kg	% TRA	mg <b>∢q</b> ∕kg	% TRR _ℓ	mg eq/kg	% TŘR	mg eq/kg
<b>Conventional extraction</b>	99.5	4.730	85.4	<b>0.010</b>	97 <b>3</b> 4	3.970	́71.₿	🏳 0 <b>.Q</b> 70
Analysed extracts	99.1	4(7)0	85.4	0.010	× <u>9</u> 7.3	\$3.964	7480	<b>£0</b> 70
Not analysed	0.4	A.020.	<u>) n.q.</u>	n.q.	× 0.2	0.006	∦ _≪ p.q.	<b>n</b> .q.
Exhaustive extraction		Å	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~~~		Ŭ	<u></u> 9.8	0 0.010
Analysed extracts*		Óv 🖌	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~~ ~	d	⁽¹⁾	S 7.6	0.008
Not analysed	â	~ ^ <u>`</u>	. 🌾		Ø	0 -	) <u> </u>	0.002
Enzymatic digestion	<u>×</u>			<b>)</b>	L -9		1.5	0.002
Acidic Extraction and partitioning					°, 6-	- 6	O ^V 11.0	0.011
Ethylacetate phase			_Ű [×]	°°'	~~~-	× _4	5.4	0.005
Water phase	4	Q	S 4	~~ [~]	w _z	§ ~~	2.7	0.003
Not analysed	A	ÔÔ		, O* (		. 6	2.9	0.003
Total extracted	Ø 99, <b>ž</b>	J 4 <b>7</b> 30	85.4	× 0.010	87.4	3.970	93.3	0.093
Post extraction solids		<b>A</b> .022		0.002		7	6.7	0.006
Accountability	100.0	🎸 4.7 <b>5.</b> ]	100.0	0.012	C 10 <b>6.</b> 0	4.076	100.0	0.099

 Table 6.2.1- 28:
 Distribution of radioactivity in the extracts of oilseed sape matrices after two foliar applications of [pyrazole-4-14C]BCS CN88460

-- not applicable (< COQ)

n.q. not quantified (< EOQ) * no individual peak above detection limit was observed in the HELC chromatogram of the exhaustive extract of seeds

Comparison of chromatograms from conventional extracts of intermediate harvest and mature plants of the current study among themselves indicated whigh grade of comparability. Conventional extract of forage contained no individual radiosignal above the background noise whereas conventional extract from seeds contained only the test compound.

The comparison of profiles of all RACs to corresponding profiles of the parallel study performed with [pheny]-UL-¹⁴C]BCS CN88460 revealed that no label specific metabolism could be observed.

In conventional extracts from intermediate harvest 92.3% of the TRR (4.384 mg eq/kg) were identified in total. The parent compound was by far the major component representing 81.9% of the TRR (3.890 mg eq/kg) whereas the BCS-CN88460-hydroxyphenyl-Gluc-MA (M23), BCS-CN88460-2propanol Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460hydroxyphenyl Glyc-MA (M24) represented 2.3, 2.2, 2.8 and 3.1% of the TRR corresponding to 0.109 0.106 0.131 and 0.48 mg eq/kg, respectively.

Acid hydrolysis (1 N HCl, 100 °C, 1 h) of the conventional extract of intermediate harvest was performed in order to analyse for hydrolysable conjugates. Comparison of metabolic profiles before and after hydrolysis indicated cleavage of the identified conjugates BCS-CN88460-hydroxyphenyl-Gluc-MA, BCS-CN88460-2-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MA and BCS-



CN88460-hydroxyphenyl-Glyc-MA to less polar compounds. Analogous hydrolysis experiments were performed in the parallel study with the phenyl-label showing good accordance with the current study.

In conventional extracts from forage 85.4% of the TRR was analysed in total (0.010 mg eq/kg). No individual radiosignal was above the background noise due to low amounts of total radioactive Ó ingredients in the extract.

In conventional extracts from mature plants 91.3% of the TRR (3.719 mg @d/kg) were identified in total. The parent compound was by far the major component representing 88.1% of the TRR (3.589 mg eq/kg), whereas the metabolites BCS-CN88460-hydroxyphenyl-Gluc-MA M23, BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24) represented 0.7, 0.9 0.6 and 1.0% of the FRR Ċ corresponding to 0.027, 0.038, 0.025 and 0.040 mg eq/kg, respectively.  $\bigcirc$ 

In conventional extracts from seeds 71.0% of the TRR (0.070 mg eq frg) were identified. The parent compound was the only component representing 71.0% of the TRR (0.070 mg eq kg). Parent compound was identified by HPLC and TLC co-chromatography with the test term as radiolabelled reference compound. L.

RR (ch) the readers in the existing of the intervention of the i Exhaustive extraction of seeds released further 9.8 % of the BRR (0.010 mg eg/kg) and 7.6 % of the TRR (0.008 mg eq/kg) were analysed by HPLC. No addividual radiosignal was above the background noise due to low amounts of total fadioactive ingredients in the exhaustive extract. Conventional extract of seeds treated under microwave extraction conditions in comparison of the corresponding conventional extract and exhaustive extract, showed that degradation a parent compound by this treatment was neglectable. treatment was neglectable. The TRR and the distribution of parent and metabolities in oilseed pape matrices are shown in the following table.



Table 6.2.1- 29:	Distribution of parent compound and metabolites the extracts of oilseed rape matrices
	after two foliar applications of [pyrazole-4- ¹⁴ C]BCS-CN88460

	intermediate c									
	harvest		fo	forage		e plants	seeds			
TRR [mg eq/kg] =		4.751		0.012		4.076		6 0.099	ď	
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg co kg	% TRR	mg eqting		
Conventional extraction	99.5	4.730	85.4	0.010	97.4	3.970	710	0.070	6	
BCS-CN88460 (parent	01.0			I	88.1	3.589		· 0 0 40	Ø	
compound) BCS-CN88460-	81.9	3.890	n.d.	n.d.	88.1	≫ 5.589 /			"Q	
hydroxyphenyl-Gluc-MA	2.3	0.109	n.d.	n.d.	00.7	0.027	, nga	n.d	Ó	
(M23) BCS-CN88460-2-propanol-		0.107	A		Ŷ,		Å.	¢ @.d.	2	
Glyc-MA (M22)	2.2	0.106	<b>212</b> .d.	n⁄d.		69038	$\sqrt{0}$ n.d	@@).d.		
BCS-CN88460-propanol-	2.0	0 1 2 1	(		0.6	× O no	n.d.			
Glyc-MA (M21) BCS-CN88460-	2.8	0.131	n.o.	n.d.	0.0 0 0		Å	n.d.		
hydroxyphenyl-Glyc-MA	3.1	Q 1 18	_ °∽n.d.	l a d	10	0.040	n.ď.	e did		
(M24)	5.1		$\sim$	y ayu.						
Total identified	92.3	Q 4.384	n d.	"", ", ", ", ", ", ", ", ", ", ", ", ",	× 91.3	3,199	71.0	0.070		
Unknown 1	n.d.	prod.	°≈p.d.	N n.d.	F.Q.	<b>0</b> 004	, n.d,			
Unknown 2	0.4	0.003	" n.d.	nd.	a.d.	n.de	n d	n.d.		
Unknown 3	p.d.	/ ? n.d.	n.dc	Provide	× 0.4	80.0 8	n.d.	n.d.		
Unknown 4	~00.1	∞ 0.003	n.@.	l n.d.	🖇 n.d.	P.d.	n.d.	n.d.		
Unknown 5	₩°010	0.887	An.d.	n.d	nd.	ش. ش. الم.	n.d.	n.d.		
Unknown 6		AD005	n.d.	n.d.		n d	n.d.	n.d.		
Unknown 7	402		$\int n d^{n}$	Qn.d.	≪ ^{n.d.}		n.d.	n.d.		
Unknown 8	A 3	¢ 0.01	5	n.d		δ. Ω	n.d.	n.d.		
Unknown 9	$\overrightarrow{0}$ 0.2		d	n.d.		L n.d.	n.d.	n.d.		
	. 0 <i>0</i>	~0007	and.		n.d.	n.d.	n.d.	n.d.		
Unknown 10 Unknown 11 Unknown 12 Unknown 13		0.008		and a	n.d.	n.d.	n.d.	n.d.		
Unknown 12		× 0,048	* 11.0%	n.de			n.d.	n.d.		
Unknown 13	.002	0° 0.912	Ön.d.	not.	Ø.d.	n.d.	n.d.	n.d.		
Unknown 14		«0.012	n.d.	n.d.	≪0.1	0.004	n.d.	n.d.		
Unknown Y		n.d.		©n d	0.1	0.004	n.d.	n.d.		
Unknown 16	and	n d	n.d.	n,d		0.003	n.d.	n.d.		
Unknown 17	$\sim 0 $	0-045	∭n.d.	s n.u.	n.d.	n.d.	n.d.	n.d.		
Unknown 18	$\int \Omega $	°≈0,045	$\sim$ n.d	∬	0.1	0.006	n.d.	n.d.		
Unknown 20	r. bæd	n 1		n.d.	0.1	0.034	n.d.	n.d.		
Unknown 22	n.d.		n.d. 0.d.	n.d.	0.0	0.010	n.d.	n.d.		
Unknown 22 Unknown 23		0 0d. 9 0044	ĭ⊗n d	≥, n.d.	0.2	0.010	n.d.	n.d.		
Unknown 26			es nda	nd	0.1	0.005	n.d.	n.d.		
Unknown 20	S'A	$\mathcal{O}$ n	91.02 91.01.	n.d.	0.1	0.003	n.d.	n.d.		
Unknown 28	$\mathcal{Q}_{0.1}^{\text{n.u.}}$	0.003	∘qa. .~On.d.	n.d.	n.d.	0.020 n.d.	n.d.	n.d.		
Unknown 29		¢ 0.003	, n.d.	n.d.	0.5	0.018	n.d.	n.d.		
Unknown 30	1.90 1.90 1.90	0.008	n.d.	n.d.	n.d.	0.018 n.d.	n.d.	n.d.		
Unknown 31	and and		n.d.	n.d.	0.3	0.012	n.d.	n.d.		
Unknown 32		0.005	n.d.	n.d.	0.3	0.012	n.d.	n.d.		
Unknown 33		<b>%</b> 0.003	n.d.	n.d.	0.4	0.017	n.d.	n.d.		
Unknown 34		0.072	n.d.	n.d.	1.3	0.014	n.d.	n.d.		
Unknown 36	On.d.	n.d.	n.d. n.d.	n.d.	0.1	0.034	n.d. n.d.	n.d.		
Characterised by HPLC	6.8	0.326	n.u. 		<b>6.0</b>	0.002		n.u. 		
Tatal Yat an Wood of S									1	
conventional extraction	0.4	0.020			0.2	0.006				
									•	

Ĉ

continued on next page



Table 6.2.1- 29	continued
-----------------	-----------

	intermediate harvest		forage		mature plants		seeds	
	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg
Exhaustive extraction						<del>م</del>	9.8	0.010
Analysed by HPLC*						S	7.6	S 0,008
Not analysed						4	20	Ø.002
Enzymatic digestion						<u> </u>	°~9.5	\$\$ 0.0 <del>0</del> 2
Acidic extraction and partitioning				~	Ű.		0 11.0	0.911
Ethylacetate phase			-7	ý	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Å	Q.4	0.00 <b>\$</b>
Water phase			4		°, t	° Å	L 2.7	0.003
Not analysed by partition			- Ø	A	$\mathbb{Q}$		2.9	Q Q Q 003
Total characterised**	6.8	0.326	&	s°, S'	≪6.0	0.245	22,3	×0.023
Total extracted	99.5	4.730	85.4	0.010	87.4	3.970	<b>L93.3</b>	<u>م</u> 0.093
Post extraction solids (PES)	0.5	0.022	×14.6	0.902	2.6		, ⁰ 6.≉	<b>0,006</b>
Accountability	100.0	Q4.751	> 100.0	0.012	Q00.0	<b>4.076</b>	100.0	0.099

In conventional extract of differenciate barvest, 22 when we characterised, individually accounting for equal to be showing for equal to be showing



Table 6.2.1- 30:	Summary of characterisation and identification of radioactive residues in oilseed rape
	matrices after two foliar applications of [pyrazole-4-14C]BCS-CN88460

		nediate rvest	fo	rage	matur	e plants	see	ds
TRR [mg eq/kg]		4.751		0.012		<u>4.076</u>	Č	0.099
Compound	% TRR		% TRR		% TRR	n@eq/kg	% TRR n	ng earling
Conventional extraction	99.5	4.730		0.010	97.4	[©] 3.970	ZI.0	20.070
BCS-CN88460 (parent compound)	81.9	3.890	n.d.	n.d.	88.1	3.589	. 071.0	0.070
BCS-CN88460-hydroxyphenyl- Gluc-MA (M23)	2.3	0.109	n d	n.d.	0.7	0.027	n:d	jard.
BCS-CN88460-2-propanol-Glyc- MA (M22)	2.2	0.106	Jn.d.	n.d	0.9 O.9	04038	Qn.d.	n.d
BCS-CN88460-propanol-Glyc-MA (M21)	2.8	0.131	n.d.	n.d.	0.6	Q 0.025	n.d.	'n.d.
BCS-CN88460-hydroxyphenyl- Glyc-MA (M24)	3.1	0448	Øn.d.	2 ⁰ n.d.		0,940	°≫n.d.	n.d.
Total identified	92.3	4.384	F ¢		<u>91</u> .3	3.712	71.0	0.070
Characterised in the conventional extract by HPLC	6.8	0.326	Ĩ		Ç ² 6.0	0.245	<u> </u>	<u> </u>
Number of unknown peaks	- R	22 y y	$\sim$	Y Z	Û.	16	ê	)
Largest unknown peak	1.5 کې	@ 0.072	r 🖌	×	S ³ 1.3	్లీ 0.05\$	, N	
Total not analysed of conventional extraction	Q.J	0,020	²	ê d	e es	<b>0</b> 006	~~	
Exhaustive extraction	, [•] ~	×		× _0 <u>×</u>	\$Q	"	<b>9.8</b>	0.010
Analysed by HPLC*	Å	b <i>ŵ</i>	<u>_</u> 0		~ ~	y .Q-	7.6	0.008
Not analysed	Ŷ	. S ^r	Å	~ ·	ľ "Ş	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	2.2	0.002
Enzymatic digestion 🔬 🔗	ĝ	Õ.,		P' 💹	&	~~ ~~	1.5	0.002
Acidic extraction and partitioning	S	Ø \$	~~ <u>~</u>	"	Õ	s	11.0	0.011
Ethylacetate phase	P 2	~	<u>, 9                                    </u>	6 4			5.4	0.005
Water phase 2 2	&,	A	б <b>у</b>	ой "С"-	×		2.7	0.003
Not analysed by partition	°	5 à	<u>í</u> à	⁽¹⁾	<i>a</i> ,		2.9	0.003
Total characterised**	6.8	0.326	<i>®</i>	a. 78	6.0	0.245	22.3	0.023
Total extracted	29.5	4.730	R 85. <del>4</del>	0.010	97.4	3.970	93.3	0.093
Post extraction solids (PES)	0.5	\$`0.0 <b>22</b>	14.6	<b>)0,002</b>	2.6	0.106	6.7	0.006
Accountability	S 100%	4,251	100.0	0.012	100.0	4.076	100.0	0.099
* no individual peak above detection	n limit wa	ıs observec	in the H	C chror	natogram	of the exh	austive ex	tract
of seeds	, Č	Ô.	Î ^v Ô	Ŷ.	-			
**by chromate@raphic@nd/or_xtrac	tion beha	vior 🔊	ð					
<ul> <li>* no individual peak above detection of seeds</li> <li>**by chromategraphic and/or extract n.d. not detected</li> <li> not applicable</li> <li> not applicable</li> </ul>			×) >>					
			nclusion	S				

The metabolism of BCS-CX\$8460 m oilsed rape was investigated after two foliar applications at BBCH 14 and BBCH 77 The oilseed tope plants were treated with [pyrazole-4-14C]BCS-CN88460 formulated as an fit 50 and single application rate of 64 and 62 g a.s./ha for the first and second spray application, respectively, corresponding to a total application rate of 126 g a.s/ha. Oilseed rape intermediate bervest was harvested at BBCH 30, 2 days after the first application and forage was harvested at BBCH055, 40 days after the first application. Mature plants and seeds were harvested at BBCH 89 21 days after the second application.

Residues in forage and seeds were significantly lower than those in intermediate harvest and mature plants. The extraction rates of intermediate harvest, forage, mature plants and seeds were high. Overall, identification rates for intermediate harvest, mature plants and seeds were high. Parent



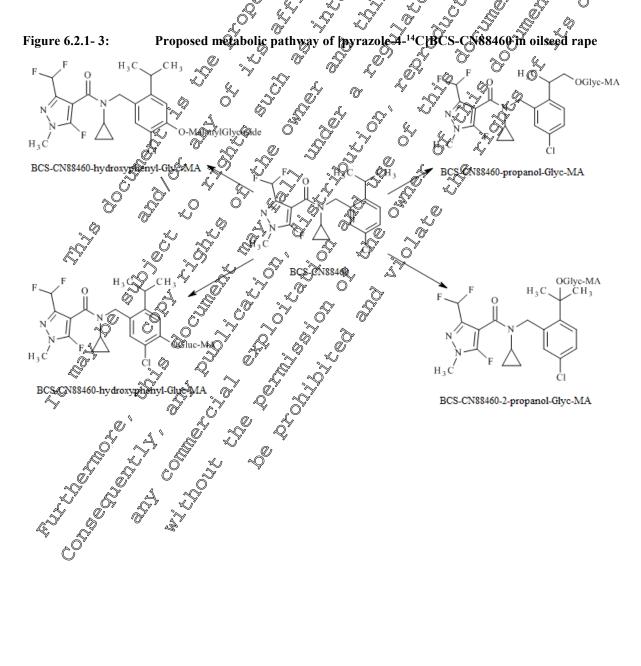
compound BCS-CN88460 was the main residue component in intermediate harvest and mature plant and the only component in seeds. Conventional extract of forage contained no residues above the limit of detection of the analytical method. Besides parent compound, four metabolites were identified in intermediate harvest and mature plants: BCS-CN88460-hydroxyphenyl-Gluc-MA (M23), CS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24).

The results in the present study are in good agreement with the results with the phenyl-label. No babel specific metabolites were observed.

The test compound [pyrazole-4-¹⁴C]BCS-CN88460 was moderately metabolised in offseed vape after two foliar applications. The main metabolic reactions observed were

- Hydroxylation in position 1 or 2 of the propyl group of the phenyl ring followed by conjugation with hexose and malonic acid
  Hydroxylation
- Hydroxylation in position 4 of the phenyl moiety followed by conjugation with Rexose and malonic acid

Based on these results, the degradation behavior of [pyrazole-4-¹⁴C]BCS-CN88460 in oilseed rabe is adequately understood and a metabolic pathway is proposed in the figure below.





Report:	KCA 6.2.1/06; J.; 2017; M-609380-01-1
Title:	Metabolism of [phenyl-UL-14C]-BCS-CN88460 in oilseed rape
Report No.:	S16-01044
Document No.:	M-609380-01-1 OECD Test Guideline No. 501
Guideline(s):	OECD Test Guideline No. 501
	EPA OCSPP Harmonized Test Guideline 860.1300 Nature of the Residue - Pants, 🔥
	Livestock (August 1996)
	PMRA Regulatory Directive Dir98-02 - Residue Chemistry Guidelines, Section 24
	Nature of the Residue - Plants, Livestock
	JMAFF guideline 12 Nousan No 814% requirement 24-1
	Regulation (EC) No. 1107/2009 of the European Parliament and of the Compril of A
	October 2009 concerning the placing of plant projection products on the market and
	repealing Council Directives 79017 /EEC and 😣 /414/EECCompletion Date O
Guideline deviation(s):	October 2009 concerning the placing of plant projection products on the warket and repealing Council Directives 79/117 /EEC and 91 /414/EECC completion Date
GLP/GEP:	yes Q Q Q Q Q

# ExecutiveSummary

The metabolism of BCS-CN88460 was investigated in oilseed rape plants after two foliar applications. For each of the two foliar applications, the test item [pheny UL-142]BCS-CN88460 was formulated as an aqueous EC 50 using a nominal application rate of 60 g a.s./ba each. The applications were performed at the growth stage of BBCH 144 trifoliolate of the D up to 5th node unfolded) and BBCH 77 (70% of pods have reached final size). The actual application rates corresponded to 63 and 63 g a.s./ha for the first and second application, respectively resulting in a total application rate of 126 g a.s./ha.

Oilseed rape intermediate harvest was harvested at BBCH 30, 2 days after the fast application, forage at BBCH 55, 40 days after the first application, and mature plants and seeds were harvested at BBCH 89, 21 days after the second application. The total radioactive residues (TRR) in intermediate harvest and mature plants were high and amounted to 3.295 mg eq/kg and 3.934 mg eq/kg, respectively. The TRR in forage was low due to the increase of plants mass from first application at BBCH 14 unter sampting of Gorage at BBCH 55 and amounted to 0.008 mg eq/kg. The TRR in seeds was low and amounted to 0.126 mg eq/kg.

Homogensed plant material from RACs was conventionally extracted with a mixture of acetonitrile/water (8/2, v/v). The extraction rates after conventional extraction of intermediate harvest, forage, mature plants and seeds were high and amounted to 99.7% (3.285 mg eq/kg) of the TRR for intermediate harvest, 77-3% (0.006 mg/eq/kg) of the TRR for forage, 96.2% (3.786 mg eq/kg) of the TRR for mature plants and 73-6% (0.093 mg/eq/kg) of the TRR for seeds.

Solids after conventional extraction of feeds were exhaustively extracted using microwave assistance with a mixture of acetonitrile/water/formic acid (50/50/1; v/v/v) releasing further 10.6% (0.013 mg eq/kg) of TRR. The post extraction solids of seeds after microwave extraction were subjected to consecutive ensume digestical with cellulase and amylase, which released further 1.3% of the TRR (0.002 mg eq/kg). Subsequent extraction under acidic conditions with HCl released 7.9% of the TRR (0.010 mg eq/kg). Subsequent extraction under acidic conditions with HCl released 7.9% of the TRR (0.010 mg eq/kg) of the residues and 2.1% of TRR (0.003 mg eq/kg) remained in the water phase.

The post extraction solids after conventional and exhaustive extractions accounted for 0.3% of the TRR (0.010 mg eq/kg), 22,7% of the TRR (0.002 mg eq/kg), 3.8% of the TRR (0.148 mg eq/kg) and 6.5% of the TRR (0.008 mg eq/kg) for intermediate harvest, forage, mature plants and seeds, respectively.

Residues in the conventional extracts were analysed and quantified by HPLC. The parent compound was identified by co-chromatography with the reference compound and metabolites were assigned by



comparison of the metabolite pattern and retention times of the current and the oilseed rape metabolism study with the pyrazole label.

The forage extract contained no residue above the limit of detection. Parent compound BCS-CN82460 represented the most prominent residue component in all RACs, accounting for 84.1% of TRR (2.770 mg eq/kg) in intermediate harvest, 72.0% of TRR (2.831 mg eq/kg) in mature plants an 27.3.6% of TRR (0.093 mg eq/kg) in seeds. Parent compound was the only component detected in the extract of seeds.

Besides parent compound four metabolites were identified in intermediate harvest and mature plants,

In intermediate harvest, BCS-CN88460-hydroxyphenyl-Cluc-MA (M23), BCS-CN88460 propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyle Glyc-MA (M24) accounted for 2.3, 1.6, 2.2, and 3.8% of the TORR corresponding to 0.07 0.052 0.071 and 0.126 mg eq/kg, respectively.

In mature plants BCS-CN88460-hydroxyphenyl-Glue MA M23 BCS-CN88460-2-propanok Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS 2018460-hydroxyphenyl-Glyc-MA (M24) accounted for 2.2, 4.6, 2.5, and 3.1%% of the TRR corresponding to 0.087, 0.181, 0.097 and 0.122 mg eq/kg, respectively.

Overall, identification rates were high and an ountee to 94.0% of TRR for intermediate Parves 84.4% of TRR for mature plants and 73.6% of TRR for seeds. If interprediate harvest, 23 Junknown metabolites were characterised in the extracts, individually accounting for equal or less than 1.2% of the TRR and 0.038 mg eq/kg and 39 were characterised in mature plants individually accounting for equal or less than 1.3% of the TRR and 0.050 mg eq/kg.

Comparison of metabolic profiles with those of parallel study with pyrazole-4 CBCS-CN88460 revealed a high correspondence and no label specific metabolite could be observed for the both labels.

Acid hydrolysis (1 KHCl, 200 2 1 h) of the convertional extract of intermediate harvest was performed in order for analyse for hydrolysable conjugates. Comparison of metabolic profiles before and after hydrolysis indicated cleavage of the identified conjugates BCS-CN88460-hydroxyphenyl-Gluc-MA, BCS-CN88460-2-propagol-Glyc-MA BCS-CN88460-propagol-Glyc-MA and BCS-CN88460-hydroxyphonyl-GPc-MA to less polar compounds. Snalogous hydrolysis experiments were performed in the parallel study with the pyrazole-label showing good accordance with the current study.

As metabolic reactions, hydroxylation in position 1 or 2 of the propyl group of the phenyl ring followed by conjugation with becose and majoric and the hydroxylation in position 4 of the phenyl moiety followed by conjugation with hexose and matonic acid were observed.

preny morely romoved by consequence with hexose and matonic acid were observed. Based on these results, the degradation behavior of [phenyl-UL-¹⁴C]BCS-CN88460 in oilseed rape is adequately understood and is proposed.



#### I. Materials and Methods

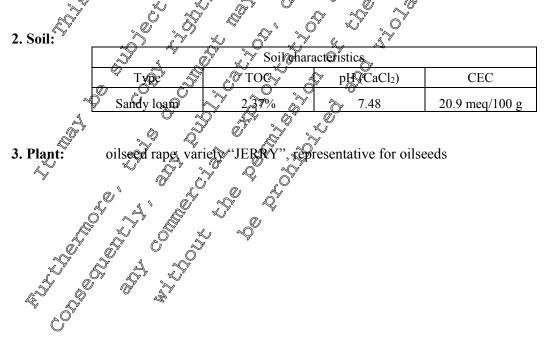
#### A. Materials

#### 1. Test Material: $H_3C$ CH₁ F Chemical structure $H_{2}$ *denotes the position of the ¹⁴C-label Radiolabel position [phenyl-UL-14 2.07 MBq/mgC Specific radioactivity > 98% Radiochemical purity > 98% Chemical purity

#### Formulation of the test compound,

The test compound was diluted as \$50:50 mixture of radiolabelled and fon-radiolabelled test compound resulting in calculated a final specific activity for the test item of 2.07 MBg/mg. A stock solution of the test compound was prepared by dissolving the test compound in acetonitrile. The purity in the stock solution for both applications and the identity of the jest compound in the application dilutions was checked by HPLE with radiodetection and was above 98%

The test compound was formulated as an EC 50 for the experiment and therefore [phenyl-UL-14C] BCS-CN88460 was dissolved in adetonitrile. For eachoof the two spray dilations, adequate parts of the stock solution were transferred into glass vials and evaporated to drypess. Blank formulation was added and the mixtures were homogenised using a magnetic stirrer. The sample was then adjusted 100 mL of the spray diffetion and homogenised by stirring. with water to a final olume of





#### **B. Study Design**

#### **1. Experimental conditions:**

The experiment was conducted with oilseed rape plants (variety: JERRY) at the rate of 275 seeds per m² in a planting container with a surface area of 1 m². The planting container was filled with sandy loam soil. The plants were cultivated in the glass-roofed greenhouse of the gest facility and were grown similar to natural temperature and light conditions, but protected from rainfall. They were watered by pouring onto the soil in the planting containers. The plants were applied at two different growth stages (BBCH 14 and 77). For both applications the target single application rate was 60 g a.s./ha. The target rate corresponds to the anticipated maximum application rate for the use type.

For each application, the plants were treated with 100 mL of the aqueous spray dilutions using a controlled track sprayer with a flat fan nozzle. To avoid contamination of the surrounding area by drift, the plants in the planting container were endosed with a foil housing. After spraying the spray dilution onto the oilseed rape plants in the planting container, the spray device and the protective plastic foil around the planting container were rinsed with acetopitrile/water (\$72; v/v). The actual amount applied was calculated by subtracting the losses from the adioactivity in the original application solution. At the 1st application 13.0 MBc of the labelled test compound were applied, corresponding to to 6.3 mg a.s.. At the 2nd application 13.1 ABq of the labelled test compound were applied, corresponding to 6.3 mg a The actual single treatment rates were 63 and 63 g a.s./ha, corresponding to a total application rate of 26 g a s./ha. 

#### 2. Sampling:

At growth stage BBCH 30, 2 days after the first application, the RAC intermediate harvest and at BBCH 55, 40 days after the first applications the BAC forge was harvested the RACs seeds and mature plant (= rest of plant including pods without seeds) were trarvested at BBCH 89, 21 days after the 2nd application.  $\cap$ 

Intermediate harvest, forage and mature plants were sampled by cut off of the plants 1-2 cm above the soil surface. Seeds were isolated from mature plants by hand. The empty pods were combined with the ×,O mature plant somple \$ X, Ô

The total weight of each sample was determined. The samples were homogenised with liquid nitrogen using a high speed blender. The sample materials were stored in a freezer ( $\leq$  -18 °C). Aliquots of the homogenates were extracted. The actual JRR values of the samples were determined by summing up the radioactivity measured in the extracts and in the remaining solids.

# C. Analytica Procedures

### 1. Extraction:

### Conventional extraction procedure and sample clean up:

For conventional extraction of filseed rape intermediate harvest, forage, mature plants and seeds, aliquots of the comogenised samples were extracted three times with a mixture of acetonitrile/water (8/2; v/v) using a high speed blender. After each extraction step, the extracts were filtered by suction and the solids were finsed with a small mount of the solvent mixture used for extraction. The solids were dried, aliquots subjected to combustion.

The extracts were combined and subjected to a clean-up step using an SPE RP 18 cartridge, which was rinsed with methanol and water and conditioned with acetonitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitrie/water (8/2; v/v). The percolate and the rinse were combined. Less polar fractions on the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v).



 $\bigcirc$ 

Each combined percolate/rinse solution obtained from SPE purification was mixed with emulsifier and evaporated to the aqueous remainder. The final conventional extracts were analysed by HPLC with the general profiling method.  $Q_{\mu}^{\circ}$ 

#### Exhaustive extraction and corresponding clean up:

Solids from the conventional extraction of oilseed rape seeds were exhaustively extracted two times with acetonitrile/water/formic acid (50/50/1; v/v/v) under microwave existence at increased temperature (0 to 5 min increase to 120 °C, 5 to 20 min at 120 °C, 800 W). The microwave extracts were cooled down at room temperature. After each extraction step, extract and solids were filtrated by suction and centrifuged and finally the extracts were combined.

Aliquots of the combined extract were subjected to a clean-up step using a SPE RP 18 which was rinsed with methanol and water beforehand. The flow-through fraction was collected and the cartridge was rinsed with acetonitrile/water (8/2; v/v). Less polar fractions on the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v)

The flow-through fraction and the rinse obtained from SPE purplication were combined and mixed with emulsifier and evaporated to the aqueous remainder the final exhaustive extractors analysed by HPLC with the general profiling method. The extracts were stored in a freezer ( $\leq -18$  °C).

#### Release of residues upon enzymatic digestion

Solids of oilseed rape seeds after extraction were further incubated with collulase in sodium acetate buffer (0.1 M) to release radioactive residues. The solids were autoclaved in buffer (121 °C, 2 bar vapour pressure) for 2 hours. After autoclaving the sample was cooled sown at room temperature and the buffer was set to pH 5 by use of acetic acid. The solution was mixed with 100 mg cellulase and incubated for 24 hours in a stater bath at 37 °C and centeringed

Solids of oilseed rape seeds remaining after ellulas treatment were further incorated with amylase in sodium acetate buffer (0.1 M) to specifically release radioactor restrues previously assimilated to carbohydrates. The folids were antoclaved in buffer (121 °C₂ bar vapor pressure) for 2 hours. After autoclaving the sample was cooled down to 20, °C and the buffer was set to pH 5 by use of acetic acid. The solution was mixed with 50.0 for amylase (1.9 units/mg) and incobated for 24 hours in a water bath at 37 °C and certuifuge. Radioactivity in remaining solids was determined by combustion.

Release of residues upon acidic extraction with HCl:

Solids of oilseed rape seeds after enzymatic digestion with collidase and amylase (approx. 5 g) were further extracted with HCL (5 M 50 ml) to release radioactive residues. After addition of the HCl solution, the mixture was included for 60 minutes at 120°C under microwave assistance and centrifuged. Radioactively in remaining solids was determined by combustion.

Residues contained in the combined extracts obtained by acidic extraction were characterised by partitioning. Therefore, the complete extract was neutralized by addition of 10M NaOH and mixed with ethylacetate (1/1; @/v) in a separatory sunner and shaken by hand. Ethylacetate and water phase were separated. The water phase was again mixed with ethylacetate (1/1; v/v) in a separatory funnel and the procedure was repeated.

### Hydrolysis of the conventional extracts:

Hydrolysis experiments in acidic medium (1 N HCl) were conducted with concentrated conventional extract from intermediate harvest. Therefore, the final purified extract was mixed with 10 N HCl to obtain a concentration of approximately 1 N HCl and incubated 100 °C for 1 hour. Afterwards, the mixture was adjusted to pH with 10 N NaOH and analysed by HPLC.

The radioactivity in liquid samples was determined by liquid scintillation counting (LSC). Solid samples were combusted. The  $CO_2$  produced by combustion was absorbed in a  $CO_2$  absorbent/ scintillation cocktail mixture and the radioactivity was measured by LSC.

Conventional and microwave extracts were analysed by HPLC with radiodetection based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient.



#### 2. Identification and characterisation:

Metabolic profiles of all RACs were compared, as analysed by HPLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the offseed rape metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the major metabolism study with the pyrazole label in which the pyrazol spectroscopically. Parent compound was identified in oilseed rape seeds expact by TLC and HECC co-chromatography with the test compound. Metabolic profiles of oilseed rape intermediate vertes extract before and after hydrolysis were compared with corresponding profiles of the metabolism study with the pyrazole label, as analysed by HPLC.

Unknown metabolites were characterised based on their extraction and chromatograph

Report name /	Chemical Name (IUPAC)
other names/codes	Strugure and formula
Parent compound	N-(5-chloro-2-isopropylbenzyl) N-
BCS-CN88460	N-(5-chloro-2-isopropylbenzyl)-N- cyclopfopyl-2-tdifluoromethyl-5- fluoro-1-meffyl-1H-hyrazole-4-
Radiolabeled reference:	
M-00002258 S1000	
, Ø	

#### Table 6.2.1-31: List of reference compound

## 3. Storage stability

All conventional extraction experiments of the raw agricultural commodities were performed within two months after hadvest of the offseed rape samples. The exhaustive extraction of seeds was performed within three months after harvest? All first quantitative analyses by HPLC of the conventional extracts were performed within one day after the state of extraction. For the exhaustive extract of seeds, not showing any ratiosignal above the background noise, first HPLC analysis was performed within ten days after start of the extraction and degradation due to microwave treatment could be excluded

It was therefore concluded, that the residues in the samples were sufficiently stable during the

It was therefore concluded, that the residues in the samples were sufficiently stable during the experimental period of the study and that the chomatograms represented the metabolic pattern in the samples at harvest.



#### II. Results and Discussion

The metabolism of [phenyl-UL-¹⁴C]BCS-CN88460 in oilseed rape was investigated after two spray applications. Oilseed rape plants were treated with [phenyl-UL-¹⁴C]BCS-CN88460 formulated as an EC 50 at BBCH 14 (trifoliolate on the 3rd up to 5th node unfolded) and BBCH 77 (70% of pods have reached final size). The actual single application rate corresponded to 63 and 63 g a.s./ha which was slightly above the anticipated maximum application rate (2 x 60g a.s./ha). The total application rate amounted to 126 g a.s./ha.

The TRR values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solids. The residue levels are shown in ing active substance equivalents per kg sample material (mg a.s.equiv./kg or simplified mg eg/kg).

TRR values in intermediate harvest and mature plans were high and amounted to 3.295 mg eq/kg and 3.934 mg eq/kg, respectively. The TRR in forage and seeds were low and amounted to 0.008 mg eq/kg and 0.126 mg eq/kg.

The high TRRs found for intermediate harvest and mature plants are due to havest shortly after the first foliar application (PHI = 2 d) in case of intermediate harvest or due to sampling after two foliar applications in case of mature plants. For forage, the low TRR can be ascribed to the increase of plant mass from the 1st foliar application at BBCH 14 to sampling 40 days after 1st application at BBCH 55.

C1108400			)
Matrix 😽	Diming and Application	CHI (days)*	ppm (=mg eq/kg)
Intermediate Harvest	Spray application at BBCH 14, Y OY	°≈>2	3.295
Forage	3 g a Sha	<i>∞</i> 40	0.008
Mature Plants	Spray applications at BBCH 14 and BBCH 77,	21	3.934
Seeds	$\beta$ and $6\beta$ g a.s. $\beta$	21	0.126

Table 6.2.1- 32: TRR values in oilseed rape matrices after tollar application of [pbenyl-UL-14C]BCS-CN88460

* PHI: preharvest interval (corresponds to days after last treatment (DAT) st harvest/sampling)

Intermediate harvest was conventionally extracted three times with acetonitrile/water mixtures releasing 99.7% of the TRR (3.285 mg eq/kg) Losses during sample clean up accounted for 0.1% of the TRR (0.004 mg eq/kg). After concentration and purification steps 99.6% of the TRR (3.281 mg eq/kg) were analysed. The post extraction solids amounted to 0.3% (0.010 mg eq/kg) of the TRR, only.

Forage was conventionally extracted three times with acetonitrile/water mixtures releasing 77.3% of the TRR (0.006 mg eq/kg). No losses of RA occurred during sample clean up and 77.3% of the TRR (0.002 mg eq/kg), only.

Mature plants were conventionally extracted three times with acetonitrile/water mixtures releasing 96.2% of the TRR (3.786 mg eq/kg). Lesses during sample clean up accounted for 0.2% of the TRR (0.010 mg/q/kg) After concentration and purification steps 96.0% of the TRR (3.776 mg eq/kg) were analysed. The post extraction solids contained 3.8% (0.148 mg eq/kg) of the TRR.

Seeds were conventionally extracted three times with acetonitrile/water mixtures releasing 73.6% of the TRR (0.093 mg eq/kg). No losses of RA occurred during sample clean up and 77.3% of the TRR (0.093 mg eq/kg) were analysed. The post extraction solids after conventional extraction accounted for 26.4% of the TRR (0.033 mg eq/kg).



The PES of seeds were subjected to exhaustive extraction under microwave support. This treatment released 10.6% of the TRR (0.013 mq eq/kg). Losses during sample clean up accounted for 1.0% of the TRR (0.001 mg eq/kg) and 9.6% of the TRR (0.012 mg eq/kg) were analysed by HPL C. Additionally, the solids remaining after exhaustive extraction were incubated consecutively with cellulase and amylase to release further residues. These extractions released 1.3% of the TRR® (0.002 mg eq/kg).

Subsequent acidic extraction additionally released 7.9% of the TRR (0.010 mg eq/kg). Losses areas during neutralization of the acidic extract accounted for 1.4% of the TRR (<0.001 mg eq/kg). The neutralized extract was further characterised by partitioning with ethylacetate. 4.4% of the TRR (0.007 mg eq/kg) was detected within the ethylacetate fraction and 2.1% of the TRB (0.002) mg eq/kg) was detected in the water phase.

In total 93.5% of the TRR (0.118 mg eq/kg) was extracted from seeds Total Asses of RA accounted for 2.4% of the TRR (0.001 mg eq/kg). The post extraction solids amounted to 6.5% (0.008 mg eq/kg) of the TRR. The distribution of the radioactive residues is shown in the following table. 

Table 6.2.1- 33:	Distribution of r applications of [	adioactivity in	the extracts of	oilseed rape	matrices at	ter two foliar
	applications of [	phenyl-@L- ¹⁴ C]	<b>B</b> ČS-CN8846		S S	ž . L

	Q.	~	^	$\sim$	<u> </u>			
	intern A har	rediate veșt	der der	age	mature	plants	sec sec	eds
TRR $[mg eq/kg] =$	N° &	3.295	L,	0.00		<i>\$</i> 3.934		0.126
Compound	©% TR <b>®</b> ″	mg eq/kg	<b>X</b> TRR	mg eq/kg	% RR	mg eq/kg	[₽] % TRR	mg eq/kg
Conventional extraction	<b>99.7</b>	3.285	77,3	<b>\$</b> 006			73.6	0.093
Analysed extracts	\$99.6 0 A	<i>©</i> 3.28⊄	07.3	v _≫ 0.006	96.0 00.2	sz,776	73.6	0.093
Not analysed	10° Q	0@04	🔊 n.q.	🖉 n.q.	00.2	%0.010	n.q.	n.q.
Exhaustive extraction	V . ))-	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	AÔ	, <u> </u>	"(, <del>-</del>	7,	10.6	0.013
Analysed extracts	~~~- ~~~~		X ^¥-	²	Ø, A	ý	9.6	0.012
Not analysed			~~~-~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~				1.0	0.001
Enzymatic digestion	ю. —	×	. Ŷ	Ъ.	_@		1.3	0.002
Acidic Extraction and partitioning	- ²	A	6 ⁷ _ ⁰		~		7.9	0.010
<b>partitioning</b> Ethylacetate phase	. 0 ^y	°, 6°			P`		4.4	0.007
Water phase		, O ^V	L, - K				2.1	0.003
Water phase Not analysed	Ű, Ö		ØŬ O	~			1.4	< 0.001
Total extracted	<b>\$99.7</b>	<b>@ 3.285</b>	<i>A</i> 7.3		96.2	3.786	93.5	0.118
Post extraction folids	Č Į3	0,910	Ø C	° 0.002	3.8	0.148	6.5	0.008
Balance	100.0	3.295		0.008	100.0	3.934	100.0	0.126
not appreable	Q		۶.					

n.q. not quantified (< 400Q) * no individual peak above detection fimit was observed in the HPLC chromatogram of the exhaustive extract of seeds

Comparison of chromatograms from conventional extracts of intermediate harvest and mature plants of the cuffent stady among themselves indicated a high grade of comparability. Conventional extract of forage contained to individual radiosignal above the background noise whereas conventional extract from Breeds contained only the test compound.

The comparison of profiles of all RACs to corresponding profiles of the parallel study performed with  $[pyraz@e^{-4-14}C]BCS-CN88460$  revealed that no label specific metabolism could be observed.

In conventional extracts from intermediate harvest 94.0% of the TRR (3.096 mg eq/kg) were identified in total. The parent compound was the major component representing 84.1% of the TRR



(2.770 mg eq/kg), whereas the metabolites BCS-CN88460-hydroxyphenyl-Gluc-MA (M23), BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M24) represented 2.3, 1.6, 2.2 and 3.8% of the TRR corresponding to 0.077, 0.052, 0.071 and 0.126 mg eg/kg, respectively.

6 Acid hydrolysis (1 N HCl, 100 °C, 1 h) of the conventional extract of intermediate harvest was performed in order to analyse for hydrolysable conjugates. Comparison of metabolic profiles before and after hydrolysis indicated cleavage of the identified conjugates BCS-CN88460-hydroxyphonyl-Gluc-MA, BCS-CN88460-2-propanol-Glyc-MA, BCS-CN88460-propanol-Glyc-MAO and BCS-CN88460-hydroxyphenyl-Glyc-MA to less polar compounds. Analogous/hydrolysis experiments were performed in the parallel study with the pyrazole-laber showing good accordance with the current study.

In conventional extracts from forage 77.3% of the FRR was analysed on total (0.006 mg eq/kg). No individual radiosignal was above the background noise due to very low amounts of total radioactive ingredients in the extract. Ò

In conventional extracts from mature plants 84.4% of the TRB (3.318 mg eq/kg) were analysed in total. The parent compound was by far the major component representing 72.0% of the PRR (2.831 mg eq/kg), whereas the metabolites BCS-CN88460-hydroxyphenyl-Glue, MA (M23) BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460 propanol-Glyc-MA (M22) and BCS-CN88460-hydroxyphenyl-Glyc-MA (M2A) represented 2.2, 4.6, 2.5 and 3.18 of the TRR corresponding to 0.087, 0.181, 0.097 and 0.122 mg eqkg, respectively. °~

In conventional extracts from seeds 73.6% of the TRR (0.093 mg/eq/kg) were dentified. The parent compound was the only component representing 73.6% of the TER (0.093 mg eq/kg). Parent compound was identified by HPIC and FLC &-chromatography with the rest item as radiolabelled reference compound.

Exhaustive extraction of seeds released further 100 % of the TER (0.043 mg 2q/kg) and 9.6 % of the TRR (0.012 mg eq 12) were analysed by HPLC. No individual radiosignal was above the background noise due to low amounts of total radioactive ingredients in the exhaustive extract. Conventional extract of seeds treated under microwave extraction conditions in comparison of the corresponding conventional extract and exhaustive extract, showed that degradation of parent compound by this

The TRR and the distribution of parent and metabolites in oilseed rape matrices are shown in the following table.



Table 6.2.1- 34:	Distribution of parent compound and metabolites in the extracts of oilseed rape
	matrices after two foliar applications of [phenyl-UL- ¹⁴ C]BCS-CN88460

	intermediate harvest		for	age	mature plants		see	ds &	<i>S</i>
TRR [mg eq/kg] =	nai	3.295		0.008		3,934		6 0.126	7
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg e@kg	
Conventional extraction	99.7	3.285	77.3	0.006	96.2	3.876	<b>Z</b> 32.6	0.093	
BCS-CN88460	0.4.1					Į.	$\sim 0^{\circ}$	6 000	Q
(parent compound)	84.1	2.770	n.d.	n.d.	72.0	2.831	×/3.6°	rs 0.025	
BCS-CN88460-				T	Į (		Q~ Q	¢ "Qʻ	
hydroxyphenyl-Gluc-MA (M23)	2.3	0.077	n.d,	n.d.	Ő 2.2	0.08Z	Qn.d.	n.d	Ů V
BCS-CN88460-2-	1.0	0.052	Å	1	Å. #6		o n.¢		
propanol-Glyc-MA (M22)	1.6	0.052	Q ⁴ .d.	n.d	¢ ¢	<b>R</b> 181.	O'n.d	@.d.	
BCS-CN88460-propanol-	2.2	0.071	ý	ຄໍ ລີນ	× ×		* * * .d.	s in the second	
Glyc-MA (M21)	2.2	0.071		n.a.	2.5	0.097	n.a.	, [~] n.d.	
BCS-CN88460-		.4			0.0		ó j		
hydroxyphenyl-Glyc-MA (M24)	3.8	0.426	°∼yn.d,	nd,	3.1	0.122	n.e.	n.d.	
Total identified	94.0	.03.096	n dł.	. "	× 84.Å	3.848	\$73.6	0.093	
Unknown 1	n.d.	n _n	°~µ.d.	N n.d		.004	S n.d		
Unknown 2	0.4	0,004	n.d.	n de	0.1	۵.00 <b>3</b>	p void.	n.d.	
Unknown 3	n.d.	n.d.	🔗 n.¢.	and.	S 0.1	0.004	n.d.	n.d.	
Unknown 4	~.0.1	`≫0.003	n.e.	√_ n.d.	n.d.	P.d.	n.d.	n.d.	
Unknown 5	[∞] 0.2	0.000	""n.d.	n da	~ ~0.2	<b>Ø</b> .006	n.d.	n.d.	
Unknown 6	õ 0.C	0.003	n.d.	n.d.	∽Sn.d.	N n.d.	n.d.	n.d.	
Unknown 7	N.d.	Qn.d.	s nas	gr.d.	[∞] 0.1	0.9005	n.d.	n.d.	
Unknown 8	Ø.1	0.004 ي		», O'n.d.	🤌 n.d.	∾_ ¶.d.	n.d.	n.d.	
Unknown 9	® 0.2	0.0007	"Sh.d.	🔊 n.d.		LØ.008	n.d.	n.d.	
Unknown 10	L n.O		[∞] ″n.d∉	n.d. p@d. pr.d. n.d.	e <0.1	<i>a</i> . 0.001	n.d.	n.d.	
Unknown 11	D n.d.	n.d.	n ng	, An.d.	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.002	n.d.	n.d.	
Unknown 12 Unknown 13	[*] %0 1	[©] 0.004	n/d.		<b>₩</b> ∛ 0.1	0.003	n.d.	n.d.	
Unknown 13 🖉 🖉		^O ntel.	© n.d.	🖉 n.af	° _@0.2	0.008	n.d.	n.d.	
Unknown 14	~~~ 0Ø	<u>Ø</u> 003	مُنْ n.d	n.d.	≪n.d.	n.d.	n.d.	n.d.	
Unknown 🗗	and.	Ø n.d.	n_d.	"n.d.	0.2	0.006	n.d.	n.d.	
Unknown 16	s Sn.d.	n_d,	().d.	≪∛ n.d.	O 0.1	0.003	n.d.	n.d.	
Unknown 17	<u>گر</u> آگر	J 0.611	<b>n.d.</b>	n d.	0.1	0.004	n.d.	n.d.	
Unknown 18	n d.	^m.d.	, 🔊 n.dC	n.d.	0.1	0.003	n.d.	n.d.	
Unknown 19 🛛 🖗	Ø.3	0.010	p.d.	n.d.	0.1	0.002	n.d.	n.d.	
Unknown 20 Unknown 21	n.d.	Ů nod ≱ m≥d.	ത്ര	‴ov n.d.	0.1	0.004	n.d.	n.d.	
Unknown 21 🆓 🔍	O n.d.	nxd.		n.d.	0.1	0.003	n.d.	n.d.	
Unknown 2		<b>0</b> .010	n.d	n.d.	0.2	0.009	n.d.	n.d.	
Unknown 💯 🕺 👘	On.d.	0° n.d	, n,d.	n.d.	0.2	0.008	n.d.	n.d.	
Unknown ² 24	[♥] 0.1	0.004	JI.u.	n.u.	n.d.	n.d.	n.d.	n.d.	
Unknewn 25 🔬		0.007	n.d.	n.d.	0.8		n.d.	n.d.	
Unknown 21 Unknown 22 Unknown 23 Unknown 24 Unknown 25 Unknown 26 Unknown 27 Unknown 28 Unknown 29 Unknown 32 Unknown 32 Unknown 36 Unknown 36 Unknown 37 Unknown 36 Unknown 37 Unknown 37 Unknown 38 Unknown 40	p*?4	0%012	$0^{\circ}$ n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Unknown 27	×0.1	© 0.003 S 0.005	⊮ n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Unknown 28	0.1	0.005	n.d.	n.d.	1.0		n.d.	n.d.	
Unknown 29		0.005 0003 n.d.	n.d.	n.d.	0.1	0.004	n.d.	n.d.	
Unknown 32	nd.	n.d.		n.d.	0.7	0.026	n.d.	n.d.	
Unknown 33		0.022	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
Unknown 36	₩ 0.4	0.013	n.d.	n.d.	0.6	0.024	n.d.	n.d.	
Unknown 37 O	n.d.	n.d.	n.d.	n.d.	0.3	0.014	n.d.	n.d.	
Unknown	n.d.	n.d.	n.d.	n.d.	0.1	0.002	n.d.	n.d.	
Unknow 1239	n.d.	n.d.	n.d.	n.d.	0.1	0.005	n.d.	n.d.	
Unknown 40	n.d.	n.d.	n.d.	n.d.	0.2	0.007	n.d.	n.d.	l

continued on next page



Table 6.2.1- 34	continued
-----------------	-----------

	interm harv		for	age	mature	plants	see	eds o
Unknown 41	n.d.	n.d.	n.d.	n.d.	0.1	0.004	n.d.	<u>∘</u>
Unknown 42	n.d.	n.d.	n.d.	n.d.	0.2	0.Q08	n.d.	6 n.d.
Unknown 43	n.d.	n.d.	n.d.	n.d.	0.2	0.007	n.d	0 <u>1</u> 00.
Unknown 44	n.d.	n.d.	n.d.	n.d.	0.6	0.023	n.d.	∽, Sn.d.
Unknown 45	0.2	0.007	n.d.	n.d.	1.3	0.050 کے	æd.	~~ n.d.
Unknown 46	n.d.	n.d.	n.d.	n.d.	0.7	0.026 ^(۲)	°∼ n.d.	n d
Unknown 47	0.1	0.003	n.d.	Ön.d.	0,9	0.035	n.d.	nd.
Unknown 48	0.1	0.004	n.d.	n.d.	Q.2	0.009	n no.	🔊 🔊 🤊 🤊 🖉
Unknown 49	n.d.	n.d.	n.d.	🖌 n.d.	0 <u>0</u> .1	0.003	Q.d.	$\sim$ n.d $\sim$
Unknown 50	n.d.	n.d.	n.d	n.d.	$\hat{Q}^{\vee}$ 0.3	• 0. <b>Q</b> }3	n.d.	C n C
Unknown 51	1.2	0.038	nod.	n.d,	Å b∮	6Q038	, ⊙ [≫] n.d	p.d.
Characterised by HPLC	5.6	0.185	ي n.d.	o n.e.	×11.6	0.458	\$ \$ *	S
Total not analysed of conventional extraction	0.1	0.004		~~-	Q 0.2	0.010	0 - 4 0	
Exhaustive extraction		5	.~~ ~~	S' Ö	- Ç,	<u>, О.</u> -ж	J 10.6	<b>Ø</b> .013
Analysed by HPLC*			\$~ <del>*</del>	· ·~~-	, O`	N À	£9.6	0.012
Not analysed			5 . T	~~~·	0		L 1.0	0.001
Enzymatic digestion			° 'Y		X X-	õ	Ĵ, <b>K</b>	0.002
Acidic extraction and partitioning	) D	ار ار ا	8-4		ý		۶.9 <u>کې ۲.9</u>	0.010
<i>Ethylacetate phase</i>	⁽		×		( ⁰ , ⁰ , ⁰	~ ø	0 <u>4.4</u>	0.005
Water phase	~		Ø	·0*	~~~-	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Q 2.1	0.003
Not analysed by partition	N A	⁶	S &	× 6 ⁹	«	<u>5</u> <u>5</u>	1.4	0.002
Total characterised**	\$5.6	0.185	<u> </u>	V	0 15.6	Q.458	19.8	0.025
Total extracted	<i>"</i> 99,7		77.3	് 0.000	96.2	<i>a</i> , <b>3.786</b>	93.5	0.118
Post extraction solids (PES)	0.3	ي 0.010	2207	0.002	3.8	0.148	6.5	0.008
Accountability	<b>√100.0</b>	3.295	<b>\$0</b> 0.0	0.008	100.0	3.934	100.0	0.126

* no individual peak above detection limit was observed in the HPLC chromatogram of the exhaustive extract of

In conventional extract of intermediate hareest, 23 unknown metabolites were characterised, individually accounting for equal or tess than 1.2% of the TRR and 0.038 mg eq/kg and 39 were characterised in mature plants individually accounting for equal or less than 1.3% of the TRR and 0.050 mg eq/kg.



Table 6.2.1- 35:	Summary of characterisation and identification of radioactive residues in oilseed rape
	matrices after two foliar applications of [phenyl-UL- ¹⁴ C]BCS-CN88460

								_ • _	
		nediate rvest	forage		mature plants		seeds		Ô
TRR [mg eq/kg]		3.295		0.008		3.934		0.126	F
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq Rg	
Conventional extraction	<b>99.</b> 7	3.285	77.3	0.006	96.2	[®] 3.786	73,6	0.093	
BCS-CN88460 (parent compound)	84.1	2.770	n.d.	n.d.	72,0	2.831	SQ3.6	© 0.093	2
BCS-CN88460-hydroxyphenyl- Gluc-MA (M23)	2.3	0.077	n.d	n.d.	2.2	0.087	n.d	Ød.	L
BCS-CN88460-2-propanol-Glyc- MA (M22)	1.6	0.052	jr.d.	n.d	<b>4.6</b>	0581	Q.d.	n.d.	0
BCS-CN88460-propanol-Glyc- MA (M21)	2.2	0.07	n.d.	∼n,d.	2.5	Q0.097	∫ n.¢	@.d.	
BCS-CN88460-hydroxyphenyl- Glyc-MA (M24)	3.8	0526	Pn.d.	n.da	, 3 ×	0,022	n.d.	n.d.	
Total identified	94.0	₹3.096	õ{	ý Q-	, 84.4	3.318	O 73.6	0,093	
Characterised in the conventional extract by HPLC	5.6	0.185	<u>_</u>		× 11.6	0,458	- Z		
Number of unknown peaks	<u> </u>	23 🌾 🚬	Q Å	¢ °		39	Ø r		
Largest unknown peak	1.2	0.038	×	~~-~~	Õ 1.3	° 0.056			
Total not analysed of conventional extraction	્રે	0.004	- ²		<b>60</b>	4,910	&		
Exhaustive extraction	«. —			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ŝ <del>-</del>	© 10.6	0.013	
Analysed by HPLC*	O,		 		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		9.6	0.012	
Not analysed			, O		l de la companya de l	- A	1.0	0.001	
Enzymatic digestion 🖉 🚿	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			y <u>o</u> y-	×	·- 🛠	1.3	0.002	
Acidic extraction and Partitioning	Ĵ, ž		,	,	y je	,	7.9	0.010	
Ethylacetate phase 🔬 🗳	" &	A	~		\$		4.4	0.007	
Water phase S	°	Ÿ ∂			<i>a,</i>		2.1	0.003	
Not analyzed by			ð	2	8		1.4	<0.001	
Total characterised**	3.6	0.185	Ő ^v -×		11.6	0.458	19.8	0.025	
Total extracted 🔬 🧳	<b>99.7</b>	O ^v 3.285	19,3	<b>∕⊕</b> .006	96.2	3.786	93.5	0.118	
Post extraction solids (PES)	Ç 03	0.910	22.7	<u>گ</u> 0.002	3.8	0.148	6.5	0.008	
Accountability	100.0	ð <b>3.29</b> 5	\$100.0	0.008	100.0	3.934	100.0	0.126	

* no individual peak above detection fimit was observed in the HPLC chromatogram of the exhaustive extract of seeds

seeds **by chromatographic and/or extraction Chavior n.d. not detected -- Aut applicable

## **III.** Conclusions

The metabolism of BCSCN88460 in Silseed rape was investigated after two foliar applications at BBCH 1 and BBCH 7. The oilseed rape plants were treated with [phenyl-UL-14C]BCS-CN88460 formulated as an EC 30 at a single application rate of 63 and 63 g a.s./ha for the first and second spray application, desperifyely, corresponding to a total application rate of 126 g a.s/ha. The oilseed rape intermediate harvest was harvested at BBCH 30, 2 days after the first application and forage was harvestee at BBCH 55, 40 days after the first application. Mature plants and seeds were harvested at BBCH 89, 21 days after the second application.



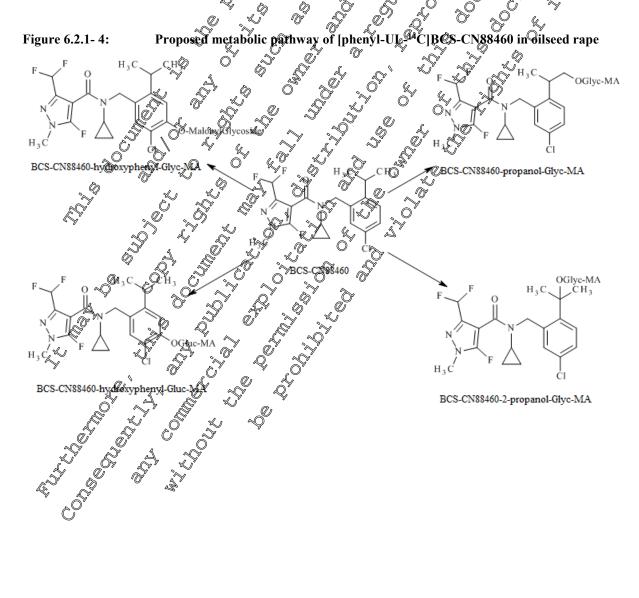
Residues in forage and seeds were significantly lower than those in intermediate harvest and mature plants. The extraction rates of intermediate harvest, forage, mature plants and seeds were high. Overall, identification rates for intermediate harvest, mature plants and seeds were high. Parent compound BCS-CN88460 was the main residue component in intermediate harvest and mature plant and the only component in seeds. Conventional extract of forage contained no residues above the limit of detection of the analytical method.

Besides parent compound, four metabolites were identified in intermediate harvest and mature plants: BCS-CN88460-hydroxyphenyl-Gluc-MA (M23), BCS-CN88460-2-propanol-Glyc-MA (M22), BCS-CN88460-propanol-Glyc-MA (M21) and BCS-CN88460 hydroxyphenyl-Glyc-MA (M24). The results in the present study are in good agreement with the results with the prazole-label. No label specific metabolites were observed.

The test compound [phenyl-UL-¹⁴C]BCS-CN88460 was moderately metabolised in obseed rape after two foliar applications. The main metabolic reactions observed were:

- Hydroxylation in position 1 or 2 of the propyl group of the phenyl ring followed by conjugation with hexose and malonic acid
- Hydroxylation in position 4 of the phenyl molecy followed by conjugation with hexose and malonic acid

Based on these results, the degradation behavior of phenoi-UL C]BCS-CN88460 in oilseed rape is adequately understood and a metabolic pathway is proposed in the figure below.





#### Metabolism, distribution and expression of residues in soybean (foliar spray application)

Metabolism studies in soybean after foliar application were conducted with [pyrazole-4-¹⁴C] and [phenyl-UL-¹⁴C]BCS-CN88460.

Plant	Application	Target application rate	BBCH Code	Reference
soybean	three foliar spray applications, pyrazole- labelled isoflucypram	3 x 60 g a.s./ha	BBCH∜51 an¢ BBCH¥51 an¢	M-609373-0051
soybean	three foliar spray applications, phenyl-labelled isoflucypram	3 x 60 g a.s./by	BBCH 14, BBCH 51 and BBCH 85	M-660376-06-1

Table 6.2.1- 36:	Overview over available soybean metabolism studies
1 4010 0.2.1 00.	over view over available soybean metabolism studies

# Summary of metabolism in soybean (Toliar spray application)

The metabolite pattern corresponds well when comparing the two metabolism studies in soybean after foliar application. Parent compound BCS-CN88460 was the main residue component in soybean straw and soybean seeds and a major residue in soybean forage and hay Parent component in soybean straw component in soybean seeds. BCS-CN88460 was moderately metabolised in soybean forage, hay and straw samples after three post-emergence applications. The main metabolic reactions were defluorination at position 5 of the ovrazole ring followed by conjugation with homoglutathione and degradation of the homoglutathione mojety followed by conjugation with malonic acid or degradation and desamination to mercapto lactic acid group and hydroxylation of the benzyl moiety or of the propyl group were observed. Furthermore glycostiation was clearly observed at the mercapto lactic acid group.

Besides parent compound, the following metabolites were identified BCS-CN88460-desfluoromercapto-lactic acid-popyl-OH-Glyc (M48), BCS-CN88460 desfluoro-homoGSH (M44), BCS-CN88460-desfluoro-piercapto-lactic acid-OH (N46), BCS-CN88460 desfluoro-mercapto-lactic acid-Glyc (M47) and BCS-CN88460 desfluoro-CySMA (M45).

Report: KCA 6 2/07; , , , 2017; M-60073-01-1
Title:
Report No.: $\sqrt{514.91089}$ $\sqrt{514.91089}$
Document No.: Mc609372-01-1
Guideline(str UECD Dest Guideline No. 50 K
Commission Regulation (EU) No 283/2013 in accordance with Regulation (EC)
No.4107 /2009 USEPA OCSPP Dest Ghadeline No. 860.1300
JAP FAMIC-ACIS Notification 12 Nousan 8147
Guideline deviation(s): $\sqrt{none} \mathcal{O}_{1}^{V} = \sqrt{\mathcal{O}_{2}^{V}}$
GLP/GEP: Vest vest
Executive Summary

The metabolism of BCS CN88460 was investigated in soybean plants after three post-emergent spray applications. For each of the three foliar applications, the test item [pyrazole-4-¹⁴C]BCS-CN88460 was formulated and applied as aqueous EC 50 using a nominal application rate of 60 g a.s./ha each. The actual single application rates corresponded to 59, 57 and 65 g BCS-CN88460/ha resulting in a total actual application rate of 181 g a.s./ha.



Soybean forage was harvested at BBCH stage 49 after the first application (PHI = 5d), hay at BBCH stage 77 after the 2nd application (PHI = 39d) and straw and seeds at BBCH stage 96, 21d after the 3rd application. The radioactive residues of soybean forage, hay, straw and seeds were determined by summing up the extractable and unextractable radioactivity. Soybean seeds contained significantly lower residue amounts than forage, hay and straw. The total radioactive residue (TRR) in soybean straw was highest and amounted to 17.715 mg eq/kg. The TRR in soybean forage and soybean hay were high and amounted to 4.371 mg eq/kg and 4.679 mg eq/kg, respectively. The TRR in seeds was low and amounted to 0.035 mg eq/kg.

Homogenised plant material from RACs was conventionally extracted with acetonititle/water mixtures. Overall, the extraction rates after conventional extraction of soybean forage, hay straw and seeds were high and amounted to 92.1, 87.4, 94.1 and 87.7% of the TRR (4.026, 4.096, 16.669 and 0.031 mg eq/kg), respectively. Exhaustive extract of soybean forage, hay and straw increased the extraction rate slightly: 5.1% of the TRR (0.222 mg eq/kg), 6.9% of the TRR (0.321 mg eq/kg) and 2.5% of the TRR (0.441 mg eq/kg) were released by this treatment, respectively.

The post extraction solids after conventional and chausive explacing accounted for 2.8% of the TRR (0.123 mg eq/kg), 5.7% of the TRR (0.266 mg eq/kg), 3.4% of the TRR (0.609 mg eq/kg) and 12.3% of the TRR (0.004 mg eq/kg) for solvern forage, hay, graw and seeds, respectively.

Residues in the conventional extracts of all RACs and in the extractive extracts of torage and straw were analysed and quantified by HPLC. The parent compound and metabolites were either identified by co-chromatography with the reference compound or by spectroscopic analysis in isolated fractions fractions from the conventional extract of soybean hay Additionally, the metabolite pattern and retention times of the current and the soybean metabolism study with the phenyl label over compared.

Profiles of forage, hay and straw showed a high grade of comparability among the selves concerning metabolization of the test item whereas the extract from soybean seeds contained only the parent compound.

The comparison of metabolic profiles of conventional extracts of all RACs with those of a parallel study with [phenyl-UIO⁴C]BCS-CN88460 revealed a high grade of comparability of the metabolization of the test compound in soybean and no label specific metabolite could be observed for the both labels

A major component in all RACs was the test compound BCS-CN88460 accounting for 18.7% of the TRR (0.899 mg eq/kg) in soybean forage, 10.4% of the TRR (0.487 mg eq/kg) in soybean hay, 64.5% of the TRR (11.424 mg eq/kg) in soybean straw and 76.6% of the TRR (0.027 mg eq/kg) in soybean seeds. Besides parent compound to other metabolite ons detected in the extract of soybean seeds.

Besides parent comported five metabolites were identified soybean forage, hay and straw.

BCS-CN88460-desfluoro percapto-lactic acid-propyl OH-Glyc (M48) accounted for 3.4, 15.2 and 3.9% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.147, 0.711 and 0.690 mg eq/kg, respectively BCS-CN88460-desfluoro-homoGSH (M44) accounted for 22.9, 7.8 and 4.8% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.997, 0.366 and 0.857 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M46) accounted for 9.5, 3.2 and 1.9% of the TRR in extracts from soybean forage, hay and straw, corresponding to 0.415, 0.151 and 0.357 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M46) accounted for 9.5, 3.2 and 1.9% of the TRR in extracts from soybean forage, hay and straw, corresponding to 0.415, 0.151 and 0.357 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc (M47) accounted for 3.0, 1.1 and 3.0% of the TRR in extracts from soybean forage, hay and straw, corresponding to 0.129, 0.520 and 0.533 mg eq/kg, respectively. BCS-CN88460-desfluoro-Cys-MA (M45) accounted for 9.2, 15 0 and 4.6% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.400, 0.723 and 0.828 mg eq/kg, respectively.

Overall, identification rates were sufficient and amounted to 66.6% of TRR for forage, 63.2% of TRR for hay \$2.8% of the TRR for straw and 76.6% of TRR for seeds. In soybean forage, hay and straw, 17, 13 and 20 unknown metabolites were characterised in the extracts by their chromatographic behaviour, individually accounting for less than 3.9% of the TRR (0.171 mg eq/kg), 4.4% of the TRR (0.208 mg eq/kg) and 1.9% of the TRR (0.329 mg eq/kg) for forage, hay and straw, respectively.



All initial profiles of conventional extracts of the raw agricultural commodities were performed within 6 months after harvest. Furthermore, storage stability of residues in stored sample matrix and extracts could be demonstrated exemplarily for soybean hay and straw for 18 and 27 months, respectively in the course of a parallel study with the phenyl-label which showed a high grade of comparability of the metabolic profiles of the individual RACs.

As metabolic reactions, de-fluorination at position 5 of the pyrazole ring followed by conjugation with homoglutathione and degradation of the homoglutathione moiety followed by conjugation with malonic acid or degradation and desamination to mercapto lactic acid group and hydrox lation of the benzyl moiety or of the propyl group were observed. Furthermore glycosilation was clearly observed at the mercapto lactic acid group.

Based on these results, the degradation behavior of [pyrazole-44] C]BCS-CN88460 B soybean adequately understood and a pathway is proposed.

	I. Materials and Methods
A. Materials	I. Materials and Methods 7 7 7 7 4
<b>1. Test Material:</b>	
Chemical structure	
Radiolabel position	[pyrázole-4 ^T C]
Specific radioactivity	4.22 MBc/mg & & &
Radiochemical purity	>98% (HPLC) ~ ~ ~ ~ ~
Chemical purity	\$ 99% \$ \$ \$ \$
Chemical purity	

Formulation of the test compound

A stock solution of the test compound was prepared by dissolving the test compound in acetonitrile to give a concentration of about 5 mg/mL. The purity in the stock solution and the identity of the test compound was checked by HPLC with radiod aceton and was 100%

The test compound was formulated as an EC 50 for the experiment and therefore [pyrazole-4-¹⁴C] BCS-CN88460 was dissolved in acetonic le. For each of the three spray dilutions, adequate parts of the stock solution were transferred into glassolials and evaporated to dryness. Blank formulation was added and the mixtures were homogenised using a magnetic stirrer. The sample was then adjusted with water to a final volume of 50 mL (1st and 2nd application) and 100 mL (3rd application) of the spray dilution and homogenised by stirring.

2. Soils		7		
le la	Ĩ,	Soil chara	acteristics	
Ċ	Туре	TOC	pH (CaCl ₂ )	CEC
	Sandy loam	2.1%	7.23	15.5 meq/100 g



**3. Plant:** soybean, variety "Amandine", representative for oilseeds

#### **B. Study Design**

#### 1. Experimental conditions:

The experiment was conducted with soybean plants (variety: Amandine) based on a plant density of 800,000 soybean plants per hectare. A planting container with a surface area of 1 m was used corresponding to the rate of 80 seeds per m². The plants were cultivated in the glass-rooted greenhouse of the test facility and grown similar to natural temperature and light conditions, but protected from rainfall. They were watered by pouring onto the soil in the planting containers. The plants were applied at three different growth stages (BBCH 14, 51 and 84). At all these growth stages the target single application rate was 60 g a.s./ha. The target rate corresponds to the anticipated maximum application rates for the use type.

For each application, the soybean plants were treated with 50 mL (d^{**} and 2nd application) and 100 mL (3rd application) of the aqueous spray dilutions using a controlled track sprayer with a flat funnoztle. To avoid contamination of the surrounding area by druft, the plants in the planting container were enclosed with a foil housing. After spraying the spray dilution onto the oilseed rape plants in the planting container were rinsed with acetonitrile/water (8/2; VV). The actual amount applied was calculated by subtracting the losses from the radioactivity in the original application solution. At the 1st application 23.9 MBq of the labelled test compound were applied, corresponding to 5.7 mg a.s., At the 3rd application 07.3 MBq of the test compound were applied, corresponding to 5.7 mg a.s., At the 3rd application 07.3 MBq of the 57 and 65 g a.s./ha resulting in a total actual application rate of 181 g a.s./ha

#### 2. Sampling:

At growth stage BBCH 49 the RAC forage, at growth stage BBCH 77 the RAC hay and at BBCH 96 the RACs straw and seeds were harvested. Plant samples were collected by cutting approximately 1-2 cm above the soft level. Plants sampled at har stage were dried in a hood for 4 days.

The total weight of each sample was determined. The samples were homogenised with liquid nitrogen using a high speed blender. The sample materials were stored in a freezer ( $\leq$  -18 °C). Aliquots of the homogenates were extracted. The actual ORR values of the samples were determined by summing up the radioactivity measured in the extracts and fit the remaining solids.

### C. Analytical Procedures

### 1. Extraction:

Conventional extraguon procedure and sample chean up:

Aliquots of the homogenised samples of soubcan forage, hay, straw and seeds were extracted three times with a maxture of acetonitrile water ( $\frac{9}{2}$ ; v/v) using a high speed blender. After each extraction step, the extracts were filtered by suction and the solids were rinsed with a small amount of the solvent mixture used for extraction. The solids were dried and aliquots were subjected to combustion and LSC.

The extracts vere combined and subjected to a clean-up step using an SPE RP 18 cartridge, which was rinsed with methanol and water and conditioned with acetonitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitrile/water (8/2; v/v). The percolate and the rinse were combined. Less polar fractions on the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v).

Each combined percolate/rinse solution obtained from SPE purification was evaporated to the aqueous



remainder. The final conventional extracts were analysed by HPLC with the general profiling method. All soybean samples and extracts were stored in a freezer ( $\leq$  -18 °C).

#### Exhaustive extraction and corresponding clean-up:

Solids from the conventional extraction of soybean forage, hay and straw were exhaustively extracted two times with acetonitrile/water/formic acid (50/50/1; v/v/v) under microwave assistance at micreased temperature (0 to 5 min increase to 120 °C, 5 to 20 min at 120 °C, 800 W). The microwave extracts were cooled down at room temperature.

For forage and hay, the individual extracts were combined and subjected to a clean up step using an SPE RP 18 cartridge, which was rinsed with methanol and water and conditioned with a acetonitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonttrile/water (8/2; v/v). The percolate and the rinse were combined. Less polar fractions on the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/1; v/v). Each combined, percolate/rinse solution obtained from SPE purification was mixed with emulsifier and evaporated to the aquecus remainder.

The exhaustive extracts of straw were directly concentrated by exaporation to the aqueous temainder. The final exhaustive extract of soybean hav was partitioned for characterisation. The final exhaustive extracts of forage and straw were analysed by HPLC with the general profiling method. The extracts were stored in a freezer ( $\leq -18$  °C).

#### Characterisation of residues by partitioning

Radioactivity released from solvean bay by exhaustive extraction under microwave assistance was characterised by partitioning. Therefore, two milliliters of the concentrate obtained during exhaustive extraction and after purification were mixed with 8 mL water and 40 mL ethylacetate in a centrifuge tube. The mixture was incubated 30 min by 150 rpm on a flatbed shaker. Four gram anhydrous magnesium sulphate, one gram sodium chloride, one gram trisodium citrate and 0.5 gram disodium citrate sesquihydrate were added to remove water and adjust the pH value. After addition of the salt mixture, the tube was immediately shaken vigorous by bands for 10 seconds and with a flatbed shaker for at least one minute and afterwards centrifuged. Huylacetate and water phase were separated, their volume was determined.

The radioactivity in liquid samples was determined by liquid scintillation counting (LSC). Solid samples were combusted. The CO₂ produced by combustion was absorbed in a CO₂ absorbent/ scintillation cocktail maxture and the radioactivity was measured by LSC.

Conventional and microwave extracts were analysed by HPLC based on reversed phase chromatography using macidie water acetometrile/THF gradient.

## 2. Identification and characterisation

For identification of radioactive ingredients in conventional extract from soybean hay, selected major radiosignals were isolated as fractions of elutent by HPLC fractionation. Isolated fractions were identified by spectroscopic analysis as following metabolites: BCS-CN88460-desfluoro-mercapto-lactic acid-prop@-OH-Glyc (M48), BCS-CN88460-desfluoro-homoGSH (M44), BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc (M47) and BCS-CN88460-desfluoro-Cys-MA(M45).

Metabolic profiles from the conventional and exhaustive extracts of all RACs were compared, as analysed by IOLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the soybean metabolism study with the phenyl label. Parent compound, was identified in the extract of soybean seeds by TLC co-chromatography with the radiolabelled test compound. Metabolites after structure elucidation in the conventional extract of soybean hay were re-assigned.

Unknown metabolites were characterised based on their extraction and chromatographic behavior.



BCS-CN88460 cycl	5-chloro-2-isopropylbenzyl)-N- lopropyl-3-(difluoromethyl)-5-	F F O H ₃ C	СКО
iterenete.	bro-1-methyl-1H-pyrazole-4-	H ₃ C C	

#### Table 6.2.1- 37: List of reference compound

#### 3. Storage stability:

The initial profiles of the conventional extracts of Soybean forage, hay, straw and seeds were analysed within 6 months after harvest of the soybean plant ray material. The stability of residues in the stored sample matrices and extracts were demonstrated in the parallel study with the phenyl label. As the profiles of the respective RACs were highly comparable between the parallel studies and no label specific metabolites were observed it was concluded, that the residues in the samples were sufficiently stable during the experimental period of the study and that the chromatograms represented the metabolic pattern in the samples at harvest.

# A II. Results and Discussion

The metabolism of pyrazole-4-14CJBCS-CN88460 in Soybean was investigated after three spray applications.

Soybean plants in a 1 m container were treated with [pyrazole-4, C]BCS-CN88460 formulated as an EC 50 at BBCH 14 (beginning of som elongation), BBCH 51 (first flower buds visible) and BBCH 84 (about 40% of pods are ripe). The actual single opplication rates corresponded to 59, 57 and 65 g a.s./ha. The total application rate amounted to 181 g a c/ha, corresponding well to the anticipated maximum application rate.

The TRR values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solids. The residue levels are shown in mg active substance equivalents for kg sample material (mg s.equip./kg or simplified mg eq/kg).

The TRR in soybean straw was high ond amounted to 17.715 mg eq/kg. Soybean forage and hay contained a TRR of 4.371 mg/eq/kg and 4.679 mg/eq/kg, respectively. The TRR determined for soybean seeds was low and amounted to 0.035 mg/eq/kg.

The residue values in the parallel study with the phenyl label were comparable for forage but significantly lower for hay, straw and seeds. This is due to differences in plant growth during cultivation of both studies regulting or vegetation differences during the second and third application.

cultivation of both studies resulting the vegetation differences during the second and third application.



	CN88400		
Matrix	Timing and Application	PHI (days)*	ppm (= mg eq/kg)°
Soybean forage	1 spray application at BBCH 14, 59 g a.s./ha	5	4.37
Soybean hay	2 spray applications at BBCH 14 and 51, 59 and 57 g a.s./ha (116 g a.s./ha, total)	39	4.679-5
Soybean straw	3 spray applications at BBCH 14, 51 and 84,	2 r	017.715 ^y
Soybean seeds	59, 57 and 65 g a.s./ha (181 g a.s./ha; in total)	<b>2</b> 1	× 0.035 f
* PHI: preharvest	interval (corresponds to days after last treatment (DAT)	at/harvest/sam	

Table 6.2.1- 38:	TRR values in soybean matrices after foliar application of [pyrazole-4-14C]BCS-
	CN88460

PHI: prenarvest interval (corresponds to

Soybean forage was conventionally extracted there times with acetomirile/water in xtures releasing 92.1% of the TRR (4.026 mg eq/kg). After concentration and purification step 91.1% of the TRR (3.981 mg eq/kg) were analysed by HPLG. For soybean forage, a microwave extraction was performed. With this exhaustive method 5.1% (0.222 mg/q/kg) of the TRR were further extracted and 4.4% of the TRR (0.193 mg eq/kg) analysed by HPLC, additionally. The residue level in the solids of soybean forage after conventional and exhaustive extraction amounted to 2.8% of the TRR and 0.123 mg eq/kg. Losses during sample ctean in of forage samples were 1.7% of the TRR Ŵ (0.074 mg eq/kg).m

Soybean hay was conventionally extracted three times with actionitric water mixtures releasing 87.4% of the TRR (4.091 mg/eq/kg), After concentration, and perification steps 86.5% of the TRR (4.048 mg eq/kg) were analysed by HPL & Exhqustive extraction of soybean hay, releasing 6.9% of the TRR and 0.321 mg eq/kg, wa further characterised by partitioning of the exhaustive extract using ethylacetate accounting for 64% of the FRR 6.299 mg eq/kg) after purification. Complete radioactivity of the exhaustive extract was found in the ethylacetate place after partitioning. This is in good accordance to results from the partitioning of experiment performed with soybean hay exhaustive extracts in a parallel study with [phenyl-UL&C]BCS-CN&460. Since the complete radioactivity of the exhaustive extracts of soybean hay in both studies was found in the ethylacetate phase, it can be assumed that the residues were highly impolar and likely ascribable to radioactivity derived from parent compound. The residue level in the solids of soybean hay after conventional and exhaustive extraction amounted to 5.7% of the TRR and 0.466 mg eq/kg. Losses during sample clean up were 4% of the TRR (0.065 mg eq/kg). Ŵ  $\cap$ 

Soybean straw was conventionally extracted three times with acetonitrile/water mixtures releasing 94.1% of the TRA (16.669 mg eq/kg) After concentration and purification steps, 93.2% of the TRR (16.516 mg eq/kg) were analysed by HPLG. For sybean straw samples, a microwave extraction was performed. With this method 2,3% (0,441 mg eq/kg) were extracted and 2.4% of the TRR (0.432 mg.oq/kg) analysed by HPLC, additionally. The residue level in the solids of soybean straw after conventional and exhaustive extraction amounted to 3.4% of the TRR and 0.605 mg eq/kg. Losses during sample clean up were 0.9% of the RR (0.163 mg eq/kg).

Soybean seeds were conventionally extracted three times with acetonitrile/water mixtures releasing 87.7% of the TBR (0.031 mg/eq/kg/ After/concentration and purification steps 76.6% of the TRR (0.027 mg eq. (we're analysed by HPLC. Losses during sample clean up were 11.0% of the TRR (0.004 mg ka/kg), The residue level if the solids of soybean seeds after conventional extraction amounted to 12.3% of the TRR and 0.004 mg eq/kg.

The distribution of the radioactive residues is shown in the following table.



	soybear	n forage	soybe	an hay	soybea	n straw	soybea	n see 🕼 🧉
	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg
<b>Conventional extraction</b>	92.1	4.026	87.4	4.091	94.1	16,669	87.7	⁽⁾ 0.031
Analysed extracts (HPLC)	91.1	3.981	86.5	4.048	93.2	16,515	76.6	0,027
Losses (not analysed) [#]	1.0	0.045	0.9	0.044	0.9	Øð.154	11.0	~ <b>Q</b> ,004
Exhaustive extraction	5.1	0.222	6.9	0.321	2.5	<u>3</u> 0.441	ð*	\$\$´\$
Analysed extracts (HPLC)	4.4	0.193		».	2,4	0.432	_°∽′	
Partitioning of purified			6.4	T 0.299	Ĩ			Ű
exhaustive extract			0.4	§* 0.299			0,3	\$~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Ethylacetate phase			64	0.299	2°	× ×	Q	ô ^y -4
Water phase			<u>Å</u> .q.	n.q.	Q" ~	V	", ·	õ "Ø
Losses (not analysed) [#]	0.7	0.029	0.5	0.022	Ø.1	⁶ .009	O ^v g	Ĩ
Total extracted	97.2	4.248	₆ , ⁹ 94,3	° 4.493	<b>96.6</b>	<i>,</i> @17.1 <i>1</i> @	×87.7	<b>9.031</b>
Post extraction solids (PES)	2.8	0.123	, <b>3.</b> 7	0.266	\$ \$	0.005	چ 12.3	≤0.004
Accountability	100.0		°~ <b>1</b> 00.0		× 100.0	<b>\$7.71</b> 5	100\$0	<b>£</b> 035
[#] losses during clean up, conc	entration, o	degreasing	centrifug	ation, etc.	4			J. J

Table 6.2.1- 39:Distribution of radioactivity in the extracts of soybean matrices after three foliar<br/>applications of [pyrazole-4-14C]BCS-CN88460

-- not performed

n.q.: not quantified

Comparison of profiles of all RACs to corresponding profiles of the parallel tudy performed with [phenyl-UL-¹⁴C]BCS-CN88460 showed good correspondence to each other and revealed that no label specific metabolism could be observed for the parallel.

In the parallel study with the phenyl-labelled test compound chromatograms obtained after exhaustive extraction were compared to the profile of conventional extract of soybean straw treated under microwave conditions. This experiment demonstrated that the parent compound and the major metabolites were not degraded by this form of extraction.

In conventional extract from soybean forage 645% of the TRR (2,977 mg eq/kg) were identified in total. The parent compound and BCS-CN88460 desfluoro-homoGSH were major component representing 17.6% of the TRR (0.770 mg eq/kg) and 21.9% of the TRR (0.955 mg eq/kg), respectively. The metabolites BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-mercapto-lactic acid-glyc and BCS-CN88460-desfluoro-fys-MA represented 3.4, 9 3.0 and 9.2% of the TRR corresponding to 0.147, 0.415, 0.129 and 0.400 mg eq/kg, respectively. In exhaustive extract 2.1% of the TRR (0.091 mg eq/kg) were further identified. The parent compound and the metabolite BCS-CN88460-desfluoro-homoGSH represented 1.4, and 1.0% of the TRR corresponding to 0.049 and 0.042 mg/kg, respectively.

In conventional extract from soybean hay 63.2% of the TRR (2.958 mg eq/kg) were identified in total. The parent compound and the metabolites BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-metcapto-factic acid-Glyc and BCS-CN88460-desfluoro-Cys-MA were major components representing 10.4, 15.2, 11.1 and 15.4% of the TRR corresponding to 0.487, 0.711, 0.520 and 0.723 mg eq/kg, respectively. The metabolites BCS-CN88460-desfluoro-homoGSH and BCS-CN88460-desfluoro-inercapto-lactic acid-OH represented 7.8 and 3.2% of the TRR corresponding to 0.366 and 0.151 mg eq/kg, respectively. Residues in the exhaustive extract of soybean hay were characterised by partitioning using ethylacetate. Complete radioactivity of the exhaustive extract was found in the ethylacetate phase after partitioning. This is in good accordance to results from the partitioning experiment performed with soybean hay exhaustive extract in a parallel study with [phenyl-UL-¹⁴C]BCS-CN88460. Since the complete radioactivity of the exhaustive extracts of soybean hay in both studies was found in the ethylacetate phase, it can be assumed that the residues were highly unpolar and likely ascribable to radioactivity derived from parent compound.



In conventional extract from soybean straw 81.2% of the TRR (14.380 mg eq/kg) were identified in total. The parent compound was by far the major component representing 63.6% of the TRR (11.262 mg eq/kg), whereas the metabolites BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-homoGSH, BCS-CN88460-desfluoro-mercapto-lactic acideOH, acid-Glyc BCS-CN88460-desfluoro-Cys-MA BCS-CN88460-desfluoro-mercapto-lactic and represented 3.8, 4.8, 1.5, 3.0 and 4.4% of the TRR corresponding to 0.667, 0.857, 0.272, 0.8533 and 0.788 mg eq/kg, respectively. In the exhaustive extract of straw further 1.6% of the TRR (0.288 mg eq/kg) were identified. The parent compound and the metabolites BSS-CNSS460desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-mercapto-hactic acid-QEV and BCS-CN88460-desfluoro-Cys-MA represented 0.9, 0.1, 0.4 and 02% of the TRR corresponding to 0.162, 0.023, 0.065 and 0.040 mg eq/kg, respectively.

Conventional extract from soybean seeds contained only parent compound representing 76.6% of the The TRR and the distribution of parents and metabolites in koybean matces are shown in the following table. TRR corresponding to 0.027 mg eq/kg. The compound was identified by TLQ co-cbomatograph, of



Table 6.2.1- 40:	Distribution of parent compound and metabolites the extracts of soybean matrices
	after three foliar applications of [pyrazole-4- ¹⁴ C]BCS-CN88460

	_	n forage	south	an hav	couho	an straw	souhor	n sood@.
TRR [mg eq/kg] =	soydea	4.371	soyb	ean hay 4.679		an straw 17.715	soyder	<u>an seed</u> €
	0/ TDD		0/ TDD				0/ TDD	
Compound	% TRR	mg eq/kg	% I K K	mg eq/kg	% I K K	mg eq/kg		mgoq/kg
<u>Conventional</u>	92.1	4.026	87.4	4.091	94.1	16.669	87.7	0.031
extraction				0.407			<b>.</b>	
BCS-CN88460	17.6	0.770	10.4	0.487	63.6	A 11.262	768	<u></u> 0.027
BCS-CN88460-desfluoro-				Ĉ&	Â	$\sim$		N N
mercapto-lactic acid-propyl-	3.4	0.147	15.2	0.711	368	0.667	_بي n.d	$\gamma$ n $Q$ .
OH-Glyc (M48)				v	<i>S</i>	1		
BCS-CN88460-desfluoro-	21.9	0.955	. TR	0.366	4.8	0.80	n.d.	on.d of
homoGSH (M44)	21.9	0.900		0.500		0.8 <b>9</b> 7		
BCS-CN88460-desfluoro-			RO .	$\sim$	, Ø	- North Anna - Nor	\O`_@	y Ji.d.
mercapto-lactic acid-OH	9.5	0.415	* 3.2	• 0 <b>,10</b> 1	<b>₹</b> 1.5	0.27 <b>2</b>	n.d.	n.d.
(M46)		Ő	Ű	K.	S.	0.272 0 6		4
BCS-CN88460-desfluoro-		4	×,	Ô	Ø 8	8 '0'	or n.de	a L°
mercapto-lactic acid-Glyc	3.0	<b>₩</b> 9.129	°¶1.1.	0.520	¥ <u>3</u> .0	07.533	Ö ^v n.de	ned.
(M47)		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Ý	y jor	S,			S Y
BCS-CN88460-desfluoro-	9.2	0.400	₩50A	à 773		^(χ) 0.76 χ	n.d.	On.d.
Cys-MA (M45)	C		, , , , , , , , , , , , , , , , ,	\$0.723	ד.ד 🖓			Ĉo,
Subtotal identified	64.5	2.817	~∕%63.2	2.958	80.2	14.380	5 76.6	0.027
Unknown 1	'n.d.	🔊 n.d.	) n.đ	ð d.	0.3	0.06		n.d.
Unknown 2	🖉 n.d.	¹ n.d.	<b>A</b> .5	<b>%</b> .025	Q ^v n.d.	Or Bel.	Kn.d.	n.d.
Unknown 3	0.8	[∞] <b>@©</b> ∕37	^{1.5}	^{~~} 0.069	🏴 n.G	nd	$O_{n.d.}$	n.d.
Unknown 4	<b>n.d</b> .	"Ön.d.	ົ້ 1.2	© 0.053	nd.	»~~ n.d.	ه n.d.	n.d.
Unknown 5	n.d.	δ n.d	× 07	0.033	≪n.d.	^♥ n,≹	n.d.	n.d.
Unknown 6	And	pad.	"Rd.	n.da	0.7	× 0A9	n.d.	n.d.
Unknown 7	609	0.041	4.4	0.20 🖉		n.d.	n.d.	n.d.
Unknown 9 🖉 🦿	<b>20</b> .9	×0.040	چە ² 3.5	0,162	n.d.	[≫] n.d.	n.d.	n.d.
Unknown 11 Unknown 12 Unknown 15 Unknown 17 Unknown 22 Unknown 23	≥~ 0.9	× 0.039		0,071	<i>√</i> n.d.	🖉 n.d.	n.d.	n.d.
Unknown 12	🗳 n.d.	nd.	£1.3	Â.060	n.d.	n.d.	n.d.	n.d.
Unknown 15	30	¢0,9136	"≪n.d.	or nat	1.9	0.329	n.d.	n.d.
Unknown 17 🔗 🖑	n.d.	n.d.	n.d.	n.d.	× 0.9	0.164	n.d.	n.d.
Unknown 🖗 🔬	× 2.0	۵.08 الم	1.2	@058	0.7	0.124	n.d.	n.d.
Unknow 22 D	n.de	n.d.	and	n.d	0.6	0.105	n.d.	n.d.
Unknown 23 😪 🗞	n.d.		°∼ n.d,	n.d.	0.6	0.098	n.d.	n.d.
Unknown 24 🔊 🗳	Æ0.8	$\infty 0.037$	🧉 n.ď	n.d.	0.8	0.138	n.d.	n.d.
Unknown 25 🖉 🦼	"Øn.d.	≪″n _k d.	° 2.2	<u>@</u> .102	1.5	0.268	n.d.	n.d.
Unknown 26	🔊 n.d.	° _`ny.d.	A.d.	n d	0.6	0.110	n.d.	n.d.
Unknown 22	્યના	~0.049	$\sim n.d.$	n.d.	n.d.	n.d.	n.d.	n.d.
Unknown 29 🎽 🔗	"M.d.	Q n.d.	ວັ 2 💲	0.115	0.7	0.125	n.d.	n.d.
Unknown 30	\$ 1.1	5 ^v 0.049		0.053		n.d.	n.d.	n.d.
Unknox 33 🔊 🖉	🖉 n.d.	, . d.	n.d.	n.d.	0.4	0.079	n.d.	n.d.
Unkpown 37	n.d.	n.d.	🔊 n.d.	n.d.	1.0		n.d.	n.d.
Unkpown 38 👋	× 3.9	Q, 0.171	1.7	0.081	n.d.	n.d.	n.d.	n.d.
Unknown 39	° n.d	», <b>"</b> """""""""""""""""""""""""""""""""""	n.d.	n.d.	0.4	0.075	n.d.	n.d.
Unknown 40 🖉 🔺 🖉	20	6Q.06	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Unknown 420 X	ñ.d.	a, n.d.	n.d.	n.d.	0.4	0.063	n.d.	n.d.
Unknown AS 🔊	≪n.d.	~ n.d.	n.d.	n.d.	0.6	0.100	n.d.	n.d.
Unknow	3.0	0.133	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Unknown 45 🔊 🦄 🔍	1.5	0.068	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Unkalown 46 X X	1.8	0.078	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Untenown 47 0 .	2.2	0.095	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Unknöwn 23 Unknown 24 Unknown 25 Unknown 26 Unknown 27 Unknown 29 Unknown 30 Unknown 33 Unknown 33 Unknown 38 Unknown 40 Unknown 40 Unknown 40 Unknown 42 Unknown 45 Unknown 45		5.070						
HPLC	26.6	1.164	23.3	1.090	12.0	2.135	n.d.	n.d.
				1				II

continued on next page



#### Table 6.2.1-40 continued

% TRR 5.1 1.1 n.d. 1.0	mg eq/kg 0.222 0.049 n.d.	% TRR 6.9	mg eq/kg 0.321	% TRR 2.5	mg eq/kg 0.441	% TRR 	mg eq@gg
1.1 n.d.	0.049	6.9	0.321		0.441		
1.1 n.d.	0.049				0.441		~ // <b></b>
n.d.				0.0			<u> </u>
	n.d.			0.9	<b>Q</b> .162		
	n.d.				1 Cr	0	
1.0				0.1	<u> </u>	Å	
1.0			۵.		,su ^y	۶×	
1.0	0.042		G	n	× nd		S 63
	0.042		· • • •		n.d.		
		0	Ş	4, O'	×	' Q	Ô ^y (
n.d.	n.d.	A		Q 0.4	0.065	s	Č,
			~			Ů,	s T
		, "V			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	) <u> </u>	
n.d.	n.d.	×	Q _~	n.d.	No no	~~ <u>~</u>	. ~
			Č.	D' ?		Å	
n d	M d	, O		₿ A2	- <b>A</b> 040	O d	
n.u.	al a	$\sim$			×	<u></u>	×
2.1	@.091		P ~~-	<b>0</b> ″1.6	<u>سٌ</u> 0.2 <b>8</b> 8	~	
1.2		×	~~	n.d	and.	J	
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مَحْ 🖓 66.6	2.998 (	°%3.2	د 2.985	82.8	14.668	76.6	0.027
28,9	⁷ <b>1,266</b>	29.7	1.389	12.8	2.279	n.d.	n.d.
95.2	4.248	6 94.3	<b>4</b> 13	96.6	17.110	87.7	0.031
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	~ 0 <u>1</u> 23	<b>5.</b> 7	[∞] 0.266	3.4	0.605	12.3	0.004
() 10000	<i>i</i> / <b>2</b> 71	A 0.0 M	<b>4.679</b>	100.0	17.715	100.0	0.035
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Overall, identification rates were sufficient and amounted to 66.6% of TRR for forage, 63.2% of TRR for hay, 82.8% of the TRE for straw and 76.6% of TRR for seeds. In soybean forage, hay and straw, 17, 13 and 20 prknown metabolites were characterised in the extracts by their chromatographic behaviour, individually accounting for less than 3.9% of the TRR (0.171 mg eq/kg), 4.4% of the TRR (0.208/mg eg/kg) and 1.9% of the TRR (0.329 mg eq/kg). à

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matric	es after th	ree foliar	applicatio	ons of [pyra	azole-4-14	CJBCS-CN	88460	
	soybea	n forage	soybe	ean hay	soybe	an straw	soybe	an seeds
TRR $[mg eq/kg] =$		4.371		4.679		17.715		s 9.035
Compound	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	mg eq/kg	% TRR	môreq/kg
BCS-CN88460	18.7	0.819	10.4	0.487	64.5	11,424	76.6	0.027
BCS-CN88460-desfluoro-						O,		
mercapto-lactic acid-	3.4	0.147	15.2	0.711	3.9	0.690 🔔	n đr	🔊 n.d.
propyl-OH-Glyc (M48)				<i>₽</i> s			N N	
BCS-CN88460-desfluoro-	22.9	0.997	7.8	© ∕₹0.366	4	0.857	Önda	À Mà
homoGSH (M44)	22.)	0.777	7.0	§ 0.500	R	0.057	0 n.a.	
BCS-CN88460-desfluoro-			G	ζ×	A	Ő	- Q	Ň,
mercapto-lactic acid-OH	9.5	0.415	32	0.151	Q* 1.9	° 0 33 7	n.d.	On de
(M46)			QD V	~	¥ . Õ		<u>`</u> ``	n.d.
BCS-CN88460-desfluoro-			б С		3.0	O C		
mercapto-lactic acid-Glyc	3.0	0.129	of 11.1	0,520	3.0	0.525	n.d.	" 🐃 n.d.
(M47)		4			6 (-	o I.u.	à 4°
BCS-CN88460-desfluoro-	9.2	0,400	.°≫5.4	\$ 0.723	× 46	60.828	n.d.	S "n.d.
Cys-MA (M45)		L.	, N				J _%/	
Total identified	66.6	2.908	× 63,2	2,958	82.8	× 14.668×	76.6	0.027
Number of unknown peaks	2.0	0.191			Ø "Ĵ	20 20.329		Å,
Largest unknown peak	3.9		4.4		r dr		S ⁿ .d	ັງ n.d.
Subtotal characterised by	28,9	× 9.266	a 23.3	1,090	Å12.8	° 2.20	// //	
HPLC			<u> </u>				- N	
Subtotal characterised by	~ "	L Ö	Su	© 0.299		, Ô	\$~	
partitioning of exhaustive extract	ĝ 70)	³ 6.4	0.299	~~~-		Q	
Total characterised	28.9	م 1.266	29.9	D 389	~~ 《 , 12.8	2.239	n.d.	n.d.
Not analysed / Losses	A 1.7	× 0.074	<u> </u>			<u> </u>		0.004
Total extracted	97,2			<u>مَنْ 4.4</u>	966	17.110	87.7	0.031
Post extraction soluts 🔍 🤇	2.8		~	\$266	3.4	_0	10.0	0.004
(PES)	- 42.8	0.123	e Re	Q266	% 3.4	S 0.605	12.3	0.004
Accountability	۵.00 D	0 4.\$ \$ 71	100.0	0 4.679	100,0	17.715	100.0	0.035
n.d.: not detected	Ň Ø			~~				
not perfôrmed	, "S	(A)	Оř "		Ž			
	. 8	R .		S.	O^{*}			
`* Š	× *		, N	G Å	¥			

Table 6.2.1- 41:	Summary of characterisation and identification of radioactive residues in soybean
	matrices after three foliar applications of [pyrazole-4- ¹⁴ CIBCS-CN88460

III. Conclusions

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The metabolism of RCS-CN88460 m soybean plants was investigated after three foliar applications at growth stages BBCH in, BBCH 51 and BBCH 84. The soybean plants were treated with [pyrazole 4-14C]BCS-CN88460 form Wated as an EC 50 at a single application rate of 59, 57 and 65 g a.s. ha for the first, second and third sprar application, respectively, corresponding to a total application rate of 181 g as ha. Soybean forage was harvested at BBCH 49, soybean hay at BBCH 77, soybean straw and seeds were horvested at BBCH 96.

The residues in soybean for the has and straw were high compared to very low residues in seed. The main portion of residues of forage, have straw and seeds were released by conventional extraction. Minor amounts were additionally released for forage, hay and straw by exhaustive extraction. Overall, identification rates in soybean forage hay, straw and seeds were sufficient. Parent compound BCS-CN884@wasthe only component in soybean seeds.

In soybean forage, hay and straw parent compound was a major component besides the identified major major metabolites: BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc (M48), BCS-CN88460-desfluoro-homoGSH (M44), BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M46), BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc (M47) and BCS-CN88460-desfluoro-Cys-MA (M45).



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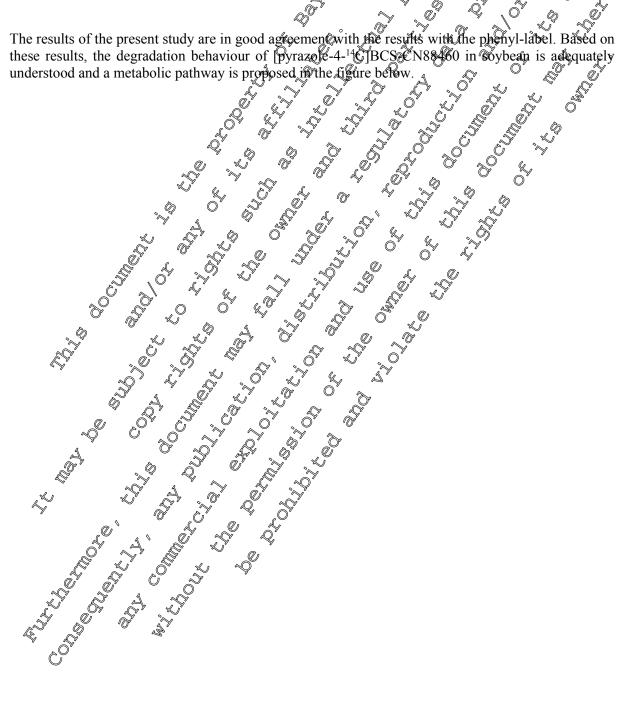
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No label specific metabolites were observed. The storage stability of matrices and extracts was demonstrated in the parallel study with the phenyl label.

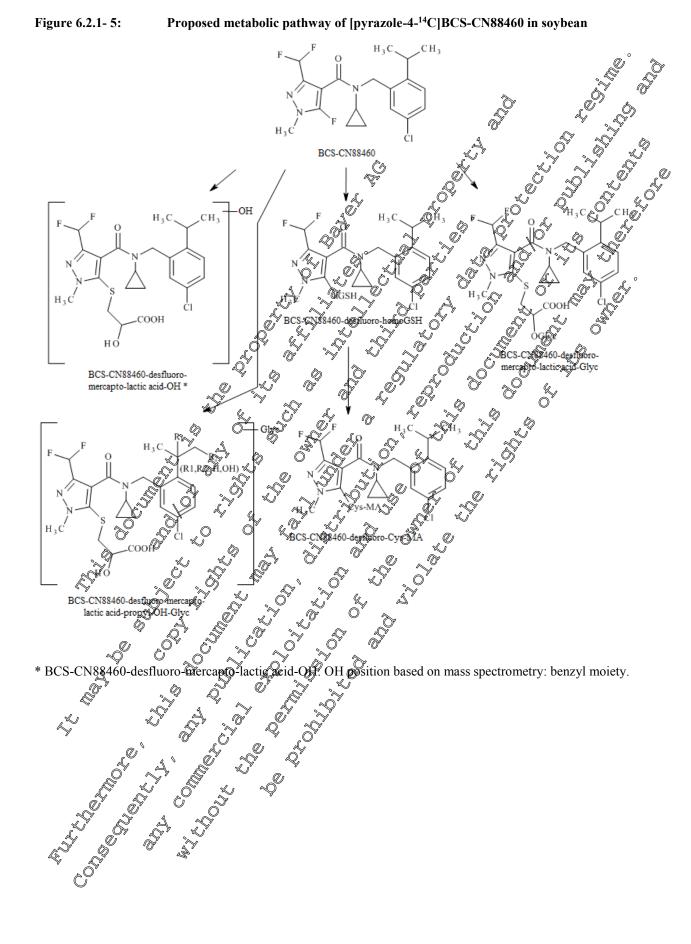
The main metabolic reactions observed were:

- de-fluorination at position 5 of the pyrazole ring followed by conjugation with homoglutathone. • BCS-CN88460-desfluoro-Cys-MA
- de-fluorination at position 5 of the pyrazole ring followed by conjugation with homogratathic ne • degradation and desamination to mercapto lactic acid group and hydroxylation of the benzyl moiety or of the propyl group T.
- glycosilation was clearly observed at the mercapto lactic acid group and could not be located to . metabolite BCS-CN88460-desfluoro-mercapto lactic acid-propyr-OH-Glyc Ś

L. The results of the present study are in good agreement with the results with the phenyl-label. Based on these results the degradation behaviour of the state of t









Report:	KCA 6.2.1/08; M.; 2017; M-609376-01-1
Title:	Metabolism of [phenyl-UL-14C]-BCS-CN88460 in soybean plants
Report No.:	S14-01090
Document No.:	M-609376-01-1 OECD Test Guideline No. 501
Guideline(s):	
	Commission Regulation (EU) No 283/2013 in accordance with Regulation (EP) No
	1107/2009
	US EPA OCSPP Test Guideline No. 860.1300
	JAP FAMIC-ACIS Notification 12 Nousan 8147
Guideline deviation(s):	none
GLP/GEP:	yes a or or or o

Executive Summary .

The metabolism of BCS-CN88460 was investigated in soybean plants after three post-emergent spray applications. For each of the three foliar applications, the test item [ptenyl-VE-14C]BCS-CN88460 was formulated and applied as aqueous EC 50 using a rominal application rate of G g a Tha each. The actual single application rates corresponded to 54, 56 and 66 g a.s./ha resulting in a total actual application rate of 176 g a.s./ha.

Soybean forage was harvested at BBCH 49 after the first application (PHL 56d) bay at BBCH 77 after the 2nd application (PHI = 38d) and straw and seeds at BBCH 56, 21d after the 3rd application. The radioactive residues of soybean forage, hay, straw and seeds were determined by summing up the extractable and unextractable radioactivity. Soybean seeds contained significantly lower residue amounts than forage, hay and straw. The total radioactive residue (TRR) in soybean straw was highest and amounted to 8.527, mg eq/kg. The TRR in soybean forage and soybean hay were high and amounted to 3.936 mg eq/kg and 1.397 mg eq/kg.

Homogenised plant material from RACs was conventionally extracted with acetonitrile/water mixtures. Overall, the extraction rates after conventional extraction of soybean forage, hay, straw and seeds were high and amounted to 0.4, 886, 928 and 69.8% of the TRR (3.597, 1.238, 7.914 and 0.011 mg eq/kg), respectively. Exhaustive extract of soybean forage, hay and straw increased the extraction rate slightly: 5.2% of the TRR (0.205 mg eq/kg), 6.3% of the TRR (0.088 mg eq/kg) and 3.1% of the TRR (0.264 mg eq/kg) were released by this treatment, respectively.

The post extraction solids after conventional and exhaustive extractions accounted for 3.4% of the TRR (0.134 mg eq/kg), 5.1% of the TRR (0.071 mg eq/kg), 4.1% of the TRR (0.349 mg eq/kg) and 30.2% of the TRR (0.095 mg eq/kg) for solve an for age, by, straw and seeds, respectively.

Residues in the conventional extracts of all RACs and in the exhaustive extracts of forage and straw were analysed and quantified by HPLC. The parent compound was identified by co-chromatography with the reference compound and metabolites were assigned by comparison of the metabolite pattern and retention times of the corrent and the bybean metabolism study with the pyrazole label.

Profiles of forage, hay and straw showed a high grade of comparability among themselves concerning metabolisation. If the test item whereas the extract from soybean seeds contained only the parent compound.

The comparison of metabolic profiles of conventional extracts of all RACs with those of a parallel study with [prazole-4-14CDBCS-CN88460 revealed a high grade of comparability of the metabolisation of the test compound in soybean and no label specific metabolite could be observed for the both labels.

A major monoment in all RACs was the test compound BCS-CN88460 accounting for 19.2% of the TRR (0.756 mg eq/kg) in soybean forage, 10.3% of the TRR (0.144 mg eq/kg) in soybean hay, 70.2% of the TRR (5.983 mg eq/kg) in soybean straw and 69.8% of the TRR (0.011 mg eq/kg) in soybean seeds. Besides parent compound no other metabolite was detected in the extract of soybean seeds.



Besides parent compound five metabolites were identified soybean forage, hay and straw.

BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc (M48) accounted for 4.8, 17.6 and 2.1% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.187, 0.246 and 0.177 mg eq/kg, respectively. BCS-CN88460-desfluoro-homoGSH (M44) accounted for 20.2, 7.8 and 2.8% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.793, 0.409 and 0.235 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M46) accounted for 17.0, 2.8 and 2.5% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.672, 0.040 and 0.215 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M46) accounted for 2.7, 10.7 and 2.8% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.107, 0.150 and 0.235 mg eq/kg, respectively. BCS-CN88460-desfluoro-mercapto-lactic acid-OH (M45) accounted for 8.2, 20.5 and 4.3% of the TRR in extracts from soybean forage hay and straw, corresponding to 0.323, 0.286 and 0.370 mg eq/kg, respectively.

Overall, identification rates were sufficient and abounted to 72.2% of FRR for forage, 69.8% of FRR for hay, 84.6% of the TRR for straw and 69.8% of TRR for seeds. In soubean forage, hay and straw 14, 5 and 20 unknown metabolites were characterised in the extracts by their chromatographic behaviour, individually accounting for less than 30% of the TRR (0.116 mg eq/kg), 0.1% of the TRR (0.230 mg eq/kg) for forage, hay and straw respectively.

All initial profiles of conventional extracts of the raw agricultural commontities were performed within 6 months after harvest. Storage stability of matrix and extract samples was demonstrated exemplarily for soybean hay and straw for 18 and 27 months, respectively.

As metabolic reactions, de-fluer nation at position 5 of the pyrazofe ring followed by conjugation with homoglutathione and degradation of the homoglutathione molety followed by conjugation with malonic acid or degradation and desamination to mercapto lactic acid group and hydroxylation of the benzyl molety or of the propyl group were observed. Furthermore glycositation was clearly observed at the mercapto lactic acid group.

Based on these results, the degradation behavior of Tphenyl-UL-¹⁴C]BCS-CN88460 in soybean is adequately understood and a pathway is proposed.

A. Materials 1. Test Material:
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A. Materials
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Chemical structure
$\downarrow \psi \qquad \vec{\psi} \qquad \vec{\phi} \qquad \vec{\psi} \qquad \vec{\phi} \qquad \vec{F} \qquad \uparrow$
γ
Chemical structure c_{1} c_{2} c_{3} c_{4} c_{5}
A. Materials 1. Test Material: Chemical structure Radiolabel position F denotes the position of the ¹⁴ C-label F denotes the position of the ¹⁴ C-label
Specific radioactivity 4.13 MBq/mg
Radiochemical purity $> 98\%$
Radiochemical purity > 98% Chemical purity > 98%
A A A



Formulation of the test compound

A stock solution of the test compound was prepared by dissolving the test compound in acetonitrile to give a concentration of about 5 mg/mL. The purity in the stock solution was checked by HPLC with radiodetection and was 100%

The test compound was formulated as an EC 50 for the experiment and the fore [pheny//UL-146] BCS-CN88460 was dissolved in acetonitrile. For each of the three spray dilutions, adequate parts of the stock solution were transferred into glass vials and evaporated to dryness. Blank forbulation was added and the mixtures were homogenised using a magnetic stirrer. The sample was then adjusted with water to a final volume of 50 mL (1st and 2nd application) and 60 mL (3rd application) of the spray dilution and homogenised by stirring.

2. Soil:

	Q			
	Soikcharactepisti	ics S L		
Туре	TOC v pH	ICCaCl20 5	CEC 🏑	
Sandy loam	2.100 ~	7.23 15	5.5 meq/100 g	
		.~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		

3. Plant:

dinger, *, représentative for bilsectes sovbean, variety "Amandine"

B. Study Design

1. Experimental conditions:

The experiment was conducted with soybear plant (variety: Amandine) based on a plant density of 800,000 soybean plants per hectare. A planting container with a surface area of 1 m² was used corresponding to the rate of 80 seeds perm². The plants were cultivated in the glass-roofed greenhouse) of the test facility and were grown signilar to natural temperature and light conditions, but protected from rainfall. They were watered by pouring onto the soil in the planting containers. The plants were applied of three different growth stages (BBCH 1651 and 85). At all these growth stages the target single application rate was 60 g a.s./ha. The target rate corresponds to the anticipated maximum application rates for the use type.

For each application the solution plants were treated with 50 mL (1st and 2nd application) and 100 mL (3rd application) of the aqueous pray divition susing a controlled track sprayer with a flat fan nozzle. To avoid contamination of the surrounding area by drift, the plants in the planting container were enclosed with a foil pousing. After spraying the spray dilution onto the oilseed rape plants in the planting container, the spray device and the protective plastic foil around the planting container were rinsed with acetonitrile/water (\$2; v/s). The actual amount applied was calculated by subtracting the losses from the radioactivity in the original application solution. At the 1st application 22.2 MBq of the labelled test comound were applied, corresponding to 5.4 mg a.s.. At the 2nd application 23.1 MBq of the test compound were applied corresponding to 5.6 mg a.s.. At the 3rd application 27.3 MBg of the test compound were applied, corresponding to 6.6 mg a.s.. The actual single application rates were 54, 56 and 66 g a stha, resulting in a total actual application rate of 176 g a.s./ha.

2. Sampling:

At growth some BBCH 49 the RAC forage, at growth stage BBCH 77 the RAC hay and at BBCH 96 the RACs straw and seeds were harvested. Plant samples were collected by cutting approximately 1-2 cm Dove the soil level. Plants sampled at hay stage were dried in a hood for 4 days.

The total weight of each sample was determined. The samples were homogenised with liquid nitrogen using a high speed blender. The sample materials were stored in a freezer (\leq -18 °C). Aliquots of the



homogenates were extracted. The actual TRR values of the samples were determined by summing up the radioactivity measured in the extracts and in the remaining solids.

C. Analytical Procedures

1. Extractiom:

Conventional extraction procedure and sample clean up:

Aliquots of the homogenised samples of soybean forage hay, straw and seeds were extracted three times with a mixture of acetonitrile/water (8/2; v/v) using a high speed blender. After each extraction step, the extracts were filtered by suction and the solids were rinsed with a small atount of the solvent of mixture used for extraction. The solids were dried and aliquots were subjected to combustion and LSC.

The extracts were combined and subjected to a clean-up step using an SPE IP 18 cartridge, which was rinsed with methanol and water and conditioned with actionitrile/water (8/2; v/v) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small colume of acetonitrile/water (8/2; v/v). The percolate and the rinse were combined. Its polar fractions of the cartridge were eluted by rinsing the cartridge with methanol/tetrahydrofurane (1/j/v/v).

Each combined percolate/rinse solution obtained from SPF purification was evaporated to the aqueous remainder. The final conventional extracts were analysed by HPLC with the general profiling method. All soybean samples and extracts were stored in a freezer (≤ 78 °C/

Exhaustive extraction and corresponding chan-up:

Solids from the conventional extraction of soybean forage, hay and straw were exhaustively extracted two times with acetonitrile/water/formic acid 50/5001; v/v6) under microwave essistance at increased temperature (0 to 5 min increase to 120 °C, 5 to 20 min at 120°C, 800 W). The microwave extracts were cooled down acroom temperature

For forage and hay, the individual extracts were combined and subjected to a clean-up step using an SPE RP 18. Cartridge, which was rinsed with methanol and water and conditioned with acetonitrile/water ($\frac{8}{2}$, $\frac{1}{2}$, $\frac{1}{2}$, $\frac{1}{2}$) beforehand. The flow-through fraction (percolate) was collected and the cartridge was rinsed with a small volume of acetonitrile/water ($\frac{8}{2}$, $\frac{1}{2}$,

The exhaustive extract of straw were directly concentrated by evaporation to the aqueous remainder. The final exhaustive extract of soybean has was partitioned for characterisation. The final exhaustive extracts of forage and straw were analysed by PPLC with the general profiling method. The extracts were stored in a freezer (≤ -18 °C).

Characterisation of residues by partitioning

Radicactivity released from sovbean hay by exhaustive extraction under microwave assistance was characterised by partitioning. Therefore, two milliliters of the concentrate obtained during exhaustive extraction and after purification were mixed with 8 mL water and 10 mL ethylacetate in a centrifuge tube. The parture was incubated 30 min by 150 rpm on a flatbed shaker. Four gram anhydrous magnesium sulplate, one gram sodium chloride, one gram trisodium citrate and 0.5 gram disodium citrate sequibidirate were added to remove water and adjust the pH value. After addition of the salt mixture, the tube was immediately shaken vigorously by hands for 10 seconds and with a flatbed shaker for at least one minute and afterwards centrifuged. Ethylacetate and water phase were separated their volume was determined. An aliquot of the concentrated ethylacetate phase was analysed by HPLC.

The radioactivity in liquid samples was determined by liquid scintillation counting (LSC). Solid samples were combusted. The CO_2 produced by combustion was absorbed in a CO_2 absorbent/



scintillation cocktail mixture and the radioactivity was measured by LSC.

Conventional and microwave extracts were analysed by HPLC based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient.

2. Identification and characterisation:

Metabolic profiles from the conventional and exhaustive extracts of all RACs were sompared, as analysed by HPLC among themselves. Metabolic profiles of all RACs were compared with metabolic profiles of corresponding RACs in the soybean metabolism study with the pyrazole label in which the major metabolites were identified spectroscopically. Parent compound was identified in soybean seeds extract by TLC co-chromatography with the test compound.

Unknown metabolites were characterised based on their extraction and from the property behavior

Table 6.2.1- 42:	List of reference compound
	List of reference compound

Report name /	Chemical Name (ILPAC)
other names/codes	Structure and formula
Parent compound BCS-CN88460	N-(\$-chloro?-isopřopylbeňzýl)-N- cyclopropyl-3-(difluoromethyl)-S-
Radiolabelled reference: S_PH_1_1000	fluoro I-methyl-1H-p@azole.f
Non-radiolabelled reference BCS-CN88460-01-02	
3. Storage stability:	

The initial profiles of the conventional extracts of soybean forage, hay, straw and seeds were analysed within 6 months after harvest of the soybean plant row material. The stability of the residues in the stored sample matrices and extracts were exemplarily demonstrated in of soybean hay and straw by reextraction followed by HPL Coffeer 18 and 27 months of storage sespectively.

The comparison of the respective HPLC chromatograms revealed that the profiles of the extracts did not significantly change after storage of the material. Therefore, the residues were sufficiently stable during the experimental period of the study and the chromatograms represent the metabolic pattern in the samples a harvest.

Results and Discussion

The metabolism of [phony]-UL C]BCS-CN88460 in soybean was investigated after three spray applications. Ø1

Soybean plants in a Tm² container were reated with [phenyl-UL-¹⁴C]BCS-CN88460 formulated as an EC 50 at BBCH 14 (begioning of stem Fongation), BBCH 51 (first flower buds visible) and BBCH 85 (about 50% of pods are ripe). The actual single application rate corresponded to 54, 56 and 66 g a sha. The total application rate amounted to 176 g a.s./ha, which was slightly below the anticipated maximum application rate of 180 g a.s./ha.

The TRE values of the individual RACs were determined by summing up the radioactivity determined in the combined extracts and the radioactivity in the solids. The residue levels are shown in mg active substance equivalents per kg sample material (mg a.s.equiv./kg or simplified mg eq/kg).



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The TRR in soybean straw was high and amounted to 8.527 mg eq/kg. Soybean forage and hay contained a TRR of 3.936 mg eq/kg and 1.397 mg eq/kg, respectively. The TRR determined for soybean seeds was low and amounted to 0.015 mg eq/kg.

The residue values in the parallel study with the pyrazole label were comparable for forage but significantly higher for hay, straw and seeds. This is due to differences in plant growth during cultivation of both studies resulting in vegetation differences during the second and third application.

Table 6.2.1- 43:	TRR values in soybean matrices	after foliar ap	plication of pheny	I-UĽ~ŸC]B C \$-
	CN88460	_0		

	C1100400	ANT THE	(/)	Ĉn		~~~
Matrix	Timing and Applic	cation	PHI (days)*	ppm (mg eq(kg)	ĵ,
Soybean forage	1 spray application at BBCH 14, 54 g a.s./ha		je ve ve	, 6 ⁴	3.936	
Soybean hay	2 spray applications at BBCH 14 54 and 56 g a.s./ha (110 g a.s./ha	, totally 🖉 🕺	x ⁷ 380		1.39	
Soybean straw	3 spray applications at BBCH 14	, 5¥ and 85,		r é	8,5 2 7 , °	
Soybean seeds	54, 56 and 66 g a.s./ha (276 g a.s.	ha; in total)		×.,	Ø.015	
* PHI: preharvest i	nterval (corresponds to days after la	st trantmenta DAT)	atharvector	mation (AL CONTRACTOR	

* PHI: preharvest interval (corresponds to days after last treatment (DAT) a harvest sampting)

Soybean forage was conventionally extracted three times with accionitrile water mixtures releasing 91.4% of the TRR (3.597 mg cq/kg). After concentration and perification steps 90.4% of the TRR (3.557 mg eq/kg) were analysed by HPLC. For soybean forage, a microwave extraction was performed. With this exhaustive method 5.2% (0.205 mg eq/kg) of the TRR were further extracted and 4.5% of the TRR (0.176 mg eq/kg) analysed by HPLC, additionally. The residue tevel in the solids of soybean forage after conventional and exhaustive extraction amounted to 54% of the TRR and 0.134 mg eq/kg. Losses during sample clean up of forage samples were 1.7% of the TRR (0.069 mg eq/kg).

Soybean hay was conventionally extracted three times with actioninfle/water mixtures releasing 88.6% of the TRR (1238 mg eq/kg). After conventration and purification steps 87.5% of the TRR (1.222 mg eq/kg) were analysed by HPLC. Exhaustive extraction of soybean hay, releasing 6.3% of the TRR and 0.088 mg eq/kg, was further characterized by partitioning of the exhaustive extract using ethylacetate accounting for 5.9% of the TRR (0.082 mg eq/kg) after purification. Complete radioactivity of the exhaustive extract was found in the ethylacetate phase after partitioning. This is in good accordance to results from the partitioning of experiment performed with soybean hay exhaustive extract in a paraftel study with [pyrazole 4⁻¹⁴C]BCS-CN88460. Since the complete radioactivity of the exhaustive extracts of Soybean hay in both studies was found in the ethylacetate phase, it can be assumed that the residues were highly unpolar and likely ascribable to radioactivity derived from parent compound. An aligned of the concentrated ethylacetate phase was further analyzed by HPLC but not peak above detection limit was detected due to low radioactivity concentrations and high matrix content of the sample. The esidue level in the solids of soybean hay after conventional and exhaustive extraction amounted to \$.1% of the TRR and 0.071 mg eq/kg. Losses during sample clean up were 15% of the TRR (0.022 mg eq/kg).

Soybean straw was convertionally extracted three times with acetonitrile/water mixtures releasing 92.8% of the TRK (7.910 mg eq/kg). After concentration and purification steps 91.8% of the TRR (7.830 mg eq/kg) were analysed by HPLC. For soybean straw samples, a microwave extraction was performed. With this method 3.1% (0.264 mg eq/kg) were extracted and 3.1% of the TRR (0.264 mg eq/kg) analysed by HPLC, additionally. The residue level in the solids of soybean straw after concentional and exhaustive extraction amounted to 4.1% of the TRR and 0.349 mg eq/kg. Losses thering sample clean up were 1.0% of the TRR (0.084 mg eq/kg).

Soybean seeds were conventionally extracted three times with acetonitrile/water mixtures releasing 69.8% of the TRR (0.011 mg eq/kg). No losses during concentration and purification steps occurred



and all of the residues in the extract (69.8% of the TRR, 0.011 mg eq/kg) were quantitatively analysed by HPLC. The residue level in the solids of soybean seeds after conventional extraction amounted to 30.2% of the TRR and 0.005 mg eq/kg.

The distribution of the radioactive residues is shown in the following table.

The distribution o	f the radioactive residues is shown in the following tal	ble.	N W
		Č,	
Table 6.2.1- 44:	Distribution of radioactivity in the extracts of soybean	The matrices after the	hred folia
Table 0.2.1- 44.	applications of [phenyl-UL- ¹⁴ C]BCS-CN88460		

			(CA)			sti a	1 24
soybear	1 forage	soybea	anthay	soybea	n straw	Ĉ soybea	n seeds
	3.936	L	, 1.397	.0¥	8.527		00015
% TRR	mg eq/kg	% TR	mg eq/kg			% ŤŘR	ang eq/kg
91.4	3.597	88.6	1.238	× 9 2 28	A 914	69,8	0.011
90.4	3.557	Ø 87.5	1.222	° .9 1.8	7.830	69,8	. 6,011
1.0	0.040	& 1 <i>0</i> 5	° 0.016	ي 1.0	0.089	°~%µ.q.	≪ [≫] n.q.
5.2	0.205) " §.3	0.088	× 3.1	r 0 2 64	s	4
4.5	0.176	n.q.	0 n.q.	2 <u>3</u> .1	0.264	Ô A	r* _{y
	K, X	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		A	Ô ^y 4		** {+
				\bigcirc		s 1	
	Q A	r \$9.9	0.082	V Ö	Į –	~~	·
7	° ~	°∼∑n.q.	√√ n∧q.	p <u></u>	, S	Ç, Ç	
Ŵ	0.029	<u>4</u> .0	, 0.006	On.q.	0 n.@	× ~~	
Ø6.6	્ર ≪ે3.8024	o 949	£326	<i>∕</i> 95.9	8,198	& 69.8	0.011
\$ 34	0,134	5.1	0.074	0×4.1	Q	° _{30.2}	0.005
2 10 0 .0	A.936	2 2 2 2 100 20	1.397	× 100.0	8.527	100.0	0.015
	% TRR 91.4 90.4 1.0 5.2 4.5 	% TRR mg eq/kg 91.4 3.597 90.4 3.557 1.0 0.040 5.2 0.205 4.5 0.1⊈6 € 0.029 0.029 0.029 0.029 0.029 0.029 0.029	3.936 % TRR mg eq/kg % TRØ 91.4 3.597 \$8.6 90.4 3.557 87.5 1.0 0.040 & 14 5.2 0.205 6.3 4.5 0.146 m.q. 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.9 5.1	3.936 1.397 % TRR mg eq/kg % TRC mg eq/kg 91.4 3.597 \$8.6 1.238 90.4 3.557 87.5 1.222 1.0 0.040 14 0.0546 5.2 0.205 6.3 0.088 4.5 0.176 m.q. n.q. 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.002 5.9 0.005 5.9 0.006 5.1 0.074	3.936 1.397 % TRR mg eq/kg % TRØ mg eq/kg 91.4 3.597 \$8.6 1.238 928 90.4 3.557 87.5 1.222 91.8 1.0 0.040 14 0.0916 1.0 5.2 0.205 6.3 0.088 3.4 4.5 0.146 m.q. 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.022 5.9 0.025 5.9 5.1 0.074 95.9	3.936 1.397 8.527 % TRR mg eq/kg % TRC mg eq/kg % TRR mg eq/kg 91.4 3.597 88.6 1.238 928 914 90.4 3.557 87.5 1.222 91.8 7.830 1.0 0.040 1.4 ° 0.046 1.0 0.082 5.2 0.205 6/3 0.088 3.0 0.264 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 5.9 0.082 <tr< td=""><td>3.936 1.397 8.527, % TRR mg eq/kg % TRC mg eq/kg % TRR mg eq/kg % TRR 91.4 3.597 88.6 1.238 928 914 69.8 90.4 3.557 87.5 1.222 91.8 7.830 698 1.0 0.040 1.4 ° 0.946 ~ 0.946 ~ 0.084 ~ 4.5 0.146 mq.q. n.q. n.q. n.q. ~ 4.5 0.146 m.q. n.q. n.q. n.q. <!--</td--></td></tr<>	3.936 1.397 8.527, % TRR mg eq/kg % TRC mg eq/kg % TRR mg eq/kg % TRR 91.4 3.597 88.6 1.238 928 914 69.8 90.4 3.557 87.5 1.222 91.8 7.830 698 1.0 0.040 1.4 ° 0.946 ~ 0.946 ~ 0.084 ~ 4.5 0.146 mq.q. n.q. n.q. n.q. ~ 4.5 0.146 m.q. n.q. n.q. n.q. </td

[#] losses during clean up, concentration, degreasing centrilligation etc.

-- not performed

n.q.: not quantified

Comparison of forofiles of all RACS to corresponding profiles of the parallel study performed with [pvrazole-4-14]BCSCN88460 showed good correspondence of eacl@other and revealed that no label specific metabolism could be observed for the pyrazole label, Ŵ

Chromatograms of conventional extracts of sorbean straw were compared to the profile of conventional extract of soybear straw treated under microwave conditions. This experiment demonstrated that the parent compound and the major metabolites were not degraded by this form of extraction.

In conventional extract from segmean torage 69.4% of the TRR (2.729 mg eq/kg) were identified in total. The parent compound BCS@N88460-desfluoro-homoGSH and BCS-CN88460-desfluoromercapto-lactic acid, OH were major components representing 17.9, 19.6 and 16.7% of the TRR corresponding to 6703, 6770 and 0.688 mg q/kg, respectively. The metabolites BCS-CN88460desfluoro-mercapto-lactic acid-propyl-OH-Gloc, BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc and BCS-CN88460-desfluor Cys-MA represented 4.8, 2.7 and 7.7% of the TRR corresponding to 0.187, 0.107 and 0.304 mg eq/kg, respectively. In the exhaustive extract of forage 2.8% of the TRR (0.108 mg eq/kg) were for ther identified. The parent compound and the metabolites BCS-CN88460desfluoro nomo SH, BCS N88460-desfluoro-mercapto-lactic acid-OH and BCS-CN88460desfluero-CyseMA represented 1.3, 0.6, 0.3 and 0.5% of the TRR corresponding to 0.053, 0.023, 0.014 and 0.019 mg/eq/kg, respectively.

In conversional extract from soybean hay 69.8% of the TRR (0.974 mg eq/kg) were identified in total. The parent compound, BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OH-Glyc, BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc and BCS-CN88460-desfluoro-Cys-MA were major components representing 10.3, 17.6, 10.7 and 20.5% of the TRR corresponding to 0.144, 0.246, 0.150



and 0.286 mg eq/kg, respectively. The metabolites BCS-CN88460-desfluoro-homoGSH and BCS-CN88460-desfluoro-mercapto-lactic acid-OH represented 7.8 and 2.8% of the TRR corresponding to 0.109 and 0.040 mg eq/kg, respectively. Residues in the exhaustive extract of soybean hay were characterized by partitioning using ethylacetate. Complete radioactivity of the exhaustive extractwas found in the ethylacetate phase after partitioning. This indicates the residues contained and previously extracted under microwave assistance were highly unpolar residues and likely ascribable to radioactivity derived from parent compound. Exhaustive extract of soybean by was partitioned using ethylacetate. Radioactivity in the concentrated ethylacetate phase was analysed by HPLC but no single ingredient in the extract was detected above the limit of detection due to low radioactivity concentration and high matrix content of the sample. 1 A

In conventional extract from soybean straw 83.3% of the TRR (7.907 mg eq/kg) were identified in total. The parent compound was by far the major component representing, 69.6% of the TR® (5.934 mg eq/kg), whereas the metabolites BCS 20188460-desfluoro-mercapt@lactic@cid-propyl-01-Glyc, BCS-CN88460-desfluoro-homoGSH, BCS-CN88460-desfluoro-mercapto-lastic acted OH, BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc and BCS CN88460-desfluoro-Cys-MA represented 2.1, 2.5, 2.4, 2.7 and 4.1% of the TRR corresponding to 0.17%, 0.210, 0.206, 0.228 and 0.350 mg eq/kg, respectively. In the exhaustive extract of straw further 3.1% of the TRR (0.264 mg @/kg) Gere identified. The parent compound and the metabolites BCS-CNS\$460-desfluoro-homoGSH_BCS-CN88460-desfluoro-mercapto-lactic acid-OFF BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc and BCS-CN88460-desfluoro-CyseMA represented 0.6, 0.3, 0.1, 0.1 and 0.2% of the TRR corresponding to 0.049, 0.024, 0.009, 0.007 and 0.020 mg eq/kg, respectively. °~~/

Conventional extract from soybean seeds contained only parent compound representing 69.8% of the TRR corresponding to 0.01 Ming eq/kg. The compound was identified by TI4C co-chromatography of the parent compound fraction isolated from conventional extract of soybean seeds with the non-

TRR corresponding to 0.011 mg eg/kg. The compound was identified by TLC co-chromatography of the parent compound fraction isolated from conventional extract of soubcan seeds with the non-radiolabelled reference compound BCS-CN8860.



Table 6.2.1- 45:	Distribution of parent compound and metabolites the extracts of soybean matrices
	after three foliar applications of [phenyl-UL- ¹⁴ C]BCS-CN88460

TRR [mg eq/kg] = 3.936 1.397 8.527 Compound % TRR mg eq/kg % TRR mg e	soybean forage soybean hay soybean straw soybean seeds							
Compound % TRR mg eq/kg								
Conventional extraction 91.4 3.597 88.6 1.238 92.8 2914 69.8 BCS-CN88460 17.9 0.703 10.3 0.144 69.6 5.934 69.8 BCS-CN88460-desfluoro- mercapto-lactic acid- propyl-OH-Glyc (M48) 4.8 0.187 17.6 0.246 2.4 0.177 n.d. BCS-CN88460-desfluoro- homoGSH (M44) 19.6 0.770 7.8 0.109 2.5 0.201 n.d. BCS-CN88460-desfluoro- mercapto-lactic acid-OH (M46) 16.7 0.658 2.8 0.000 2.4 0.206 n.d. BCS-CN88460-desfluoro- mercapto-lactic acid-Glyc 2.7 0.167 0.150 2.7 0.228 n.d. BCS-CN88460-desfluoro- Cys-MA (M45) 7.7 0.304 203 0286 4.1 0.300 fd.d. Subtotal identified 69.4 2.729 69.8 0.974 833 7.107 69.8 Unknown 3 1.2 69.47 n.d. n.d. n.d. n.d. n.d. n.d. n.d.	9.015							
extraction 91.4 3.39 88.6 1.238 92.8 2914 69.8 BCS-CN88460 17.9 0.703 10.3 0.144 69.6 5.934 69.8 BCS-CN88460-desfluoro- mercapto-lactic acid- propl-OH-Glyc (M48) 4.8 0.187 17.6 0.246 2.0 0.177 n.d BCS-CN88460-desfluoro- homoGSH (M44) 19.6 0.770 7.8 0.109 2.5 0.201 n.d BCS-CN88460-desfluoro- mercapto-lactic acid-OH (M46) 16.7 0.658 2.8 0.040 2.4 0.206 n.d BCS-CN88460-desfluoro- mercapto-lactic acid-Glyc 2.7 0.167 0.150 2.7 0.228 n.d BCS-CN88460-desfluoro- mercapto-lactic acid-Glyc 2.7 0.304 2.03 0.286 4.1 0.300 n.d Subtotal identified 69.4 2.729 69.8 0.974 833 7.107 69.8 Unknown 3 1.2 0.049 n.d n.d n.d n.d n.d n.d Unknown	eq/kg							
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BCS-CN88460-desfluoro- mercapto-lactic acid- propyl-OH-Glyc (M48) 4.8 0.187 17.6 0.246 2.0 0.177 n.d. BCS-CN88460-desfluoro- homoGSH (M44) 19.6 0.770 7.8 0.109 2.5 0.201 n.d. BCS-CN88460-desfluoro- mercapto-lactic acid-OH (M46) 16.7 0.658 2.8 0.040 2.4 0.206 n.d. BCS-CN88460-desfluoro- mercapto-lactic acid-Glyc (M47) 2.7 0.167 0.150 2.7 0.228 n.d. Subtotal identified 69.4 2.729 69.8 0.972 833 7.107 69.8////////////////////////////////////								
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Cys-MA (M45) Image: Cost of the second s	2°							
Subtotal identified 69.4 2.729 69.8 0.973 83.3 7.107 69.8 Unknown 3 1.2 0.047 n.d. n	n.d.							
Unknown 3 1.2 0047 n.d.	0.011							
Unknown 7 \$\$\u03cm\$0.669\$ \$\$\u03cm\$666\$ \$\$\u03cm\$0.866\$ \$\$\u03cm\$n.d.\$ \$\$\$\u03cm\$n.d.\$ \$\$\$\u03cm\$n.d.\$ \$	n.d.							
Unknown 9 0.8 0.036 4.6 0.065 n.d. n.d. n.d. Unknown 11 1.1 0.042 n.d. n.d. n.d. n.d. n.d. n.d. Unknown 13 1.5 0.057 n.d. n.d. n.d. n.d. n.d. n.d. Unknown 14 1.5 0.057 n.d. n.d. n.d. n.d. n.d. Unknown 15 3.0 0.116 7 0.038 2% 0.230 n.d. Unknown 15 3.0 0.116 7 0.038 2% 0.230 n.d. Unknown 24 9 0.031 n.d. 9.033 n.d. n.d. n.d. Unknown 25 9 0.049 2.4 0.033 n.d. n.d. n.d. Unknown 26 9 0.049 1.3 0.049 1.4 0.068 n.d. n.d. Unknown 27 1.3 0.049 n.d. n.d. 0.8 0.064 n.d.	n.d.							
Unknown 11 1.1 0.042 n.d.	n.d.							
Unknown 13 1.5 0057 n.d.	n.d.							
Unknown 14 n.d.	n.d.							
Unknown 15 3.0 0.116 7.7 0.038 2.8 0.230 n.d. Unknown 19 2.5 0.099 2.4 0.033 m.d. n.d. n.d. Unknown 24 9 0.031 n.d. 9.4 0.033 m.d. n.d. n.d. Unknown 24 9 0.031 n.d. 9.4 0.033 m.d. n.d. n.d. Unknown 25 9 0.049 9 9 9.24 0.033 m.d. n.d. n.d. Unknown 26 9 1.3 0.049 9 </td <td>n.d.</td>	n.d.							
Unknown 24 0.8 0.031 n.d. 0.1 n.d.	n.d.							
Unknown 25 (n, d, n, d) $(n, d, n$	n.d.							
Unknown 26	n.d.							
Unknown 27 🖉 🔊 式 1.3 0.049 😓 9 d 🖉 n 🖗 🖉 48 0.068 n d	n.d.							
$ \text{Unknown } 27 \qquad \text{m}^{2} \swarrow 1.3 \qquad 0.049 \text{m} $	n.d.							
Unknown 29 41 00044 n.d. 00.7 0.057 n.d. Unknown 30 1.1 0.042 n.d. n.d. 1.0 0.083 n.d. Unknown 38 2.9 0.104 n.d. n.d. n.d. 1.3 0.103 n.d. Unknown 39 n.d. n.d. n.d. n.d. n.d. n.d. n.d. n.d. Unknown 40 48 0.033 n.d. n.d. n.d. n.d. n.d. n.d. n.d. Subtotal characterised by 21.40 0.828 17.7 0.248 8.5 0.723 n.d.	n.d.							
Unknown 30 VI.1 0.042 nd 1.0 0.083 n.d. Unknown 38 VI.1 0.042 nd n.d. n.d. n.d. n.d. n.d. n.d. Unknown 39 Image: State of the state of	n.d.							
Unknown 38 Unknown 39 Unknown 40 Unknown 44 Subtotal characterised by HPLC 2.9 0.104 0.103 n.d. n.d. 0.103 n.d. 0.103 n.d. 0.6 0.047 n.d. 0.6 0.047 n.d. n.d. 0.6 0.047 n.d. n.d. 0.6 0.047 n.d. n.d. 0.6 0.047 n.d. n.d. n.d. 0.103 n.d. 0.047 n.d.	n.d.							
Unknown 39 0 1.3 1.4	n.d.							
Unknown 40 Unknown 44 Subtotal characterised by HPLC	n.d.							
Unknown 44 State 0.052* For. n.d.	n.d.							
Subtotal characterised by 2140 0828 717.7 0.248 8.5 0.723 n.d.	n.d.							
	n.d.							



Table 6.2.1-45 continued

		n forage		oybean hay soybean straw			soybean seeds		
Compound	% TRR mg eq/kg % TRR mg eq/kg		% TRR	mg eq/kg	% TRR mg eq				
Exhaustive	5.2	0.205	6.3	0.088	3.1	0.264		ľ M	
extraction	5.2	0.203	0.5	0.000	5.1			Ő	
BCS-CN88460	1.3	0.053	n.d.	n.d.	0.6	Q.949			
BCS-CN88460-desfluoro-						- Cr		· ~ ~	
mercapto-lactic acid-	n.d.	n.d.	n.d.	n.d.	n.d.	🔬 n.d.	Ş	ŝ	
propyl-OH-Glyc (M48)				a		×,×	°~		
BCS-CN88460-desfluoro-	0.6	0.022		<u>G</u>	~ \@	0.024	×	S -	
homoGSH (M44)	0.6	0.023	n.d.	🕎 n.d.		0.024		p ku	
BCS-CN88460-desfluoro-				S.		×	~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		
mercapto-lactic acid-OH	0.3	0.014	n.d	n.d.	Q^{\vee} 0.1	0.009	.√ √	õ, õ	
(M46)			je v	~		?Q"	, ô ^g		
BCS-CN88460-desfluoro-			~~	0		n ×	\	· ~	
mercapto-lactic acid-Glyc	n.d.	n.d.	🖇 n.d.	🖉 "n.d.	0.1	L 0.007		Ś	
(M47)			O' (a a	Ø Ø	ó	A co	
BCS-CN88460-desfluoro-	0.5		fod.	🗋 🖉 n.d.			O″	Q' 4	
Cys-MA (M45)	0.5	0.019		N N	· <u></u>	0 ⁰ .020	4		
Subtotal identified	2.8	Ø.108	, 🔊 n.d.	0 × 1×d.	01.3	× 0.1 09	×		
Unknown 7	0.8	\$0.032	n.d.	~ ⊘n d	n d		 		
Unknown 13	n.d.	√ n.032	n.d.	w [™] n A				Q	
Unknown 21	n.ď.	gn.d.	۵ n.d.		0	0.010		J	
Unknown 23	n.u.	v <i>G</i> n.d.	\mathcal{O} n.d.	Ø.d.	0.1	0.010	(n		
Unknown 30	n.d.	nat.	n.d.	√ n.d.		0.005			
Unknown 31	n.d.	nd	and.	∞ n.d.	0.07 10 10.07	. 0.003	پ		
Unknown 32			n d				Q		
Unknown 34	n.d.	n.d.	n da	n.d.	0.1	2 0.00a			
Unknown 35	and.	√ n.d.		Ŷ∧ [−] 1		* 0 au 1			
Unknown 37	n de		agei.	y n.d.	0 0.4 0.1	[∞] 0 012			
Unknown 38	n.d.		⊘n.u. n da		Ø.1	© 0.012			
Unknown 39	∫ ^r nac nac	n.d.	n.d.	♥ m.d. ●		§ 0.010			
Unknown 40 $\sqrt{2}$	nd	× nA	n.d.	. 1		0.007			
Unknown 41	∞ ^{11.d.}	0.036	s h.d.	$n.d_{2}$		0.009			
Unknown 46	Ğ,	0.030	s n.d. ≫ n.d.	o nd	₩ ^{0.3}	0.023			
	n.c.		0° 11.0.	Ø ^v Ø.d.	A .0				
Unknown 47 O	pr.d.	n.d.	n d	"Sn.d.	0.1	0.011			
Subtotal characterised by	<u>کې</u> 1.7	0.068	X	&, A	1.8	0.155			
HPLC			- m	0^{\vee}					
Partitioning of purified			Ķ .~						
exhaustive extract	, P	Ο n	, Ô'.	- OF					
Ethylacetateghase		D	°~5.9	> 0.082					
Water phase [°]	Ô _n ộ	<u> </u>	n.q.	n.q.					
Subtotal characterised by	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Û L	× 50	0.082					
partition 🏘 🦄	~~~		~0	0.002					
Total not analysed 🖉 🚽	A 14	69	~~" 1.5	0.022	1.0	0.084	na	n a	
Losses				0.022	1.0	0.004	n.q.	n.q.	
Total identified 🔊	AZ.2	@ 2.837	69.8	0.974	84.6	7.216	69.8	0.011	
Total characterised 🔬 🔪	22.8				10.3	0.878	n.d.	n.d.	
Total extracted	96,6	~ ~	94.9			8.178	69.8	0.011	
Post extraction solids									
(PES)	3 .4	0.134	5.1	0.071	4.1	0.349	30.2	0.005	
	× 100.0		100.0	1 207	100.0	0 577	100.0	A A1 5	
Accountabilit	<u>[ະ</u> ພາບບ.ບ	3.936	100.0	1.397	100.0	8.527	100.0	0.015	
n.d.: not detected 0	<u>s</u>								

n.d.: not detected -- not performed n.q.: not quantified



Overall, identification rates were sufficient and amounted to 72.2% of TRR for forage, 69.8% of TRR for hay, 84.6% of the TRR for straw and 69.8% of TRR for seeds. In soybean forage, hay and straw, 14, 5 and 20 unknown metabolites were characterised in the extracts by their chromatographic behaviour, individually accounting for less than 3.0% of the TRR (0.116 mg eq/kg), 6.1% of the TRR ((0.086 mg eq/kg) and 2.8% of the TRR (0.230 mg eq/kg).

(0.000 mg eq/kg)	anu 2.8	70 OF the TKK (0.25	o ing eq/kg).	J.	
Table 6.2.1- 46:	Summ matric	ary of characterisati es after three foliar a	ion and identificatio applications of [phe	on of radioactive residue nyl-UL-4(¹⁴ C]BCS-CN8	s th soybean 19460 7 7
		and hand former	a a sub a a su ka su	and Dean stream	

					Q	Ň	<u> Ĉ</u>	<u>a Vi</u>
	soybea	n forage	soybe	an hay	soybea	an straw	Ø soybe	an seeds
TRR $[mg eq/kg] =$		3.936	O	1.397 🔆	L.	8.52	, Q	0.015
Compound	% TRR	mg eq/kg	% TRA	mg eq/kg	%QŤRR,	ing eq/kg	% TRR	mg eq/kg
BCS-CN88460	19.2	0.756	4 0.3	0.144	× 70Ø	5.983	69.8	© 0 01 1
BCS-CN88460-desfluoro-			×	· 2			\ %	
mercapto-lactic acid-	4.8	0.187	17.6	0246	2.1	0.177	n.d.	" n.d.
propyl-OH-Glyc (M48)		a		Ø	jo i		n.d.	
BCS-CN88460-desfluoro-	20.2	0:493	×78		× 18	<u>َ</u> 60.235	n d"	
homoGSH (M44)	20.2		× 1.0		s s s s s s s s s s s s s s s s s s s			
BCS-CN88460-desfluoro-					×,	× ô	Q.	Õ
mercapto-lactic acid-OH	17.0	0.672	, \$ \$	\$ 0.040	° 2.5	¢ ¢ (§215	"n.d.	رض n.d.
(M46)	d C	S O			y Q'	Č,		J.
BCS-CN88460-desfluoro-			8 10 4	ç ş	Å		, ^>	
mercapto-lactic acid-Glyc	Ø.7	× 0.107	° 10\$	je 09450	Q* 2.8	° 0.28	&p.d.	n.d.
(M47)	w w		, d) in	O'	
BCS-CN88460-desfluoro-	6) 8.D	\$ \$323	20.5	0.286	A.3	گَرُونَ 370	n.d.	n.d.
Cys-MA (M45)							,	
Total identified 🔬	73 .2	م 2.837		0 974	84.6	7.2.6	69.8	0.011
Number of unknown peaks			\$6.1	5	p 👋	20 ×		0
Largest unknown pea	3.0	2 0. 16	~~6.1	0.086 کې	2.8	0.230	n.d.	n.d.
Subtotal characterised by	22.8	0.896	17,7	6 248	© 10.3	S 0.878	n.d.	n.d.
HPLC	~~···					رور مر	in.u.	in.u.
Subtotal characterized by		0 40						
partitioning of exhaustive	~~	2	5.9 کچې 5.9	S 0.082	🔊			
extract 🕎 🦂		<u></u>			Z.			
Total characterised	ð 2 2.8	0.896	23:6	Ø.330	\bigcirc^{7} 10.3	0.878		
Not analysed / Losses			^∕∿1.5	<u>د 0.022</u>			n.q.	n.q.
Total extracted	^{∽⊗} 9656	°3,802	94.9	1.326	95.9	8.178	69.8	0.011
Post extraction solds		0.134		.	4.1	0.349	30.2	0.005
(PES)	2.1				7.1	0.347	50.2	0.003
Accountability	0 100.0	× 3,936		>> 1.397	100.0	8.527	100.0	0.015
n.d.: not detected	° ₂	A.V	6°, (Ŭ				

-- not perf@med

H. Conclusions

The metabolism of BCS-6N88460 in so bean plants was investigated after three foliar applications at growth stages BBCH 4, BBCH 51 and BBCH 85. The soybean plants were treated with [phenyl-UL-14] BCS-CN88960 formulated as an EC 50 at a single application rate of 54, 56 and 66 g a.s./ha/ for the first, second and third spray application, respectively, corresponding to a total application rate of 176 g s.s/ha. Soybean forage was harvested at BBCH 49, soybean hay at BBCH 77, soybean@traw and seeds were harvested at BBCH 96.

Residues in soybean forage, hay and straw were high compared to very low residues in seeds. The main portion of residues of forage, hay, straw and seeds were released by conventional extraction.



Minor amounts were additionally released for forage, hay and straw by exhaustive extraction. Overall, identification rates in soybean forage hay, straw and seeds were sufficient. Parent compound BCS-CN88460 was the only component in soybean seeds.

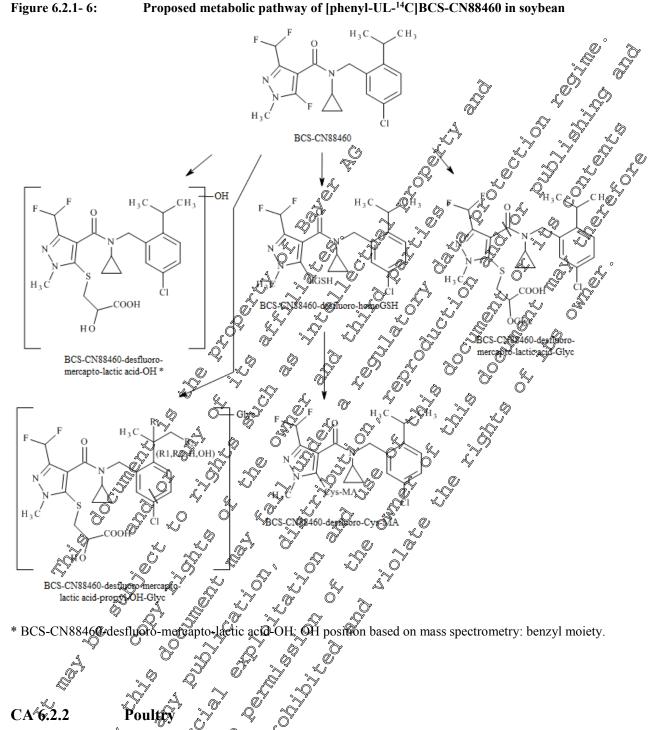
In soybean forage, hay and straw parent compound was a major component besides the identified major metabolites: BCS-CN88460-desfluoro-mercapto-lactic acid-propyl-OIA-Glyc (M48) BCS-CN88460-desfluoro-homoGSH (M44), BCS-CN88460-desfluoro-mercapto actic acid-Off (M46), BCS-CN88460-desfluoro-mercapto-lactic acid-Glyc (M47) and BCS-CN88460-desfluoro-CysMA (M45). No label specific metabolites were observed. Storage stability of matrices an Oextracts demonstrated for a period of 18 and 27 months.

The main metabolic reactions observed were:

- de-fluorination at position 5 of the pyrazole ring followed by onjugation with homoglutathione. Degradation of the homoglutathione mojety followed by an interview of the pyrazole ring followed by an intervi Degradation of the homoglutathione moiety followed by conjugation with malon acid deading to BCS-CN88460-desfluoro-Cys-MA
- de-fluorination at position 5 of the pyrazofe ring followed by conjugation with homoglutathione, . degradation and desamination to mercapto lactic acid group and hydroxylation of the benefit Ô moiety or of the propyl group
- glycosilation was clearly observed at the mercapt@lactic acid group and could not be located for metabolite BCS-CN88460-desflução-metrapto factic açid-propyl-OIC-Gl

Based on these results, the degradation belravior of [phaty]-UB *CIBOS-CN88460 in soybean is adequately understood and a metabolic pattyray is proposed in the figure below.





CA 6.2.2 Pointry The metabolism of the fungiolde isoflucypram in laying hens was investigated after administration with isoflucypram either labelled in the phenyl or in the pyrazole moiety. Parent compound and metabolites were isolated from the eggs (6 - 13 days) and the extract of excreta and identified in the isolated fractions by spectroscopic methods in the study with the pyrazole-label and assigned to the metabolites in the laying her study with phenyl-UL-¹⁴C label by comparison of metabolite profiles and retention times.

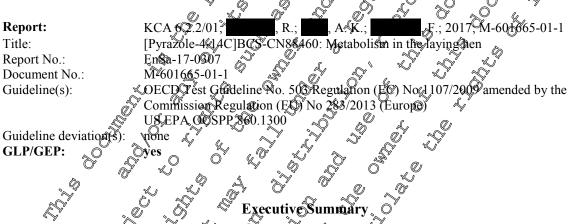


Poultry	Application	Dose	Reference
Laying hen	14 daily administrations of pyrazole- labelled isoflucypram in aqueous 0.5% Tragacanth suspension via gavage	1.0 mg/kg bw	M-601665-01-1
Laying hen	14 daily administrations of phenyl- labelled isoflucypram in aqueous 0.5% Tragacanth suspension via gavage	1.0 mg/kg bw	M-601667-01-Y

Table 6.2.2-1: Overview over available poultry metabolism studies

Summary of metabolism in poultry

The metabolite pattern corresponds well when comparing the two metabolism studies in laying hers. Isoflucypram was metabolised extensively in liver of hens. With the exception of fat, only low amounts of the parent compound were detected in the edible tissues and eggs. The major metabolites detected were BCS-CN88460-desmethyl-1,2-proparation (M06), BCS-CN88460-desmethyl-carboxylic acid (M11), BCS-CN88460-desmethyl-propanol (M06), BCS-CN88460-carboxylic acid (M12) and BCS-CN88460-propanol (M01). The main metabolity reactions were hydroxylations with further oxidation or demethylation of the pyracole morety.



The metabolism and excretion of pyrazole-4-¹⁴C BCS CN88460 was investigated in laying hens as a model for poulty. The test compound was orally administered to six hens as aqueous 0.5% Tragacanth suspension at an intended dose bate of 1 mg per kg body weight. Based on the daily feed consumption the dose level corresponded up to 16.57 mg a.s./kg dry feed/day. The hens received 14 doses at 24 hour intervals in the morning and were accrificed approx. 6 hours after the last dosing. Throughout the experiment, the hens were housed in metabolism cages, which permitted separate collection of eggs and excreta. The eggs were collected once daily and before sacrifice. Total radioactive residues (TRR) were determined in each egg (mixed sample from egg white and yolk) and in dissected organs and tissues (musclé, fac liver, kidney, skin and eggs from ovary/ oviduct) at sacrifice. The total radioactivity (% of total dose administered) was additionally determined in each excrete sample

and unscelled organs and unscle, have niver, kidney, skin and eggs from ovary/ oviduct) at sacrifice. The total radioactivity (% of total dose administered) was additionally determined in each excreta sample.



Recovery and Elimination of Radioactivity

The overall recovery amounted to 96% of the total dose and up to the time of sacrifice the excretion accounted for up to 95.8% of the total dose. After the third administration the daily excretion rate was on a more or less constant level of about 6.3 to 7.7% within 24 hours. The remaining amount of radioactivity (approx. 4%) was expected to still be present in the gastrointestinal tract at particle, because of the short period of time between last administration and sacrifice (approx. 6 hours).

An average amount of approx. 0.12% of the total dose was measured in the eggs At satisfice or radioactive residues in the organs and tissues dissected from the bodies were calculated or estimated to be about 0.22% of the total dose.

Total Radioactive Residues in Eggs, Organs and Tissues

The TRR-values and transfer factors for eggs and organs and tissues were very low compared to the dose level of 16.57 mg a.s. /kg feed/day and a dosing period of 14 days. The TRR-values in eggs ranged from 0.029 mg/kg at day two to 0.057 mg/kg at sacrifice. Following a limit increase a residue plateau-level of 0.050 mg/kg was reached at day six after the first administration.

Regarding organs and tissues, the TRR values amounted to 0.370 mg/kg in liver, 0.396 mg/kg in kidney, 0.042 mg/kg in subcutaneous rat, 0.075 mg/kg in skin 0.029 mg/kg in leg muscle and 0.018 mg/kg in thorax muscle.

Metabolism

The majority of the residues in the eggs as well as organs and tissues were efficiently extracted (83.9% to 93.4%) using acetonitrile/vater mixtures. In case of liver, the solids after conventional extraction were exhaustively extracted with microwave treatment. Only up to 8.2% of the TBR or 0.003 mg/kg of the residues remained in the post extraction solids (PES).

For sample preparation the extracts were partitioned against n preptane except the extract from fat. Very low amounts of radioactivity were recovered in the n-heptane phases and amounted to $\leq 1.3\%$ (0.001 mg/kg) of the TRR

Metabolites were isolated from extracts of eggs and excrete and identified by spectroscopic investigations parent compound and metabolites were further dentified based on co-chromatography with the isolated metabolites and by comparison of the metabolite pattern and retention times. In addition, the assignment of parent compound and metabolites in the current study was performed based on a comparison of the extracts from excrete of the current study and the hen metabolism study with the phenyl labol

The identification rates amounted to 59.6% of the TRR for eggs, 73.5% for leg muscle, 67.6% for thorax muscle 55.5% for fat and 54.9% for liver.

Parent compound was only detected in eggs, 16g muscle and fat and amounted to 0.002 mg/kg (3.7% of the TRR) for eggs, 0.001 mg/kg (23.6% of the TRR) for leg muscle and to 0.010 mg/kg (23.6% of the TRR) for fat.

Metabolites BCS-CN88460-desmethylo,2-propandiol (M07), BCS-CN88460-desmethyl-propanol (M06), BCS-CN88460-carboxylic acid (M12) and BCS-CN88460-propanol (M01) were detected in all edible materials and eggs

The amount of BCS-CN88460-desmethol-1,2-propandiol ranged from 5.1% to 17.9% of the TRR and it represented a major tesidue (>10% of the TRR) in leg and thorax muscle. The amount of BCS-CN88460-desmethyl-propanol (representing a major compound in eggs, both muscles and fat) ranged from 5.3% to 29.7% of the TRR and the amount of BCS-CN88460-carboxylic acid (representing a major compound in thorax muscle and liver) ranged from 3.4% to 11.9% of the TRR. The amount of BCS-CN88460-propanol (representing a major residue in eggs and fat) ranged from 1.7% to 35.5% of the TRR.

BCS-CN88460-desmethyl-carboxylic acid (M11) was only detected in leg and thorax muscle and liver accounting for between 12.0% and 14.4% of the TRR.



BCS-CN88460-desmethyl-1,2-propandiol-N-GlucA (M36), BCS-CN88460-desmethyl-propanol-N-

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Table 6.2.2- 2: Overview Radioactive residues of parent compound and metabolites in eggs and edible organs and tissues of laying hens following oral administration of 14 daily doses of [pyrazole-4-14C]BCS-CN88460 at a dose rate of 1.04 mg/kg *°*

						3.5				1	
Sampl		Eg			le Leg	Mu Tho	orax	4	at	Liver	
FRR	[mg/kg]	0.0	50	0.0	29	0.0	18	Q.(4 <u>2</u>	0.3	
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of OFRR (org/kg
Conve	ntional extraction	93.4	0.047	92.8	0.027	🌑 91.8	0.01		0.039	8349	0310
37	parent compound	3.7	0.002	2.3	0.001	×		23.6	0@10		~~
6	desmethyl-1,2- propandiol-N-GlucA (M36)) <u>-</u>		~ € 5.¥	0.020
13	desmethyl-propanol- N-GlucA (M37)			%		Ly y		~~~		°م م 6.1	0.023
14	desmethyl-2- propanol-N-GlucA (M38)			Ĵ.~						\$2.5	¢009
17	desmethyl-1,2- propandiol (M07)	5.2	0903	د ¥5.0	0.004	×17.9	×0.003	ې 5.1	0.002	Ô	0.025
27	desmethyl- carboxylic acid (M11)			1 <i>2</i> 31	0,094	03.0	Q 002	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		` ^س ا4.4	0.053
29	desmethyl-propanol (M06)	22.3	¢0.011	^{29.} 7	∲ 0.00₽	20.9	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	.1621	0,004	5.3	0.020
31	carboxylic acid (M12)	* 1 4	0,002	9 .1	200 3	A1.0	0.002	× 4.8	\$0.002	11.9	0.044
32	propanol (M01)	035.0	8 0.018	7, 5.3			0.061	ų, š	0.005	1.7	0.006
	identified	s 69. 6				67.6	9.012	- <u></u>	0.023	54.3	0.201
	cterised by μPLC	2Q,4	<i>Q.0</i> Ĭ1	18.7	ð ð ð 05	ي24.2	Ø.004	Ş 37.1	0.016	29.0	0.107
phase	cterised in A-heptode	L ^O 1.3	Ø.001	Ç 0.6	×0.00					0.6	0.002
	istive extraction	t de la companya de l		<u> </u>	<u>'0"</u>		<u>~~</u>			16.0	0.060
	/watter extract	<u> </u>	Ø		S,	S	5×			4.5	0.017
- 0.1 N	A HCL extract	<u>م</u> لاً المح	s	Ş <u>-</u> *	× c					11.5	0.043
	characterised 🖇 🤺	> 23	0.012	1953	0.005	24.2	0.004	37.1	0.016	45.6	0.169
	extractable 🧳 🍌	93.4	0,047	<u>م</u>	(A) V	91.8	0.017	92.7	0.039	99.9	0.370
Unext	ractable (PES)	ð 6.6	Ø.00 <u>3</u>	©″7,2	$0^{\circ}0.002^{\prime}$	8.2	0.001	7.3	0.003	0.1	< 0.001
	ntability 🔗	^O 100,0	0.050	1000	0.029	100.0	0.018	100.0	0.042	100.0	0.370

The main metabolic reactions were the hydroxylation in the propyl group of the phenyl ring and demethylation of the pyrazole moiety. Hydroxylation in the propyl group was leading to mono- or dihydroxy compounds. Conjugation with glucuronic acid was observed after demethylation of the pyrazole moiety and conjugation with sulphuric acid after hydroxylation in position 1 of the propyl group. Another metabolic reaction was further oxidation of BCS-CN88460-propanol to BCS-CN88460-corboxydc acid

Based on the results the methodism of [pyrazole-4-14C]BCS-CN88460 in the laying hen is considered as adequately understood and a metabolic pathway is proposed.



I. Materials and Methods

A. Materials

1 Test Materials

A. Materials	
1. Test Materials	
Chemical structure	F + F + G + G + G + G + G + G + G + G +
Radiolabelled test material	$[pyrazole-4_{2}^{14}C]BCS^{2}CN88460 \qquad \bigcirc \qquad $
Specific radioactivity	4.22 Wildowig -2.93 X to up at ing -2.9
Radiochemical purity	>98% (HPLC) >99% (FLC) < > > > > > > > > > > > > > > > > > >
Chemical purity	
Dose level	14 otal doses of 1657 mg a.s./kg feed/day (1,04 mg a s./kg bw/day)
Vehicle	0.5% agazeous Tragacanth® suspension 0 0 2
2. Test Animals	

2 Test Animals

2. Test Animals	
Species	Laying hen (Gallus gallus gomesticus)
Strain	LB Lokenann White"
Breeder	δ
Animal numbers	8 animals in total, from which 6 (no's 409 - 408) were chosen for the test. The hens were
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	selected by ma@mumegg production
Mean body weights	1.54 kg at delivery (2015-01-75)
2	1.63 kg at the first administration (2015-00-28)
<u> </u>	1,68 kg arsacrifice (2015-02-10)
Identification	During the acelimation period, the animals were identified by individual cage cards (1 –
J. J.	8). During the testine period an individual animal number (see above) was allocated on
<u> </u>	the cage cards and additionally by foot rite.
Acclimation period	Bydays a contraction of the cont
Husbandry 🔊	Convertional hygienic conditions in air-conditioned rooms
Housing	During the acclimation period and the whole testing period, the hens were kept
	individually in electro-polished stainless steel metabolism cages for laying hens, supplied
	t by . These
	cages allow almost parate and quantitative collection of excreta and eggs.
Dietary regimen	During the whole residence time, the hens were fed with "RWZ-LegeGold Mehl", a
Dietary regimen	pulverised chicken feed This feed was not a certified diet, i.e. it was not checked for
	contamination according to current standards. The feed was supplemented by eggshells
	during the acclimation period. The feed consumption during the testing period was
	recorded by back-weighing.
	Tap water from the local mains supply was given ad libitum during the whole residence
Environmental	Tereperature: $19 - 21^{\circ}$ C
conditions	Relative humidity: $20 - 38\%$
Ŭ	Photoperiod: alternating 16- to 8-hours light / dark cycles
	Air change: $10 - 15$ times per hour



# **B. Study Design**

### Preparation of the Test Item for Administration

The radiolabelled test compound was delivered in solid form and dissolved in 50 mL acetonitrie for preparation of the stock solution. The radiochemical purity amounted to >98% as assured by PLC? The identity of the test compound was confirmed by LC/MS/MS.

Four administration suspensions were prepared and each suspension was applied for three to your administrations. Definite volumes of the stock solution were concentrated to the dryness by a gentle stream of nitrogen gas. Afterwards, the residue was suspended in a 0.5% aqueous Tragacanthe suspension. Aliquots were taken for determination of the total radioactivity by LSC. The suspensions were kept permanently under stirring at +5 °C in a cooling cabinet until the administrations at which they were stirred at room temperature and were proved to be stable until the last cose.

#### Dosing

All oral administrations were performed by gavage using a stringe attached to an animal-feeding knob cannula once daily for 14 consecutive days in the morning in relation to the individual body weights. The laying hens received on each day an average amount of 1.69 mg ¹⁴C-BCS-CN8800, which corresponded to 7.13 MBq (mean per gainal and day). The total administered average amount and radioactivity accounted for 23.70 mg and 100.01 MBq, respectively. The administration volume was 1.0 mL/kg body weight.

The total amount of radioactivity administered to each animal server as reference value ( $A_0 = 100\%$ ) for the percentage calculation of the total radioactivity in the biological samples  $A_0 = 100\%$ )

Based upon the experimentally determined daily feed consumption during the testing period of 102 g dry feed per day (= 6.12% of the body weight), the dose of 1.04 mg as 4 kg bw corresponded to a concentration of 16.57 mg as 4 kg dry feed per day in the diet. This dose was tolerated without any observable toxicological effects.

# Collection of eggs

The egg production of the laying hens was checked during the occlimation period (beginning of the laying phase) and during the testing period. Assuming on average laying rate of 314 eggs per hen and year the mean egg production during the acclimation period was 109% and 123% during the testing period. Therefore, the egg production exceeded the target value for laying hens being in good egg production.

During the test, the cages were inspected for egg production once daily (in the morning before administration) and the number of eggs was recorded for all hens. After removal of the shells, the contents of each egg overe weighed and thoroughly mixed afterwards. Aliquots of each homogenate were mixed with scintillator for determination of the radioactivity by LSC. The remaining samples were stored in a freezer until star of metabolite analysis.

# Collection of excreta

The excreta of each hen were collected from the collecting tins as far as possible quantitatively in daily intervals until sacrifice. Individual samples were weighed after water was added. Afterwards, the individual samples were homogenised. Aliquots of each sample were processed for radioactivity measurement by combustion / LSC. The remaining samples were stored in a freezer until start of metabolite analysis.

#### Sacrifice

The minal were sacrified approx. 6 hours after the last administration, a time distance that is consistent with normal slaughtering practices. Each laying hen was transferred into a special cage, weighed and anaesthetized using carbon dioxide gas. Under general anaesthesia the animals were sacrificed by decapitation followed by exsanguination.



#### Preparation of organs and tissues

After exsanguination, the following edible organs and tissues were dissected: muscle (leg and thorax), fat (subcutaneous), liver (without gall bladder), skin (without subcutaneous fat), kidneys and eggs from the ovary and oviduct.

The organs or tissue samples were transferred into tared weight plastic vessels. After determination and recording of the individual weights, muscle, fat, liver, skin, kidney samples and eggs dissected from the ovary and oviduct were passed several times through a mincing machine in half-frozen state or blended with an Ultra Turrax in thawed state. Aliquots of the individual organ and tissue samples were combusted and the radioactivity measured by LSC Ø

The organ and tissue samples of the six hens were pooled separatel? For each sample type, divided in suitable portions that were stored frozen at  $\leq$  -18 °C until the start of metabolite analysis. For kin, the remaining homogenates of kidneys and eggs from the ovary/oviduct, metabolite analysis was optional.

All individual samples were identified with a specific sample number. The individual excreta, egg, as well as organ and tissue samples were kept for 2 - 1 or 2 - 1 or 2 - 1 we can be except during aliquotation for analysis. During the analytical work the samples and extracts of samples, were stored other in a freezer at  $\leq$  -18 °C or for a short period in a refrigerator at +4 %C.

#### **Radioactivity measurement**

The radioactivity measurement in Viquid Samples was carried out by liquid scipfillation counting (LSC). The solid samples were either desolved in BOLUTES and adjustivity determined by LSC or combusted in an oxygen achosphere using an oxidiser. The released ¹⁴CO₂ was trapped in an alkaline scintillation cocktaik and the radioactivity was determined by LSC.

C. Analytical Procedures Aliquot samples from eggs, muscle, fat, liver and excreta were conventionally extracted three times with a mixture of accountrile/ water (8/2) wing a Polytron homogeniser. For sample preparation the combined convertional extracts from eggs, muscle, liver and excreta were partitioned against nheptane. The purified conventional expacts were concentrated by fotary evaporation and subjected to HPLC analysis based on refersed phase chromatography using an acidic water/acetonitrile/THF gradient. **%**_/ Å Ċ

Solids of liver from the first conventional extraction overe exhaustively extracted twice with acetonitrile/water (8/2 V/v) using microwave assistance followed by microwave treatment with 0.1 M hydrochlorie acid. The exhaustive extracts were characterised using TLC analysis.

Aliquots of the conventional liver extracts were incubated for 96 hours at 37°C with a defined amount of B-glucuronidase/ary/sulfatase. After incubation, the enzymatic suspensions were purified and analysed by HPLC

# Metabolite analysis

Parent compound and metabolites, were quantified in the extracts by HPLC based on reversed phase chromatography using an acidic water/a@tonitrile/THF gradient.

The following strategy was used for identification of the parent compound and metabolites:

All metabolites were assigned based on a comparison of the metabolite profiles and retention times. Metabolites were isplated from extracts of egg pool and excreta and used as reference compounds after structure elucidation. Parent compound and metabolites were identified by HPLC co-chromatography with radiolabelled reference compounds in selected samples. The conventional extract of liver was enzymatically digested. The glucuronic acid and sulphate conjugates of BCS-CN88460 were thereby digested and converted into the corresponding BCS-CN88460-aglycons.



The HPLC profile of excreta was compared to the profile of excreta from the phenyl labelled hen metabolism study conducted in parallel to demonstrate the comparability.

Unknown metabolites were characterised based on their extraction and chromatographic behaviou  $\hat{\mathbb{Q}}^{\circ}$ 

#### II. Results and Discussion

#### A. Recovery and Elimination of Radioactivity

The overall recovery accounted for 96.14% of the total dose and up to the time of sacrifice, 95.8% of the total dose was excreted. After the third administration the daily excretion rate was on a more or less constant level of about 6.3 to 7.7% within 24 hours. The remaining amount of adioactivity (approx. 4%) was expected to still be present in the gastrointestinal tract at sacrifice, due to the show period of time between last administration and sacrifice (approx. six pours). An average amount of 0.12% of the total dose was measured in the eggs. At sacrifice, the radioactive residues in the organs and tissues dissected from the bodies were calculated or estimated to be about 0.22% of the total dose.

All TRRs for eggs and dissected organs and tissues were calculated as radioactivity originating from the radiolabelled test compound. Therefore, all concentration data in the report represent active substance equivalents (mg a.s. equiv./kg/ample).

Table 6.2.2- 3:	Overview Distribution obresidues in liver, kitney, eggs, muscle, skittand tor of laying
	hens following oral administration oci 4 daily doses of [pycazole-4]4C]BCS-CN88460
	at a dose rate of 1.04 mg/kg 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2

Sample	Collection	√ TRR⊘ ∞ [mg/kg] *)^	Transfer factor **	Percent of total
Liver Kidney Eggs from ovar voviduet Total skeleter musche [#] )		Ø.370 -	⁶ 0.022	0.07
Kidney		\$ 0.390 C	0.024	0.02
Eggs from ovary oviduet	approx. 6 h	~ 0.390 > 0.976 5	0.005	0.01
Total skelen musche	after last		0.001	0.07
Total body skin #)		0.023 0.00 0.00 0.00 0.00		0.02
Totat body fat #)		<b>9</b> .042	0.003	0.04
Total of organs/tigues				0.22
	$dav_{av} = 13.29^{\circ}$	$\int_{-\infty}^{\infty} O_{0.044} O^{2}$	0.003	0.12
Eggs, plateau-level	Qay 6 - PS	0.050	0.003	
	Ŝ, ^U E			
Exercta, total	da 01 - 13 25	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		95.79
		,0°		
Total Recovery		,		96.14
Feeding evel	<u></u> 16.5₽	[mg a.s. /kg dry fe	ed/day	

*) Percentage values were calculated from the body weights at sacrifice, assuming 40%, 12% and 4% of the body weight for total skeletal muscle, fat, or skin (without subcutaneous fat), respectively.

(F) weighted mean TRR-values of the individual animals

**) The transfer factor was calculated by dividing the TRR-value of the respective

Sample by the feeding level (milligrams of a.s. per kilograms dry feed on each day).



## **B.** Levels and Time Course of Total Radioactive Residues in Eggs

The TRR-values in eggs ranged from 0.029 mg/kg at day two to 0.057 mg/kg at sacrifice. Following a increase a residue plateau-level of 0.050 mg/kg was reached at day six after the grst li administration.

Table 6.2.2- 4:	Overview Time course of total radioactivity in eggs following oral administration of 14 daily doses of [pyrazole-4-14C]BCS-CN88460 at a dose rate of 1.04 mg/kg	
	daily doses of [pyrazole-4-14C]BCS-CN88460 at a dose rate of 1.04 mg/kg	

	,	-	CA A	
Animal no's.	Time after the first admin. [d]	Admin.	Câmulative secretion [% of total dose admin.] (mean) (mean) (************************************	<b>ÚRR</b> <b>ÚRR</b> <b>(meám)</b> <b>(meám)</b> <b>(meám)</b> <b>(</b> , <b>(</b> , <b>(</b> , <b>(</b> , <b>(</b> )))) <b>(</b> , <b>(</b> , <b>(</b> )))) <b>(</b> , <b>(</b> ))) <b>(</b> , <b>(</b> ))) <b>(</b> , <b>(</b> ))) <b>(</b> ))) <b>(</b> ))) <b>(</b> ))))))))))))))))))))))))))))))))))))
110 5.	in st aunin. [u]	110.	"⊘ ^v (mean)γ	[,O`(mean) , P` , Y
	0	1	<b>*</b> 6	6 <u>-</u> +
	1	2 Q		
	2	2 4		
	2			
	3	4°		
	4	x 5 m	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.038 &
	5	6.	2 LO.03 5 3	0.038 0.044 0.044 0.0453
	6		× × 00%	
403 -				
408		"08		39:054 J
100	8	Ø 9 Ø		0.049
	$ \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 4 \\ 9 \\ 10 \\ 4 \\ 9 \\ 10 \\ 4 \\ 9 \\ 10 \\ 4 \\ 9 \\ 10 \\ 10 \\ 4 \\ 9 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	10		° 0,051
	16 6	Î		0.049
				20.050
				0.030
		132		<b>6</b> ³ 0.047
	x 190° ×	_{@14}	× × 0.00 × 1	0.049
	12 13 13 13 13 13 13 13 13 13 13	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		0.057
Moon * 🌋		$\sim$		0.044
wiean ~ ~				0.044
# ~no	egg collected O			
* weighted	mean-value	A ~~		
n.es no	ot calculated	S, Q		
ALRR nlate	au-level (da 🛱 – 13).	ُ م ۹ ۵ ۱	50 mg/kg	
s greet, plate				
,	N N A	N W	Õ »	
4-1 D - 12 - 0				

C. Total Radioactive Residues in Dissected Organs and Tissues The highest TRR-value was determined in kidney (0.390 mg/kg; 0.02% of total admin. dose) followed by liver (01370 mg/kg; 0.07% of total admine dose indicating the significance of these organs for metabolism and excretion. The TRR-value of the eggs collected from the ovary and oviduct at sacrifice (0.076 mg/kg) was by a factor of 1.3 Righer than the levels of the laid eggs collected at sacrifice (0.057 mg/kg). This showed that the egg yolk was a preferential site for secretion of test compound related radioactivity Lower TRR values were detected for subcutaneous fat (0.042 mg/kg), skin (0.075 mg/kg) and total keleta muscle (0.029 mg/kg). The TRR-values of the total subcutaneous fat, skin and Guscle corresponded to about 0.04%, 0.02% and 0.07% of the total dose assuming values

of 12%, 4% and 40% of the body weight for these tissues, respectively.



# **D. Extraction Efficiency of Residues**

The majority of the residues in the eggs as well as organs and tissues were efficiently extracted (83.9% to 93.4%) using acetonitrile/water mixtures. In case of liver, the solids after conventional extraction were further extracted using microwave treatment. Only up to 8.2% of the TRR or 0.003 mg/kg of the residues remained in the post extraction solids (PES).

For sample preparation, the extracts were partitioned against n-heptane except the extract from rat. Very low amounts of radioactivity were recovered in the n-heptane phases amounting to \$1.3% (0.001 mg/kg) of the TRR. Concentration procedures of the aqueous phases caused no hosses, so all the residues in the aqueous phases were quantitatively analysed by HPIC.

A summary of the extraction efficiency is shown in the table below,

Table 6.2.2- 5:	Overview Extraction effic administration of 14 daily	ciency of doses of	eggs, f [pyra	muscle, azole#- ¹	fat and ⁴C[ <b>B</b> ¢S	iver s 5-CN88	amples 3460 at :	followir a dose r	ig oral
	1.04 mg/kg	×,	Q	, N	store in the second sec	×,		°	K)

1001 112			Oľ	. O`	×.	×.	O a		4	
Sample		ggs ↓ – 13) ूँ	Muše	lẽ Leg	* .	scle orax	, ĵ [©] F	at	Liv	
TRR [mg/kg]	0.0	)50 Q	ر کې 0.0	)29			5 0.0 %@f	<b>4</b> 2		\$° 70
		Qmg/kg		y∛ ≪ mg/kg	% of	mgokg	∧ TCR R	mgkg	°∜of TRR	mg/kg
Conventional extraction	<b>93</b> .4	*	≈ ⁹ 2.8	0.027	-100,€ ≪91.80	20.01Z	92.7	0.029	83.9	0.310
Exhaustive extraction	~~(	×		<u> 0</u>		~~~-		Ø	16.0	0.060
Total extracted	924	0,047	92.8	<b>2</b> 027	<b>9</b> 1.8	0.017	€ 92.7≱	$\sim$	99.9	0.370
Post-extraction solids	6.6	Ç0.003	¢ 7.2	0.002	× C 8.2	0.091	× ¥.3	0.003	0.1	<0.001
Accountability	1060	0.050	100.0	0.029	Â00.0	©.018	§100.0	0.042	100.0	0.370
	0	O' (		(s) 🐐	7 4	, v				

# E. Quantification, Identification and Characterisation of Residues

Parent compound and metabolites were quantified in the conventional extracts by HPLC chromatography based on reversed phase chromatography asing an acidic water/acetonitrile/THF gradient. Metabolites in the expracts were assigned to each other by comparison of the metabolite profiles and their retengon times. Corresponding metabolites were named with the same peak ID.

The identification of metabolites was performed in polated fractions from the extract of eggs and excreta by spectroscopic methods and by enzymatic cleavage of selected conjugates. The identified metabolites and aglycons in the isolated fractions were used as reference compounds. BCS-CN88460 metabolites were identified by co-chromatography with radiolabelled reference compounds. Metabolites in edible organs and tissues were assigned by comparison of the metabolic profiles and retention times. In addition, the assignment of parent compound and metabolites in the current study was performed based on a comparison of the extracts from excreta of the current study and the hen metabolism study with the phenyl label.

# F. Distribution of Parent Compound and Metabolites in Eggs, Organs and Tissues

The identification rates amounted to 69.6% of the TRR for eggs, 73.5% for leg muscle, 67.6% for thorax poscle, 55.5% for fat, 54.3% for liver and 60.1% for excreta.

Parent compound was only detected in eggs, leg muscle and fat and amounted to 0.002 mg/kg (3.7% of the TRR) for eggs, 0.001 mg/kg (2.3% of the TRR) for leg muscle and to 0.010 mg/kg (23.6% of the TRR) for fat.



#### Metabolites in eggs

Metabolites BCS-CN88460-propanol and BCS-CN88460-desmethyl-propanol were the main residues in eggs and accounted for 35.0% (0.018 mg/kg) of the TRR and 22.3% (0.011 mg/kg) of the TRR. respectively. Other prominent metabolites in eggs were BCS-CN88460-desmethyl-1,2-propardiol Ì BCS-CN88460-carboxylic acid and parent compound, each  $\leq$  5.2% of TRR.

#### Metabolites in leg and thorax muscle

The main residues in leg muscle were BCS-CN88460-desmethyl-propanol (29.7% (0,009 mg/kg) of the TRR), BCS-CN88460-desmethyl-1.2-propandiol (15.0% (0.004/mg/kg) of the TRR) and BCS-CN88460-desmethyl-carboxylic acid (12.1% (0.004 mg/kg) of the TRR). These Direction main metabolites were also detected in the thorax muscle and amounted between 20.9% and 2.0% of the TRB BCS-CN88460 corbowilie and an amounted between 20.9% and 2.0% of the TRR. BCS-CN88460-carboxylic acid was also a main residue in thorax muscle with 11.0% of the TRR (0.002 mg/kg) which was a prominent metabolite in leg muscle amounting to 61% of the TRR. Another prominent metabolite in muscle was BCS-CN88460 propared, amounting to 5.3% and \$.9% of the TRR in leg and thorax muscle, respectively.

#### Metabolites in fat

Besides parent compound as the main fesidue in fat, two main merabolites were identified, minely BCS-CN88460-propanol with 11.9% of the TRK (0.005 mg/kg) and BCS CN88460-desinethylpropanol with 10.1% of the TRR (0.004 prg/kg). Other prominent metabolites were identified and named as BCS-CN88460-desmetbyl-1,2-propandiol and BCS+CN88460-carboxyhe acid. These two metabolites amounted to between 4.8% and 51% of the TRR?

#### Metabolites in liver

The main residue in liver were identified as BGS-CN88460-desmethor-carboxylic acid (14.4% (0.053 mg/kg) of the TRR) and BCS-CN88460-carboxylic acid (11.9% (0.044 mg/kg) of the TRR). Prominent metabolites in the diver were BCS-CN88460-desmethyl-12-propandiol-N-GlucA, BCS-CN88460-desmethyl-1.2-propandiol and BCS-CN88460-desmeth @-propanol and amounted to between 5.3% and 6.9% of the TRR. Two minor metabolites named as BCS-CN88460-desmethyl-2-propanol-N OlucA and BCS-CN88460-propanol were detected toth 2.5 of  $\mathbb{P}RR$ ).

More motabolites in the mattices may be present as indicated by broad non-resolved zones in the chromatograms. Albunknown metabolites in the extracts were characterised by their extraction and chromatographic behaviour and mounted to each  $\leq 19.5\%$  of the TRR or 0.004 mg/kg.

The distribution of the parent compound and met folite m milk, organs and tissues is summarised in

The set of the set of



# Table 6.2.2- 6:Overview Radioactive residues of parent compound and metabolites in eggs and<br/>edible organs and tissues of laying hens following oral administration of 14 daily doses<br/>of [pyrazole-4-14C]BCS-CN88460 at a dose rate of 1.04 mg/kg

	or (by)	1201e-4-	CIDCS	-CN0040	bu at a d	ose rate	01 1.04	mg/kg			a,°
Sample		Eggs		Muscle Leg		Muscle Thorax		Fat		Liver	
TRR [mg/kg]		0.050		0.029		0.018		6,042		<b>49.370</b>	
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of	mg/kg	A of TRR	mg/kg	% of a	mg/kg
Conve	ntional extraction	93.4	0.047	92.8	0.027	91.8	0.07	92.7	ØØ39	<b>383.9</b>	9.310
-	parent compound	3.7	0.002	2.3	00001		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	23.6	00.010	Q	
6 p	lesmethyl-1,2- propandiol-N-GlucA M36)					U.S.				\$5.4 \$	\$020
	lesmethyl-propanol- N-GlucA (M37)				2		9 <del>(</del>			G.	0.023
	lesmethyl-2-propanol- N-GlucA (M38)								~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	2.5	\$0.009
1/ p	lesmethyl-1,2- propandiol (M07)	5.2	6003	& 15.0	\$0.004 \$	\$17.9 \$	0.003		0.002	\$ .9	0.025
27 a	desmethyl-carboxylic acid (M11)	 	?" ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	122	0.004	\$ <u>3</u> .0	0.002	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		°≫14.4	
/4	desmethyl-propanol M06)	22.3	0.011	°C 29.7	0.009	²⁰ .9	0.Q0 <b>4</b>	10.1	0.094	5.3	0.020
31 c	carboxylic acid (M12)	<b>Q</b> 3.4	0.002		0.003	11.0	Q.902	4.8	×0.002	11.9	0.044
32 p	propanol (M01)	350	0,018	5.3	<b>20</b> 002	Õ ^v 5.9	0.001	[©] 11.8	0.005	1.7	0.006
Total i	identified	<b>8</b> 9.6	<b>\$9.035</b>	73.5	Ç 0.021	> 67.6	0.012	55,5	0.023	54.3	0.201
conven by HPI		22.4	0.011	<b>18</b> .7	9,905	24.2	Ø.004	\$37.1	0.016	29.0	0.107
Numł peaks	ber of unknown				Î Ş			(	5	1	8
	est unknown peak 🖉	<b>29</b> .7	<b>0</b> 004	9.9	£0.003	× 19.5	0.004	11.2	0.005	8.4	0.031
	cterised by parttrion tane phase)	₹ ⁷ 1.3	\$0.00E	\$``Q`E	×<0.001					0.6	0.002
Exhau	istive extraction 🔬		\$	<u> </u>		ð				16.0	0.060
- ACN/	/water extract	ð"	, Č [.]	Ő	ő <i>–</i>	÷				4.5	0.017
peak										-	5
Larg	est wiknown		~		\$ }					2.8	0.010
~	PHCL extract 🖉 🦼		r Q		, 					11.5	0.043
Num peak	ber of unknown		¥	2						2	4
peak			n A	,						8.2	0.031
	charaeterised	Å.7	0.012	19.3	0.005	24.2	0.004	37.1	0.016	45.6	0.169
	extractable 🌧	٦٩٤ 🔇	0.047	92.8	0.027	91.8	0.017	92.7	0.039	99.9	0.370
- 0 mm											
	ractable (PES)	₿ 6.6	0.003	7.2	0.002	8.2	0.001	7.3	0.003	0.1	< 0.001



Conjugates in the liver like BCS-CN88460-desmethyl-1,2-propandiol-N-GlucA, BCS-CN88460desmethyl-propanol-N-GlucA and BCS-CN88460-desmethyl-2-propanol-N-GlucA could be enzymatically cleaved to their aglycons. The cleavage of some unknown conjugates in non-resolved zones resulted in higher amounts of the aglycons. None of the unknown compounds after clearage accounted for more than 0.010 mg/kg (2.6% of the TRR) after enzymatic cleavage. The following main aglycons could be clearly identified after enzymatic cleavage: BCS-CN88460-desmethyl-123propandiol and BCS-CN88460-desmethyl-propanol.

	experiment 1	and 2		A	Ŵ	( Ca	4	L Č	, , ,
Sample		Liver- & 1 st conventional extraction		Livers Conventional extraction		extract -		Liver- enzymatic cleavage of 2 nd conventional extract - experiment 2	
peak ID	Compound (Report name) BCS-CN88460-	% & FRR	mg/kg	TRR		%of PRR	forg/kg	% of TRR	) mg/kg
Extract	t used for HPLC analysis	^{~~~} 83,\$	0.308	\$3.3	Ø.308	0, 750,	0278	75.2	0.278
6	desmethyl-1,2-propandiol	×3.4	~0.020	5.3	0.0219	ری میں 0.5	0.002	O 0.7	0.003
13	desmethyl-propanol-No GlucA (M37)	0 6.¢		5.6					
14	desmethyl-2-propanol-N	2.5	0.009	2,2	0,008	لام الحي	×0.002	0.5	0.002
17	desmethyl-1,2propandiol (M07)	62	0.025	<b>\$</b> 7.6		106	0.043	11.3	0.042
27	desmethy carboo fic acid (M11)	0 ¹ 4.4	¢0.053	145	0,054	17.4	0.065	17.0	0.063
29	desmothyl-propanol (M06)	S 5.4	0:920	Ø <b>5</b> .1	0.019	y 14.7	0.054	14.5	0.054
31	carboxylic acid (MQ2)	£\$.9	0.044	S 11.9	0.044	16.4	0.061	16.8	0.062
32	propanol (M01)	ا.7	\$0.006	2.1	0008	1.5	0.006	1.8	0.007
	dentified	54.3	0.201	<b>(5</b> 4.1	0.200	62.6	0.232	62.7	0.232
Total c	haracterised	29.0	>0.107	S 29.2	0.108	12.6	0.046	12.5	0.046
Account	ntability of o	°∼y83.3∧	0.308	83.3	0.308	75.2	0.278	75.2	0.278

			A A		L.
Table 6.2.2- 7:	Overview Radioactive residu	es of parent compou	ind and metabolit	es in liver samples	
	of first and second conventio experiment 1 and 2				KO'

Metaboldes in Excreta

The excreta extract of day 1 was analysed by HPLC. Parent compound accounted for 2.6% of the dose. BCS-CN88460-desmeth decarboxylic acid and BCS-CN88460-carboxylic acid were the most prominent compound, accounting for 170% and 15.4% of the dose, respectively. Further eight identified mcabolites ranger from 1.4% to 8.6% of the dose.

Generally metabolites in the same as in eggs, organs and tissues, except for metabolites BCS-CN88460-desmethyl-1,2-propandiol-SA, BCS-CN88460-1,2-propandiol-SA and BCS-CN88469-1,2-propandiol which accounted for equal or less than 8.6% of the dose, respectively.

in the second se



### G. Storage Stability of Residues

All samples of eggs, excreta, edible organs and tissues were extracted within five months after sample collection. Quantitative analysis by HPLC was performed either on the day of extraction or up to four days after the start of extraction. A second conventional extraction of liver was performed approx 20 months after sampling. The extract was used for enzymatic cleavage experiments. The storage stability was exemplarily demonstrated for these liver samples. It was therefore concluded, that the metabolic profiles represent the residues in the matrices and analysed samples at sacrifice

# III. Conclusion

The metabolic behaviour of [pyrazole-4-¹⁴C]BCS-CN 88460 in the aying hen can be character ded by the following observations:

The TRR-values and even transfer factors for eggs and edible dissues were very low with respect to the dose level and the dosing period of 14 days. This indicates that test compound related radioactivity does not accumulate during the time of feeding. The evaluations of the TRR-values should however consider the fact that an exaggerated dose level of 16.57 mg a.s. 4kg feed/day was administered. Furthermore, the fact that the entire radioactivity was detected in the excreta and the relatively high TRR in kidney and liver at sacrifice approx. 6 hours after the last administration revealed that the test compound related residues are further metabolised and finally eliminated from the hen's bodies. A residue plateau level in eggs was clearly reached during the course of the experiment approx. at day six after the first administration.

The ideation with conventional methods from eggs and tissues; extraction rates ranged from 83.9% to 93.4% Extraction with conventional and exhaustive prethods from edible organs accounted for 99.9% for the liver?

The identification rates in easily, and edible organs and tissues anged between 54.3% and 73.5% for the TRR.

Parent compound was delected as major compound in fat and miner in eggs, leg and muscle.

Overall eight metabolites were identified in eggs, etible organs and tissues. Metabolites BCS-CN88460-desmethyl-propanol (M06), BCS-CN88460-propanol (M01), BCS-CN88460-desmethylcarboxylic acid (M11), BCS-CN88460-carboxylic, acid (M12), and BCS-CN8840-desmethyl-1,2propandiol (M07) were major residues in eggs, log muscle, thorax muscle, fat and liver. Prominent metabolites BCS-CN88460-desmethyl-propanol-N-GlucA (M97) and BCS-CN88460-desmethyl-1,2propandiol-N-GlucA (M36) were found in liver, only. Minor metabolites in liver were BCS-CN88460propanol (M01) and BCS-CN88460-desmethyl-2-propanol-N-GlucA (M38).

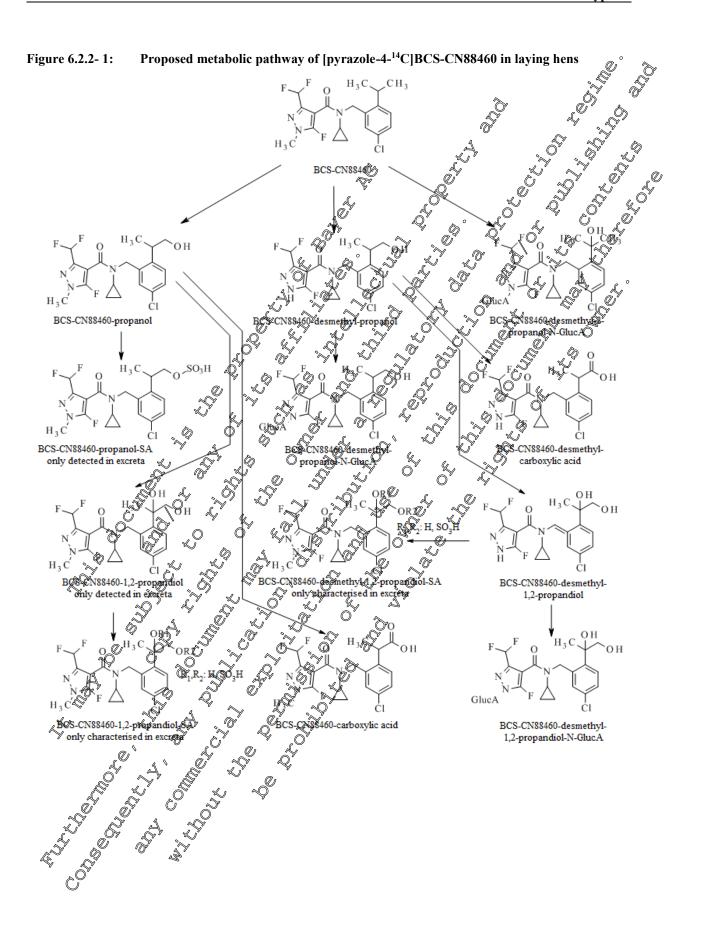
The metabolic profile of exercta from day 1 was similar to the profiles of edible materials, especially liver, with the difference that metabolites BCS-CN88460-desmethyl-1,2-propandiol-SA (M42), BCS-CN88460-1,2-propandiol (M03) and BCS-CN88460-propanol-SA (M26) were present.

The principal metabolic reactions of [pyracile-4-14C]BCS-CN88460 in the laying hen are listed below:

- demethylation of the pyrazole moiety
- Conjugation with gluearonic acid after demethylation of the pyrazole moiety
- A hydroxylation in position 1 and/or position 2 of the propyl group
  - further oxidation of the 1-propanol group leading to a carboxylic acid group
- Conjugation with sulphuric acid after hydroxylation in position 1 or position 2 of the propyl

Based on these results, the metabolism of [pyrazole-4-¹⁴C]BCS-CN88460 in the laying hen is considered as sufficiently understood and a metabolic pathway is proposed in the figure below.







Report:	KCA 6.2.2/02; , R.; , F.; 2017; M-601667-01-1
Title:	[Phenyl-UL-14C]BCS-CN88460: Metabolism in the laying hen
Report No.:	EnSa-17-0306
Document No.:	M-601667-01-1
Guideline(s):	M-601667-01-1 OECD Test Guideline No. 503 Commission Regulation (EU) No 283/2013 in accordance with Regulation (EC) No 1107/2009 US EPA OCSPP Test Guideline No. 860.1300
Guideline deviation(s):	
GLP/GEP:	yes
Guideline deviation(s):	none

# Executive Summary

The metabolism and excretion of [phenyl-UL-¹⁴ClBCS-CN88460 was investigated in faying hens as a model for poultry. The test compound was orally administered to six, hens as aqueous 055% Tragacanth suspension at an intended dose rate of 1 mg per kg body weight. Based on the daily feed consumption, the dose level corresponded up to 18.12 mg a.s./kg dry feed/day. The tens received 14 doses at 24-hour intervals in the morning and were sacrificed approx. 6 hours after the test doorng. Throughout the experiment, the hens were housed in metabolism cages, which permitted separate collection of eggs and excreta. The eggs were collected once daily and before sacrifice. Total radioactive residues (TRR) were determined in each egg (nixed sample from egg white and yolk) and in dissected organs and tissues (muscle, fat, liver, kidney, skin and egg from ovary/ oviduct) at sacrifice. The total radioactivity (% of total dose administered) was additionally determined in each excreta sample.

# Recovery and Elimination of Radioactivity

The overall recovery amounted to 103.36% of the total dose, and up to the time of sacrifice the excretion accounted for up to 102.97% of the total dose. After the third administration the daily excretion rate was on a more or less constant level of about 7.1 to 8.8% within 24 hours.

An average amount of approx 0.14% of the total dose was measured in the eggs. At sacrifice, radioactive residues in the organs and tissues dissected from the bodies were calculated to be about 0.24% of the total dose.

# Total Radioactive Residues in Eggs Organs and Tissues

The TRR-values and transfer factors for eggs and organs and tissues were very low compared to the dose level of 18.12 mg a.s. kg feed/day and a dosing period of 14 days.

The TRR-values in eggs ranges from 0.032 mg/kg at day three to 0.066 mg/kg at sacrifice. Following a limit increase a residue plateau-level of 0.090 mg/kg was reached at day four after the first administration.

Regarding organs and pissues the TRR-values amounted to 0.373 mg/kg in liver, 0.360 mg/kg in kidney, 0.047 mg/kg in subcutaneous fat, 0.109 mg/kg in skin, 0.029 mg/kg in leg muscle and 0.017 mg/kg in thorax muscle.

#### Metabolism

The majority of the residues in the eggs as well as organs and tissues were efficiently extracted (85.4% to 93.3%) using acetonitole/water (8/2 v/v) mixtures. In case of liver, the solids after conventional extraction were exhaustively extracted using acetonitrile/water (1/1; v/v) mixtures and 0.1 M hydrochloric acid with mix forwave treatment. Only up to 8.2% of the TRR (0.004 mg/kg) of the residues remained in the post extraction solids (PES).

For sample preparation the extracts were partitioned against n-heptane except the extract from fat. Very low amounts of radioactivity were recovered in the n-heptane phases and amounted to  $\leq 1.2\%$  (0.001 mg/kg) of the TRR.



Parent compound and metabolites were identified based on co-chromatography with reference compounds or by comparison of the metabolite pattern and retention times. Reference compounds were taken from the hen metabolism study with the pyrazole label or the goat metabolism study with the phenyl label.

The identification rates amounted to 79.2% of the TRR for eggs, 79.8% for beg muscle, 76 for thorax muscle, 51.5% for fat and 62.0% for liver.

Parent compound was only detected in eggs, leg muscle and fat and amounted to 0.003 mg/kg (6.4%) of the TRR) for eggs, 0.001 mg/kg (2.9% of the TRR) for leg muscle and to 0.009 mg/kg (20.1% the TRR) for fat.

Metabolites BCS-CN88460-desmethyl-1,2-propandial (M07), BOS-CN88460 desmethyl-propanol (M06), BCS-CN88460-carboxylic acid (M12) and BCS-CN88460-propanol (M01) were detected in all edible materials and eggs. Q,

The amount of BCS-CN88460-desmethyl-1,2 propandiol ranged from 5.6% to 22% of the TRR and it represented a major residue (>10% of the TRR) in leg and therax spassele. The amount of BCS-CN88460-desmethyl-propanol (representing a moror compound in eggs and both muscles) ranged from 2.7% to 25.8% of the TRR and the amount of BCS-CM88460 propagol (representing a grajor compound in eggs) ranged from 1.7% to 33.9% of the TRR, while the amount of BCS-CN\$8460carboxylic acid ranged from 3.0% to \$6% of the TRR. BCS-CN\$8460-desmetoyl-carboxylic acid was detected as major residue in muscle and liver, while it was detected in minor aprounts in fat. Its amount ranged thereby from 7.9% to 2109% of the TRP.

BCS-CN88460-desmethyl-1,2 propandiol-N-GlucA (M36) was detected in leg moscle and liver, accounting for 4.1% to 9.2% of the TRR Grespectively. BCS-CN88469-desmethyl propanol-N-GlucA (M37) was detected in eggs, leg muscle and liver, ranging from 3.0% to 1068% of the TRR.

Metabolites BCS-CN88460-desmeth@-2-propanolon-GlucA (MS8) and BCS-CN88460-propanol-SA (M26) were only detected in fiver (both equal or tess than 3.0% of the ORR).

The metabolic profile of excreta from day 1 was similar to the profiles of edible materials, especially liver, with the difference that metabolites BCS-CN\$8460-desmethyl-1,2-propandiol-SA (M42), BCS-CN88460-1,2 proparatiol-SA (M27) and BCS-CA88460-1,2 propandial (M03) were only detected in

excreta. A summary of the distribution of parent compound and metabolites for edible materials is provided in the table overleaf.



# Table 6.2.2- 8:Overview Radioactive residues of parent compound and metabolites in eggs and<br/>edible organs and tissues of laying hens following oral administration of 14 daily doses<br/>of [phenyl-UL-14C]BCS-CN88460 at a dose rate of 1.01 mg/kg

Samp	e	Eggs Muscle Leg		Muscle Fat			at	t Liver			
_		(day 4 – 13)		-		Thorax		~		$\mathcal{O}$	
TRR [mg/kg]		0.050		0.029		0.017		0:047		<b>.</b> 9.3	73
peak ID	Compound (Report name) BCS- CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	OTRR Q	mg/kg0
Conve	ntional extraction	<i>92.8</i>	0.046	93.3	0.027	92.4	0.01	<b>91.8</b>	0.043	85.4	<i>0</i> Ø18
42	parent compound	6.4	0.003	2.9	0.001			20.1	0,009	ð	- v
7	desmethyl-1,2- propandiol-N- GlucA (M36)			4.1	Ø.001	<i>(</i>	کم لگرانی	° Q		9.2	0.634
18	desmethyl- propanol-N-GlucA (M37)	3.0	0.002	©.8	<b>9.90</b> 1					* ¥	0.040
19	desmethyl-2- propanol-N-GlucA (M38)		20- 20- 20-							≪ 3.0¢	0.011
22	desmethyl-1,2- propandiol (M07)	6.2	Q.003	®14.2	0.004	223	0.004	6.9	0.003	<u>,</u> ∜5.6	0.021
29	propanol-SA (M26)	Į.	_ ¢ ¢		<i>\$</i>	х ^о	2	<u>``</u> ĉ	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	• 1.2	0.005
33	desmethyl- carboxylic acid (M11)	\$	б ^у ;	0 ⁴ 19,9	0.006		Q.003	\$7.9	20.004	21.9	0.082
35	desmethyl-	202.6	<b>6</b> .011	25.8		<u>م</u> ر 20.90		9.8 19.	0.004	2.7	0.010
37	carboxylic aged (M12)	72		6,6	0.092	\$8.6	<b>6</b> 2001	<b>3</b> .0	0.001	5.8	0.022
38	propanel M01	<u></u> @3.9	0017	¢°2.5	<b>\$0</b> .001		0.	6.5	0.003	1.7	0.006
Total	identified O	[%] 79.2	0.040	79.8	0.023	76.3	0:013	51.5	0.024	62.0	0.231
	cterised by HPLC	12	0.000	13.2	0.004	~6.1	0.003	40.3	0.019	23.1	0.086
	cterised in ane phase		~0.001		\$0.001 \$	, ^r h 2	) 			0.3	0.001
n-heptane phase		Q	× +	×P	<u>Q</u> _	~~				14.5	0.054
-ACN/water extract		- <u>-</u>	. 8	<u>م</u>	S	Ş				4.8	0.018
		~~~ <i>~</i>	J [	<u>م</u> کړ	¥ 🍾					9.6	0.036
Total characterised 13.5 0.00			,1 <i>35</i> 5	0,604	16.1	0.003	40.3	0.019	37.9	0.142	
	extractable 📎	9 2 8	0.046	3.3	20 .027	92.4	0.016	91.8	0.043	99.9	0.373
Unext	ractable (PES)	A 7.2	0.004	¢ 6.7	0.002	7.6	0.001	8.2	0.004	0.1	< 0.001
Accor	Intability (100,0	0.050	10 00 Q	0.029	100.0	0.017	100.0	0.047	100.0	0.373

The main metabolic reactions were the demethylation of the pyrazole moiety and hydroxylation in the propyl group of the phenyl ring. Hydroxylation in the propyl group was leading to mono- or dihydroxy compounds. Conjugation with glucuronic acid was observed after demethylation of the pyrazole moiety and conjugation with sulphuric acid after hydroxylation in position 1 of the propyl group. Another metabolic reaction was further oxidation of BCS-CN88460-propanol to BCS-CN88460-carboxyla acid.

Based on the results the metabolism of [phenyl-UL-¹⁴C]BCS-CN88460 in the laying hen is considered as adequately understood and a metabolic pathway is proposed.



I. Materials and Methods

A. Materials

1. Test Material

A. Materials	
1. Test Material	
Chemical structure	$F + F + H_3C + CH_3 + H_3C +$
Radiolabelled test mat	
Specific radioactivity	$\frac{4.13 \text{ MBq/mg} = 2.48 \times 10^{8} \text{ dpm/mg}}{>98\% (HPLC)} \xrightarrow{2} \xrightarrow{2} \xrightarrow{2} \xrightarrow{2} \xrightarrow{2} \xrightarrow{2} \xrightarrow{2} 2$
Radiochemical purity	$>98\%$ (HP4 \tilde{C}) γ γ γ γ A γ A
Chemical purity	>98% (HPLC) ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Dose level	14 ora doses of 18.12 mg a s./kg feed/da@(1 mg a.s./kg bw/day)
Vehicle	0.5 % aque traga can the suspension of the suspe
2. Test Animals	>98% (HPLC) >98% (HPLC) 14 orac loses of 18.12 mg.acs/kg feed/dac (1 mg.acs/kg bw/day) 0.5 % aqueons Tragacanthe suspension
Spacios	Louing hon (Stilling Arthur demostion)

Species	Laying hen (Gallus gallus danesticus)
Strain	"LB Lohndann Brown"
Breeder	
Animal numbers	8 animals in total, from which 6 (no \$493 - 498) were chosen for the test. The hens were
A.	selected by maximum egg production.
Mean body weight	
ð í	0.82 kg at the first administration (20 $0^{-10-243}$
	(1.80 kg at sagerifice (2015-(1+0.03)))
Identification	Duting the acclimation period, the animal were identified by individual cage cards (1 -
Ľ,	& During the testing period an individual animal number (see above) was allocated on
~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	the cage cards and additionally by foot ring. 1
Acclimation period	15 dáýs ý v v v
Husbandry 🖉	Conventional hygichic conditions in air-conditioned rooms
Housing	String the acclimation period and the shole testing period, the hens were kept
	Undividually in electro polished staipless steel metabolism cages for laying hens, supplied
4	by . These
	cages allow almost separate and quantitative collection of excreta and eggs.
Dietary regimen 🔬	During the whole residence time, the hens were fed with "RWZ-LegeGold Mehl", a
	pulversed charken feed. This feed was not a certified diet, i.e. it was not checked for
2	commination according to current standards. The feed was supplemented by eggshells
ĴØ`	during the acclination period. The feed consumption during the testing period was
	recorded by back-weighing.
	Tap water from the beal mains supply was given <i>ad libitum</i> during the whole residence
	ting.
Environmental conditions	Temperature: $19 - 23^{\circ}C$
conditions of	field two humidity: 23 - 78%
	Photoperiod: alternating 16- to 8-hours light / dark cycles
	Air change: $10 - 15$ times per hour
õ	



B. Study Design

Preparation of the Test Item for Administration

The radiolabelled test compound was delivered in solid form and dissolved in 25 mL acetonitries for preparation of the stock solution. The radiochemical purity amounted to >98% as assured by PLC. The identity of the test compound was confirmed by LC/MS/MS.

Four administration suspensions were prepared and each suspension was applied for three to your administrations. Definite volumes of the stock solution were concentrated to the dryness by a gentle stream of nitrogen gas. Afterwards, the residue was duspended in a 0.5% aqueous Tragacanthe suspension. Aliquots were taken for determination of the total radioactivity by LSC. The suspensions were kept permanently under stirring at +5 °C in a cooling cabinet until the administrations at which they were stirred at room temperature and were proved to be stable until the last cose.

Dosing

All oral administrations were performed by gavage using a stringe attached to an animal-feeding knob cannula once daily for 14 consecutive days in the morning in relation to the individual body weights. The laying hens received on each day an average amount of 1.83 mg ¹⁴C-BCS-CN88600, which corresponded to 7.56 MBq (mean per daimal and day). The total administered average amount and radioactivity accounted for 25.56 mg and 105.56 MBq, respectively. The administered average amount of 1.0 mL/kg body weight.

The total amount of radioactivity administered to eacleaning) served as reference value (A0 = 100%) for the percentage calculation of the total radioactivity in the biological samples %

Based upon the experimentally determined daily feed consumption doing the testing period of 101 g dry feed per day (= 5.61% of the body weight), the dose of 1.01 mg as kg by corresponded to a concentration of 18.12 mg as kg dry feed per day in the diet. This dose was tolerated without any observable toxicological effects.

Collection of eggs

The egg production of the laying hens was checked during the occlimation period (beginning of the laying phase) and during the testing period. Assuming on average laying rate of 314 eggs per hen and year the mean egg production during the acclimation period was 143% and 121% during the testing period. Therefore, the egg production exceeded the target value for laying hens being in good egg production.

During the test, the grates of the cages were inspected for egg production once daily and the number of eggs was recorded for all hens. After removal of the shells, the contents of each egg were weighed and thoroughly mixed afterwards. All quots of each hornogenate were mixed with scintillator for determination of the radioactivity by LSO. The remaining samples were stored in a freezer until start of metabolite analysis.

Collection of excreta

The excreta of each hen were collected from the collecting tins as far as possible quantitatively in daily intervals until sacrifice. Individual samples were weighed after water was added. Afterwards, the individual samples were homogenised. Aliquots of each sample were processed for radioactivity measurement by combustion / LSC. The remaining samples were stored in a freezer until start of metabolite analysis.

Sacrifice

The minus were sacrificed approx. 6 hours after the last administration, a time distance that is consistent with normal slaughtering practices. Each laying hen was transferred into a special cage, weighed and anaesthetized using carbon dioxide gas. Under general anaesthesia the animals were sacrificed by decapitation followed by exsanguination.



Preparation of organs and tissues

After exsanguination, the following edible organs and tissues were dissected: muscle (leg and thorax), fat (subcutaneous), liver (without gall bladder), skin (without subcutaneous fat), kidneys and eggs from the ovary and oviduct.

The organs or tissue samples were transferred into tared weight plastic vessels. After determination and recording of the individual weights, muscle, fat, liver, skin, kidney samples and eggs dissected from the ovary and oviduct were passed several times through a mincing machine in half-frozen state or blended with an Ultra Turrax in thawed state. Aliquots of the individual organ and vissue samples were combusted and the radioactivity measured by LSC Ø

The organ and tissue samples of the six hens were pooled separatel provided in the sample type, divided in suitable portions that were stored frozen at \leq -18 °C until the start of metabolite analysis. For kin, the remaining homogenates of kidneys and eggs from the ovary/oviduct, merabolite analysis was optional.

All individual samples were identified with a specific sample number. The individual excreta, egg, as well as organ and tissue samples were kept for 2 -1 of C at all times except during aliquotation for analysis. During the analytical work the samples and extracts of samples, were stored other in a freezer at \leq -18 °C or for a short period in a refrigerator at +4 %

Radioactivity measurement

The radioactivity measurement in viquid samples was carried out by liquid scinfillation counting (LSC). The solid samples were either desolved in BOLUTES and adjustivity determined by LSC or combusted in an oxygen approsphere using an oxidiser. The released ¹⁴CO₂ was trapped in an alkaline scintillation cocktaikand the radioactivity was determined by LSC.

C. Analytical Procedures Aliquot samples from eggs, muscle fat, liver and excreta were conventionally extracted three times with a mixture of accumultric water (8/2) with a mixture of a mixtu the combined conventional extracts from eggs, muscle, liver and excreta were partitioned against n-heptane. The purified conventional extracts were concentrated by rotary evaporation and subjected to HPL analysis based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient. **%**_/ Š

Solids of liver from the first conventional extraction overe exhaustively extracted twice with acetonitrile/water (8/2, 9/v) using microwaxe assistance followed by further treatment with microwave and 0.1 M hydrochloric acid, All exhaustive extracts were characterised using TLC analysis.

Aliquots of the conventional liver extracts were incubated for 96 hours at 37°C with a defined amount of B-glucuronidase/ary/sulfatase. After incubation, the enzymatic suspensions were purified and analysed by HPLC

Metabolite analysis

Parent compound and metabolites, were quantified in the extracts by HPLC based on reversed phase chromatography using an acidic water/actonitrile/THF gradient.

The following strategy was used for identification of the parent compound and metabolites:

All metabolites were assigned based on a comparison of the metabolite profiles and retention times analysed in the her metabolism study after administration of pyrazole labelled BCS-CN88460. Parent compound and metabolities were identified in selected samples by HPLC or TLC co-chromatography with radiabelled reference compounds taken from the hen metabolism with the pyrazole label or from the goat metabolism study with the phenyl label. The assignment of parent compound and metabolites in all samples was then achieved by comparison of HPLC metabolite profiles of the analysed samples among each other. The conventional extract of liver was enzymatically digested.



Atton to be and the second of the second of

behavior behavi The glucuronic acid and sulphate conjugates were thereby digested and converted into their corresponding aglycons.

Unknown metabolites were characterised based on their extraction and chromatographic behavious



Report name/ other names/codes	Chemical Name (IUPAC)	Chemical Structure
Parent compound	N-(5-chloro-2-isopropylbenzyl)-	F F H ₃ C H ₃ C
•	N-cyclopropyl-3-	
D: BN5005A	(difluoromethyl)-5-fluoro-1-	
ID. BINSOUSA	methyl-1H-pyrazole-4- carboxamide	
		F B S
	S.	Q ³ ^C Q S ^C Q A
BCS-CN88460-desmethyl-1,2-	N-[5-chloro-2-(1,2-	Y O LOY AL OH
propandiol-N-GlucA	dihydroxypropan yl)benzyl]-N-y cyclopropyl-3 (difluoromethyl)	
	fluoro-1-(glucopyran@onosyl)	
D: BN4115A	1H-pyrazole-4-carboxamide	
DCS CN00/(A damasth 1 1 4		
BCS-CN88460-desmethyl-1,2- propandiol-SA	not available of the second	To the second se
	net available	F G H G OR2
- Alexandre - A		R ₁ ,R ₂ :H,SO ₃ H
ID: BN4115B		
, Q		
· ¥ _ 3		
BCS-CN88460-desmettbyl-	N=19-chloro-2-(1-19 droxxpropan-0	С С С С С С С С С С С С С С С С С С С
propanol-N-GlucA	Syl)bengyl]-N-cyclopropyl-3-@	
	(difluoromethy))-5-fluoro-1-	
	(glucopyranuronosyl)-1H-	
		ClucA F
		C1
BCS-C888460-desmethel-2-	N-[5-chlore-2-(2-hodroxypropan-	ОН
propanol-N-GlucA	2. vl)ben@l]-N-cyclopropyl-3-	$F \qquad F \qquad H_3C \qquad CH_3$
	difluoromethy)-5-fluoro-1-	
	(glucopyranuronosyd)-1H-	N
	pytazole-4-carboxamide	
A Ó		GlucA F
		Cl
BCS-CN88460-1.2-mandrol-	& Q' X	OR ₁
SA V	pot available	F F O H ₃ C OR ₂
D: BN4115E		N R ₁ ,R ₂ :H, SO ₃ H
	Ų ~\$ [™]	
	~	H ₃ C Cl
BCS-CN88460-desmethyl-2- propanol-N-GlucA D: BN4115D BCS-CN88460-1,2-propandiot- SA D: BN4115E D: BN4115E Cable is continued on the next page		

 Table 6.2.2- 9:
 Overview List of reference compounds



Report name/ other names/codes	Chemical Name (IUPAC)	Chemical Structure
BCS-CN88460-desmethyl-1,2- propandiol	N-[5-chloro-2-(1,2- dihydroxypropan-2-yl)benzyl]-N- cyclopropyl-3-(difluoromethyl)-5-	
ID: BN4115X	fluoro-1H-pyrazole-4-carb@amide	
BCS-CN88460-1,2-propandiol	N-[5-chloro-2-(1,2) dihydroxypropen-2-yl)@nzyl]	
ID: BN4115E2	cyclopropyl-3Qdifluoromethyl)-5- fluoro-1-methyl-110pyraz de-4- carboxamide	
BCS-CN88460-propanol-SA	2-{4-enforo-2-decyclopropyl{} (difluoromethyl)-5-fluoro-1-methyl 11d-pyrazot 4-	F 0 0 H 3 C 0 SO3H
ID: BN4114A	propyl hydrogen sulfat	
BCS-CN88460-desthethyl	2-{4-chłoro-2-{cyclopropyl {3- (diffuoromethyl)-5-thoro-1ff- pyfazol-4	
BCS-CX99/99° &	sj]carbonyl}aninso)methyl]phenyl}	OH OH
ID: BN494B	pyfazol-44 g]carbonyl}amino)methyl]phenyl} proparatic acid	H H F Cl
BCS-CN88460-desmethyr-	N-[&chloro-2-(1-hydroxypropan-2- xi)benzy]}-N-cychopropyl-3- ddifluoromethy}-5-fluoro-1H-	F F 0 H ₃ C 0H
	pyrazole-4-carboxantide	
and		H F Cl
ID: BNANAAB		



Table 6.2.2- 9	continued
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Report name / other names/codes	Chemical Name (IUPAC)	Chemical Structure					
BCS-CN88460-carboxylic acid/ BCS-CY26497	2-{4-chloro-2-[(cyclopropyl{[3- (difluoromethyl)-5-fluoro-1-methyl- 1H-pyrazol-4-						
ID: BN4114F	yl]carbonyl}amino)methyl]phenyl}pro panoic acid						
BCS-CN88460-propanol	N-[5-chloro-2-(1-hydroxypropan-2-	F F G H OH					
BCS-CY24813	yl)benzyl]-N-OcloprOpyl-3- (difluoromethyl)-5 Haoro-1 methyb 1H-pyrazolo 4-carboxamide						
ID: BN4183B	1H-pyrazolo 4-carboxamide						
ID: BN4183B							

A. Recovery and Elimination of Radioactivity

¢, The overall recovery accounted for 193.36% of the total dose and up to the time of sacrifice, 102.97% of the total dose was excreted. After the third administration the daily excretion rate was on a more or less constant level of about 7.1 to 8.8 % within 24 hours. In average amount of 0.14% of the total dose was measured in the eggs. At sacrifice, the radioactive residues in the organs and tissues dissected from the bodies were calculated or estimated to be about 0.24% of the total dose.

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All TRRs for eggs and dissected organs and bissues were calculated as radioactivity originating from

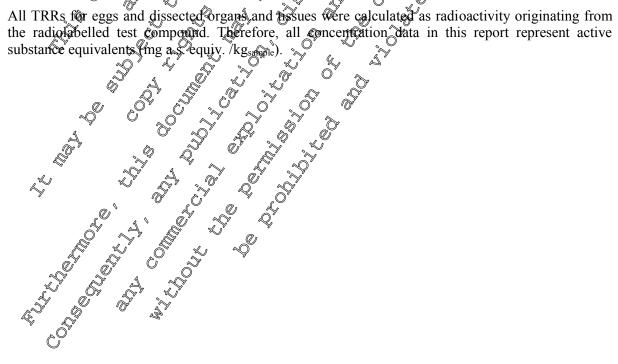




Table 6.2.2-10: Distribution of residues in liver, kidney, eggs, muscle, skin and fat of laying hens following oral administration of 14 daily doses of [phenyl-UL-14C]BCS-CN88460 at a dose rate of 1.01 mg/kg

[phenyl-UL- ¹⁴ C]BCS-CN88460 at a dose rate of 1.01 mg/kg								
Sample	Collection time	TRR [mg/kg] *)	Transfer factor **)	Percent of A total dose administered				
Liver		0.373	0.021	0.07 20 0				
Kidney		0.360 💍	0.021					
Eggs from ovary/oviduct	approx. 6 h	0.096	0-005					
Total skeletal muscle #)	after last admin.	0.024	0.001	0.01 0.02 0.02 0.07 0 0.07 0 0 0 0 0 0 0 0 0 0 0 0 0				
Total body skin [#])		0.109	0.0006					
Total body fat [#])		& 0.0 4 7 ~	× × × × × × × × × × × × × × × × × × ×	0:04 V				
Total of organs/tissues	4		Ø Ø	0° 20.24 2 2°				
	, C	27 2 °	× A ó					
Eggs, total	day 1 - 3.25	€ 60 47 ~	0.003	\$ \$14 O				
Eggs, plateau-level	dax(4 - 13%	°~0.050°	0.9993	§				
Excreta, total	Sday 1 - 13.25		0 ⁴	D02.97				
Total Recovery	A A			8 103.36				
Feeding level	18.12 Q		ng a.s. /lo dry fe	d/day]				

#) Percentage ralues were calculated from the body weights at sacrifice, assuming 40%, 12% and 4% of the body weight for total skeletal muscle, fat, or skin (without subcutations fat), respectively.

L)

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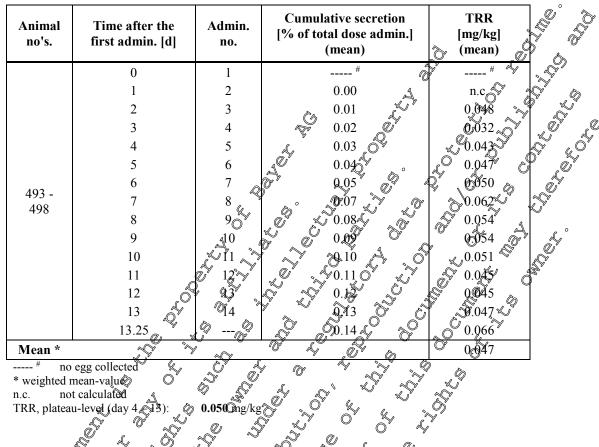
- *) weighted mean TRR-values of the individual mimals
- **) The mansfer factor was calculated by dividing the TRR-vane of the respective sample by the feeding lever (milligrams of a.s. perkilograms dry feed on each day). Ø

B. Levels and Time Dourse of Total Radioactive Residues in Eggs

B. Levels and Time Course of Total Radioactive Residues in Eggs The TRR-values in eggs ranged from 0.032 mg/kg at day three to 0.066 mg/kg at sacrifice. Following a lime increase a residue platear level of 0.050 mg/kg was reached at day four after the first administration



Table 6.2.2- 11:	Time course of total radioactivity in eggs following oral administration of 14 daily
	doses of [phenyl-UL- ¹⁴ C]BCS-CN88460 at a dose rate of 1.01 mg/kg



C. Total Radioactive Residues in Dissected Organs and Fissues

The highest TRR-value was determined in liver (0.373 mg/kg 0.07% of total admin. dose) followed by kidney (0.360 mg/kg; 0.01% of total admin, dose) indicating the significance of these organs for metabolism, and excretion. The TRR-value of the eggs collected from the ovary and oviduct at sacrifice (0.096 mg/kg) was by a factor of 1.5 bigher than the levels of the laid eggs collected at sacrifice (0.066 mg/kg). This showed that the egg yolk was a preferential site for secretion of test compound related adioactivity dower PRR-values were detected for subcutaneous fat (0.047 mg/kg), skin (0.109 mg/kg) and total skeletal muscle (0.024 mg/kg). The TRR-values of the total subcutaneous fat, skin and purscle corresponded to about 0.04% 0.03% and 0.07% of the total dose assuming values of 12%, 4% and 40% of the body weight or these tissues, respectively.

D. Extraction Efficiency of Residues

The majority of the residues in the eggs as well as organs and tissues were efficiently extracted (85.4% to 93.3%) using acetonitrile water mixtures. In case of liver, the solids after conventional extraction were further extracted using microwave treatment releasing 14.5% of the TRR (0.054 mg/kg). Only up to 8.2% of the TRR (0.000 mg/kg) of the residues remained in the post extraction solids (PES).

For sample preparation, the extracts were partitioned against n-heptane except the extract from fat. Very low amounts of radioactivity were recovered in the n-heptane phases amounting to $\leq 1.2\%$ (0.007 mg/kg) of the TRR. Concentration procedures of the aqueous phases caused no losses, so all of the residues in the aqueous phases were quantitatively analysed by HPLC.

A summary of the extraction efficiency is shown in the table below.



 Table 6.2.2- 12:
 Extraction efficiency of eggs, muscle, fat and liver samples following oral administration of 14 daily doses of [phenyl-UL-¹⁴C]BCS-CN88460 at a dose rate of 1.01 mg/kg

1.01 mg/ng										o s
Sample		ggs 4 – 13)	Musc	le Leg		scle orax	(at)	Lôye	r r
TRR [mg/kg]	0.0)50	0.0)29	0.0)17	Ŵ.()47	0.374	i ș
	% of TRR	mg/kg	% of TRR	mg/kg	% of ØTRR	mg/kg	TRR	mg/kĝ	O% of TRR [®] ⁿ	ng/kg
Conventional extraction	92.8	0.046	93.3	0.027	92.4	0,686	91.8	0,043	ÃŐ .	2:318 6 ⁵
Exhaustive extraction						á	。	,	[©] 14.50 [°]).0 5@
Total extracted	92.8	0.046	93.3	0.027	92.4	0.016	91.8	0,043	9 9.9	Q. 373
Post-extraction solids (PES)	7.2	0.004	5 .7		92.4 \$7.6	\$.001	~ (°	0.004		0.001
Accountability	100.0	0.050	J100.0	0.029	100.0	0.017	100.0	0.047	190.0	\$373
		s s		@, [¥]	a .	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	×.	~	d i de la constante de la const	/

E. Quantification, Identification and Characterisation of Residues

Parent compound and metabolites were quantified in the conventional extracts by HPLC chromatography based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient. Metabolites in the extracts were assigned to each other by comparison of the metabolite profiles and their retention times. Corresponding metabolites were named with the same peak ID.

BCS-CN88460 metabolites were identified by co-chromatography with radiolabelled reference compounds taken from the her metabolism study after administration of pyrazole labelled BCS-CN88460 or from the goat metabolism study after administration of phenyl labelled BCS-CN88460. Metabolites in other organs and tissues were assigned by comparison of the metabolic profiles and retention times. In addition, the assignment of parent compound and metabolites in the current study was performed based on a comparison of the retention times and metabolic profile of the current study and the her metabolism study will the perazole label

F. Distribution of Parent Compound and Metabolites in Eggs, Organs and Tissues

C

The identification rates amounted to 79.2% of the TRR for eggs, 79.8% for leg muscle, 76.3% for thorax muscle $\mathfrak{S}1.5\%$ for fat and 62.9% for log liver.

Parent compound was only detected in eggs, bg muscle and fat and amounted to 0.003 mg/kg (6.4% of the TRR) for eggs, 0.001 mg/kg (20.1% of the TRR) for leg muscle and to 0.009 mg/kg (20.1% of the TRR) for fat.

Metabolites in eggs (day 42-13)

Metabolites BCS-CN88460-propanol and BCS-CN88460-desmethyl-propanol were the main residues in eggs and accounted for 0.017 mg/kg (33.9% of the TRR) and 0.011 mg/kg (22.6% of the TRR), respectively. Other prominent metabolitos in eggs were BCS-CN88460-desmethyl-propanol-N-GlucA, BCS-CN88460-desmethyl-1,2-propandiol and BCS-CN88460-carboxylic acid, each \leq 7.2% of TRR.



Metabolites in leg and thorax muscle

The main residues in leg muscle were BCS-CN88460-desmethyl-propanol (25.8 % (0.007 mg/kg) of the TRR), BCS-CN88460-desmethyl-carboxylic acid (19.9% (0.006 mg/kg) of the TRR) and BCS-CN88460-desmethyl-1.2-propandiol (14.2% (0.004 mg/kg) of the TRR). These three main metabolites were also detected in the thorax muscle and amounted between 202% and 22.3% of the TRR. BCS-CN88460-carboxylic acid was a prominent metabolite in leg and thorax muscle and amounted to 6.6% and 8.6% of the TRR, respectively. Minor metabolites in puscle were BCS-CN88460-desmethyl-propanol-NaGlucA BCS-CN88460-desmethyl-1,2-propandiol-N-GlucA, (both only detected in leg muscle) and BCS-CN88460-propanol (all $\leq 4.3\%$ of TRR).

Metabolites in fat

Besides parent compound as the main residue in far, five abundant metabolites were identified and named as BCS-CN88460-desmethyl-1,2-proparatiol, BCS-CN88460-desmethyl-carboxylic æid, BCS-CN88460-desmethyl-propanol, BCS-CN88460-carboxy/bc actor and BCS-CN88460-propanol. These five metabolites amounted between 3.0% and \$,0% of the TRR.

Metabolites in liver

The main residue in liver was identified as BC\$2CN88460-desmethy-carboxylic acid \$1.9% (0.082 mg/kg) of the TRR). Prominent metabolites in the liver were BCS-CN@8460 desmethyl-1,2propandiol-N-GlucA, BCS-CN88460-desmethyl-propanol-N-GlucA, BCS-CN88460-desmethyl-1,2propandiol and BCS-CN88460-carboxylic acid and appounted between 5.5% and 10.8% of the TRR. Four minor metabolites named as BCS-CNSS460-CESmethyl-2-propanceN-GLOCA, BCS-CN88460propanol-SA, BCS-CN88460 desmethyl-propanol and BCS-CN88460 propanol were detected (all

More metabolites in the matrices may be present as indicated by broad non-resolved zones in the chromatograms. All@inknown metabolites in the extracts were characterised by their extraction and

The distribution of the parent compound and metabolites in milk, organs and tissues is summarised in

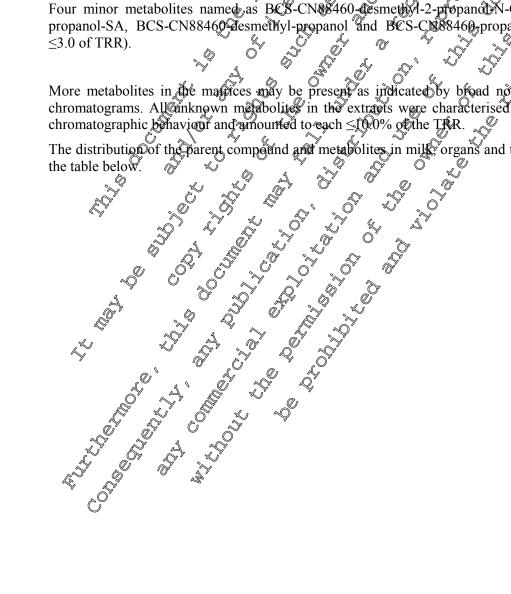




Table 6.2.2- 13:Radioactive residues of parent compound and metabolites in eggs and edible organs
and tissues of laying hens following oral administration of 14 daily doses of [phenyl-
UL-14C]BCS-CN88460 at a dose rate of 1.01 mg/kg

	UL- ¹⁴ C]BCS-CN88460 at a dose rate of 1.01 mg/kg										
SampleEggs (day 4 - 13)Muscle LegMuscle ThoraxFat Sample							Li				
TRR [[mg/kg]	0.0	50	0.0	29	0.0	17		47	. (9.3	73 🔊
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg		
Conve	entional extraction	92.8	0.046	93.3	0.027	92.4	0.016	91.8	0.043	85%4	0318
42	parent compound	6.4	0.003	2.9	0.001			20.1	0,009	S	ő ő
7	desmethyl-1,2- propandiol-N- GlucA (M36)			L.	9,001		Q	Ŷ		9.2 9.2	0.034
18	desmethyl- propanol-N-GlucA (M37)	3.0	0.002	ð.8	00001						0.040
19	desmethyl-2- propanol-N-GlucA (M38)									20 20 20 20 20 20 20 20 20 20 20 20 20 2	\$0.011
22	desmethyl-1,2- propandiol (M07)	6.2	n″	@14.2°	≫0.004 →	22.5	0.000	5.9	0.693	× 3.6	0.021
29	propanol-SA (M26)	<u>.</u>		- A-			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>	<u>0 k</u>	1.2	0.005
33	desmethyl- carboxylic acid (M11)	\$ <u>}</u>			0.006		~~		0,004	21.9	0.082
35	desmethyl-propanol (M06)	22.6	0.011	35.8	Q007	620.9¢	0.004	×.)* 8.0	§0.004	2.7	0.010
37	carboxylic acid (M12)	7.2°	\$0.004	6.6		\$,6		3.0	0.001	5.8	0.022
38	propanol (M01)	33,9	0.017	2.5	0 001	ي 4.3	Ø.001 [*]	S 6.5	0.003	1.7	0.006
	identified [©]	79.2	0 :040	@ Ť9.8 3	<u>(</u>)0.023		-	51.5	0.024	62.0	0.231
conver by HP.	cterised in the 7 ntional extract LGT	124 25	0.000	182	0.004	0 d.6.1	10-003	40.3	0.019	23.1	0.086
Num peaks	bervof unknown s				y %		2	,	7	17	
	est unknown peak 🔬	49	0.002	& 6 .7	0.002	€8.5	0.001	10.0	0.005	8.0	0.030
Chara (n-hep	cterised by partition," ptane phase)	49 2 1.2	9.001		\$0.001 	ð				0.3	0.001
Exhau	istive extraction	× 10		62	<u></u>					14.5	0.054
- ACN	/water extract		Ŵ	<u>~</u>	"»					4.8	0.018
peak	- 4	4			₽″					5	5
Largest unknown @ peak @										2.4	0.009
	A HCL extract _ → `	<u> </u>	Ž	····						9.6	0.036
Number of onknown peaks Larges of unknown		A A	Ŷ.							4	L
реақ		\$~								6.6	0.025
16.25	characterised	13.6	0.007	13.5	0.004	16.1	0.003	40.3	0.019	37.9	0.142
	extractable	92.8	0.046	93.3	0.027	92.4	0.016	91.8	0.043	99.9	0.373
	ractable (PES)	7.2	0.004	6.7	0.002	7.6	0.001	8.2	0.004	0.1	< 0.001
Accou	intability	100.0	0.050	100.0	0.029	100.0	0.017	100.0	0.047	100.0	0.373



Conjugates in the liver like BCS-CN88460-desmethyl-1,2-propandiol-N-GlucA, BCS-CN88460desmethyl-propanol-N-GlucA, BCS-CN88460-desmethyl-2-propanol-N-GlucA and BCS-CN88460propanol-SA could be enzymatically cleaved to their aglycons. The cleavage of some unknown conjugates in non-resolved zones resulted in higher amounts of the aglycons. None of the unknown compounds after cleavage accounted for more than 5.4% (0.020 mg/kg) of the TRR. The following main aglycons could be clearly identified after enzymatic cleavage: BCS-CN 88460-desm en yl-123propandiol and BCS-CN88460-desmethyl-propanol.

					2		<u> </u>		
		Liver-		Liv	er-		ntic cleava	ge of five liver extra	aliquots
Samj	ble	1 st conv extra		2 nd Conv	2 nd conventional extraction		vælues 🔊	standard	
				k, ô				`≊~devi	ation
Peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	%x0f _\$TRR	æg/kg (7% of TRR	mg/kg	[%] of [*] O _{TRR}	mg/kg°
Extra analy	ct used for HPLC sis	85.1	0.317	84.6	ר,315	78.3	0292	<u>ک</u> 1.0	Õ 0.004
	desmethyl-1,2-	9.2 ₍	0.034	°~~~9.5	× 0.035	D.4	\$.005	QQ 0.90	0.000
7	propandiol-N-GlucA (M36)	Ą,							
18	desmethyl-propanol- N-GlucA (M37)	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	°∼y 0.040	10.1 L	¢0.041 م م		0.903	0.1	0.000
19	desmethyl-2- propanol-N-GlucA (M38)	, dy , dy , o	6)011 6) Ô	3.4	0.013	~~~0.6 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	× 0.002	0.2	0.001
22	desmethyl-1,2-	560	0.021	5 ⁹ 4.3	0.016 ©	01.0	م م م	0.4	0.001
29	propanol-SA (M26)	£1.2	0.005	× 13	. 005	Ô -S			
33	desmethyl Carbox Oc acid (M19)	21.9	5 0.Q82	21.1	0.07 %	25.7	0.096	0.8	0.003
35	desmetbyl-propanol	19:7 29:7	A,010	2. 9	0,009	7 14.1	0.053	0.4	0.002
37	carboxylic acid (X42)	\$ 5.8	0.022	×06.9	0.026	9.0	0.033	0.6	0.002
38	propanol (M0 b)	V K	<u>∘</u> Q,006	× 1,2×	0.004	1.7	0.006	0.2	0.001
Tota	identified 6 A	62.0	×0.23K	61.3	0.229	64.4	0.240	1.3	0.005
Total	characterised	23.1	0.088	22.8	0.085	14.0	0.052	0.6	0.002
Acco	untability 🖓 🖉 🔊	O 85.J	Q ¥17	84.₽	<i>v</i> 0.314	78.4	0.292	1.0	0.004
	C	<u>`</u>	<u>1</u>	ñ Ũ					

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		A	
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	<i>⊳</i> a	l C	
Table 6.2.2- 14:	Radioactive residues of parent compound and	motobolitos in live	manmalas of first
1 abic 0.2.2- 14.	Radioactive residues of parent compound and	inceasines in nye	si sampies ur musi
	and second conventional extraction and after en	nzvimatic cleavage	tor 96 m 🔍 🖓

The excreta extract of day 1 was analysed by HPLC. Parent compound accounted for 1.2% of the dose. BCS-CN88460-desmethyl-carboxylic acid was the most prominent compound and amounted to 20.0% of the dose. Further rone identified metabolites ranged from 0.8% to 9.6% of the dose.

Generally metabolites in the extract from excreta were the same as in eggs, organs and tissues, except for metabolites BCS-CN88460-desmethyl-1,2-propandiol-SA, BCS-CN88460-1,2-propandiol-SA and BCS-CM8846 1,2-propandfol which accounted for equal or less than 7.2% of the dose, respectively.



G. Storage Stability of Residues

All samples of eggs, excreta, edible organs and tissues were extracted within three months after sample collection. Quantitative analysis by HPLC was performed either on the day of extraction of up to one day after the start of extraction.

A second conventional extraction of liver was performed approx. 9 months after sampling. The extract was used for enzymatic cleavage experiments. The storage stability was exemplarily demonstrated for these liver samples.

It was therefore concluded, that the metabolic profiles represent the residues in the matrices and analysed samples at sacrifice.

III. Conclusion

The metabolic behaviour of [phenyl-UL-¹⁴C]BCS-CN88460 in the laying then can be characterised by the following observations:

The TRR-values and even the transfer factors in eggs and edible tissues were low with respect to the dose level and the dosing period of 14 days. This indicates that test compound related radioactivity does not accumulate during the time of feeding. The evaluations of the TRR values hould however consider the fact that an exaggerated dose level of 18.12 mg a.s. a feedbay was administered. Furthermore, the fact that the entire radioactivity was detected in the exceta and the relatively high TRR in kidney and liver at sactifice approx. Chours after the last administration reveated that the test compound related residues are further metabolised and finally eliminated from the hen's bodies. A residue plateau level in eggs was reached during the course of the experiment at day four after the first administration.

The radioactive residues were extracted with conventional methods from eggs and tissues; extraction rates ranged from 92.8% to 93.3% Extraction with conventional and exhaustive methods from edible organs accounted for 99.0% for the liver.

The identification rates in eggs, edible organs and tissues ranged between 51.5% and 79.8% of the TRR.

Parent compound was detected in eggs leg muscle and fat

Overall nine metabolites were identified in eggs, edible organs and tissues. Metabolites BCS-CN88460-propanol (M01), BCS-CN88460-desmethyl-propanol (M06), BCS-CN88460-desmethylcarboxylic acid (M11), BCS-CN88460-desmethyl-1,2-propanol (M06), BCS-CN88460-desmethylcarboxylic acid (M12), BCS-CN88460-desmethyl-1,2-propandiol (M07) and BCS-CN88460carboxylic acid (M12), BCS-CN88460-desmethyl-1,2-propandiol (M07) and BCS-CN88460-desmethylresidues in eggs, leg ouscle, thorax muscle, fat and liver. In liver, metabolites BCS-CN88460-desmethyl-propanol N-GlucA (M37) and BCS-CN88460-desmethyl-1,2propandiol N-GlucA (M36) were further prominent metabolites. Minor metabolites were BCS-CN88460-desmethyl-2 propanol-N-GlucA (M38) and BCS-CN88460-propanol-SA (M26).

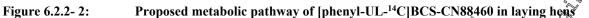
The rectabolic profile of exerct from day 1 was similar to the profiles of edible materials, especially liver, with the difference that netabolites BCS-CN88460-desmethyl-1,2-propandiol-SA (M42), BCS-CN88460-1,2-propandiol-SA (M27) and BCS-CN88460-1,2-propandiol (M03) were present.

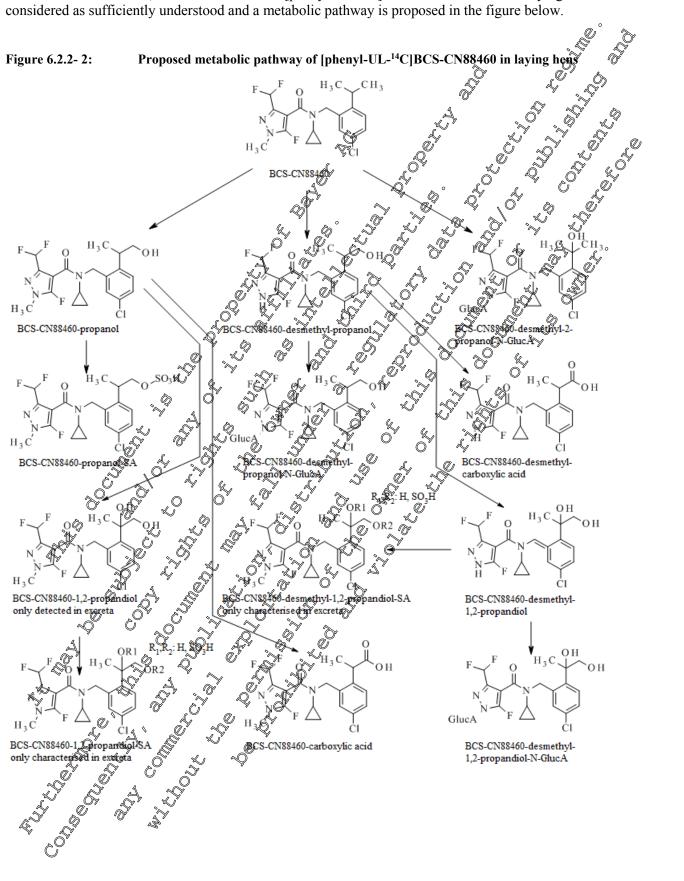
The principal metabolic reactions of [phenyl-UL-¹⁴C]BCS-CN88460 in the laying hen are listed below:

- demethy ation of the pyrazole moiety
 - Conjugation with glucuronic acid after demethylation of the pyrazole moiety
 - $\mathbb{R}_{p}^{\mathbb{P}}$ hydroxylation in position 1 and position 2 of the propyl group in the phenyl ring
 - further oxidation of the 1-propanol group was leading to a carboxylic acid group
 - conjugation with sulphuric acid after hydroxylation in position 1 or position 2 of the propyl group



Based on these results, the metabolism of [phenyl-UL-14C]BCS-CN88460 in the laying hen is considered as sufficiently understood and a metabolic pathway is proposed in the figure below.







CA 6.2.3 Lactating ruminants

The metabolism of the fungicide isoflucypram in lactating goats was investigated after administration with isoflucypram either labelled in the pyrazole or in the phenyl moiety.

Overview over available lactating goats metabolism studies Table 6.2.3-1:

Poultry	Application	Dose 🗸	Reference
Lactating goat	5 daily doses over 5 days of pyrazole- labelled isoflucypram via gelatine capsules	1.0 mg/kg bw	M-604291-0147
Lactating goat	5 daily doses over 5 days of phenyl- labelled isoflucypram via gelatine capsules	A.0 mg/kg bw β°	\$4+6042 8 6-01-1
	O.A.		

Summary of metabolism in ruminants

A

The metabolite pattern corresponds well when comparing the two metabolism studies in lactating goats. Parent compound was detected in milk, muscle, fat liver and kidpey. It was a major compound in milk, muscle and fat and a miner compound in liver and kiepey. BOS-CN884602-propanol (M02), BCS-CN88460-propanol (M01), BCS-CN88460-2-propanol Oluca (M20), BCS-CN88460-propanol-GlucA (isomer 1, M19 - isomer 1) and BCS-CN88400-carboxylic acid (M12) were major metabolites. The metabolic reactions were hydroxylation in position 1 and/or position 2 of the propyl group following conjugation with gluculonic acid.

Report: $KCA 6.2.901;$ $KCA 6.2.901$
Report: $\sqrt{8}$ KCA 6.3 $\sqrt{1}$ R · · · · A · K $\sqrt{2}$ F · 2017· M-
Title: (Pyrazole-4-CIC)BC CN88460 - Metabolism in the lactating goat EnSa-17-0309
Title: [Pyrazole-4-@C]B&CN88460 - Metabolism in the lactating goat
Document No.: $M_{r}6042$ $V_{r}01$ V_{r}
Guideline S: @ECD Pest Godeline No. 503 Commission Regulation (EU) No 283/2013 in
accordance with Regulation (EC) No 1107/2009
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Guideline deviation (S): none (C) (C) (C)
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Executive Summary

The motabolism and excrement of pyrazole-4-14 BCS-CN88460 was investigated in the lactating goat as a model for ruminants The test compound was orally administered to a lactating goat in gelatine capsules at a dose of approx. Img perkg body weight. Based on the daily feed consumption, the dose level corresponded to 45.19 mg a. Kg dry feed/day. The goat received five doses at 24-hour intervals in the morning after milking and was sacrificed approx. 6 hours after the last dosing.

Throughout the experiment, the goat was housed in a metabolism cage, which permitted separate collection of time and facees. The goat was milked in the morning immediately prior to each administration, about eight hours later in the afternoon and approx. 1 hour before sacrifice. The total radioactive residues (TRRs) were determined in each milk sample and in dissected organs and tissues (muscle, fat, liver and kidney) at sacrifice. The total radioactivity (% of total dose administered) was additionally determined in each urine and faeces sample.



Recovery and Elimination of Radioactivity

The overall recovery accounted for approx. 64% of the total dose. The remaining amount of radioactivity (approx. 36%) was expected to still be present in the non-edible part of the animal wedy and especially in the gastrointestinal tract at sacrifice due to the short time period between last administration and sacrifice (approx. six hours).

An amount of approx. 0.03% of the total dose was secreted with the milk, only. At sacrifice, radioactive residues in the edible organs and tissues dissected from the body were calculated to be approx. 0.72% of the total dose and were very low.

Up to the time of sacrifice, approx. 6.9% of the total dose was excreted with the trine and approx. 56.1% with faeces. The daily renal excretion of the radioactivity started shortly after the first dosing before the daily renal excretion rate reached a more or less constant level with round about 0.1% to 1.9%. The daily faecal excretion of the radioactivity started after the first dosing. The daily faecal excretion was characterised by a limer increase from 24 h until sacrifice.

Total Radioactive Residues in Milk, Organs and Tissues

The TRR-values and transfer factors for milk, organs and tissues were very low compared to the dose level of 45.19 mg a.s./kg feed/day and a dosing period of tive days.

The TRR-values in milk samples ranged from 0.009 mg/kg to 0.021 mg/kg after the first and third administration, respectively. The time course of TRR-values of the evening and norning milk samples indicated a diurnal pattern for the testing period. The radioactive residues increased significantly during the eight-hour period after cach administration.

Regarding organs and tissues the TRR-values another do 0.038 mg/kg for muscle (composite of round and loin muscle), 0.102 mg/kg for fat (composite of perirenal and omental fat), 0.717 mg/kg for liver and 0.189 mg/kg for kidney

Metabolism

The majority of the residues in the milk as well as organs and tissues were efficiently extracted (extraction rates between 89.2% and 98.7%) using acetonitrile/water (8/2; v/v) mixtures. In case of muscle and liver, the solide after conventional extraction were exhaustively extracted using acetonitrile/water mixtures with microwave treatment. Up to 7.8% of the TRR or 0.036 mg/kg of the residues remained in the post extraction collids (PES). After partitioning of the conventional extracts against n-heptane very low amounts of radioactivity were detected in the organic phases amounting to $\leq 1.4\%$ of the TRR, only \sim

Parent compound and metabolites were identified based on co-chromatography with isolated metabolites and reference compounds or by comparison of the metabolite pattern and retention times. Metabolites were isolated from urine and identified by spectroscopic investigations.

The identification rates appointed to 530% of the TRR for milk, 67.7% for muscle, 81.5% for fat, 58.3% for liver, and 65.4% for kidney.

Parent compound was detected in milk, muscle, fat, liver and kidney. It was the major compound in milk, muscle and fat and appinor compound in liver and kidney. Overall up to eleven metabolites were identified.

Metabolite BCS-CN88460-2 propanol (M02) was detected in all matrices, amounting from 2.6% to 20.3% of the TRR and represented a major residue (>10% of the TRR) in milk, muscle and fat. Metabolite BCS-CN88460-carboxylic acid (M12, representing a major metabolite in kidney) and BCS-CN88460-propanol (M01, representing a major metabolite in muscle) were detected in muscle, fat, liver and kidney. The amount of BCS-CN88460-carboxylic acid (M12) amounted between 3.3% and 18.0% of the TRR, while the amount of BCS-CN88460-propanol (M01) amounted between 2.7% and 10.2% of the TRR. BCS-CN88460-2-propanol-GlucA (M20) and BCS-CN88460-propanol-GlucA



(isomer 1, M19 – isomer 1) (both representing a major metabolite in liver) were detected in liver and kidney and ranged between 2.6% and 13.8% of the TRR. Metabolites BCS-CN88460-propanol-GlucA (isomer 2, M19 - isomer 2) and BCS-CN88460-desmethyl-propanol (M06) were detected in muscle, liver and kidney and their amount ranged between 0.5% and 7.7% of the TRR. BCS-CN88460 actic acid (M10) and BCS-CN88460-desmethyl-carboxylic acid (M11) were identified in liver and addrey. BCS-CN88460-N-methyl-pyrazole-carboxylic acid (M50) and BCS-CN88460 propenol-Glue (M25) were detected in kidney, only. All metabolites were minor abundant and accounted for equal or jess than 6.1% of the TRR.

More metabolites in the matrices may be present as indicated by broad non-resolved zones in the chromatograms. All unknown metabolites in the extracts were characterised by their extraction and chromatographic behaviour and amounted to $\leq 14.3\%$ of the TRR.

The metabolic profiles of urine and faeces were similar to the profiles of edible materials, especially liver and kidney, except that parent compound was not present with a e^{it} is the specially interval.

The metabolic profiles of urine and faces were similar to the profiles of edipte materials, especially live and kidney, except that parent compound and metabolite, for edipte materials is provided in the following table:



Table 6.2.3- 2:Radioactive residues of parent compound and metabolites in milk and edible organs
of lactating goats following oral administration of 5 daily doses of [pyrazole-4-
14C]BCS-CN88460 at a dose rate of 1.0 mg/kg

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peak ID ID ID BCS-CN88460 Compound (Report name) BCS-CN88460 % of TRR mg/kg % of TRR % of TRR % of TRR % of TRR % of TRR <td>Samp</td> <td>le</td> <td>Μ</td> <td>lilk</td> <td>Mı</td> <td>ıscle</td> <td>ŀ</td> <td>^rat</td> <td colspan="2">Liver</td> <td>Kie</td> <td>hney</td> <td>Ş</td>	Samp	le	Μ	lilk	Mı	ıscle	ŀ	^r at	Liver		Kie	hney	Ş
Peak ID BCS-CN88460- BCS-CN88460- generational extraction % 01 TRR mg/kg % 01 TRR 0.012 % 01 TRR 0.012 % 01 TRR % 01	TRR		0.	015	0.	036	0.	104	0.'	747	0.	()8 9	0°
39 parent compound 33.4 0.005 22.3 0.008 58.7 0.066 3.5 0.025 27 0.905 4 pyrazole- carboxylic acid (M50) 5.85 0.016 25 GlucA*(M20) 5.85 0.005 25 propenol-GlucA* (M25) <t< td=""><td></td><td>(Report name)</td><td></td><td>mg/kg</td><td></td><td>mg/kg</td><td></td><td>mg/kg</td><td>TRR</td><td>mg/kg</td><td>% ốF TORR</td><td>mg/kg</td><td>þ</td></t<>		(Report name)		mg/kg		mg/kg		mg/kg	TRR	mg/kg	% ốF TORR	mg/kg	þ
39 parent compound 33.4 0.005 22.3 0.008 58.7 0.066 3.5 0.025 27 0.905 4 pyrazole- carboxylic acid (M50) 5.85 0.016 25 GlucA*(M20) 5.85 0.005 25 propenol-GlucA* (M25) <t< th=""><th>Conve</th><th>ntional extraction</th><th>98.7</th><th>0.015</th><th>89.2</th><th>0.032</th><th>≥98.3</th><th>0.102</th><th>90.1</th><th>0.646</th><th>¥ 92.2</th><th>0.174</th><th>Ĩ</th></t<>	Conve	ntional extraction	98. 7	0.015	89.2	0.032	≥98.3	0.102	90.1	0.646	¥ 92.2	0.174	Ĩ
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25 propenol-GlucA* (M25)	4	pyrazole- carboxylic acid (M50)							° ? ?		Q 5.80		
25 (M25) <td< td=""><td>25</td><td>GlucA* (M20)</td><td></td><td></td><td></td><td>Ô</td><td></td><td>, ,</td><td>43.8</td><td>0.099</td><td>≥≈2.6</td><td>[%]0.005</td><td></td></td<>	25	GlucA* (M20)				Ô		, ,	4 3.8	0.099	≥≈2.6	[%] 0.005	
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Accountability 7 200.0 0.015 100.0 0.036 100.0 0.104 100.0 0.717 100.0 0.189	Accou		<u> </u>		£100.0	0.036	100.0	0.104	100.0	0.717	100.0	0.189]

* BCS-CN\$8460,2 proparol-GlucA and BCS-CN88460-propenol-GlucA were co-eluting in the kidney and were submantified by A.C.

The many metabolic reaction was the hydroxylation in the propyl group of the phenyl ring. Conjugation with glucuronic acid was observed after hydroxylation in position 1 or 2 of the propyl group. Another important metabolic reaction was the carboxylation of the 1-propanol group, leading to a carboxylic acid or with a hydroxy group in position 2 of the propyl group to a lactic acid. Minor



metabolic reactions were the demethylation of the pyrazole moiety, the cleavage of the phenyl moiety in combination with cleavage of the cyclopropyl ring and the dehydration after hydroxylation in position 1 and 2 of the propyl group followed by conjugation with glucuronic acid.

is 5 Based on the results the metabolism of [pyrazole-4-¹⁴C]BCS-CN88460 in the lactating solat considered as adequately understood and a metabolic pathway is proposed. I. Materials and Methods A. Materials 1. Test Material <u>z</u> Chemical structure -label position Contraction of the second seco denotes the Ø dpm/mg 11 Mg/mg 1.27 x 10⁸ dpm/mg (sample after adjoint and a strain a st



2. Test Animals

Species	Lactating goat (<i>Capra hircus</i>)
Strain	"Weiße Deutsche Edelziege"
Breeding facility	
Body weight	99 kg at delivery (2015-06-08)
	89 kg at first administration (2015-06-15)
	90 kg at sacrifice (2015-06-19)
Acclimatization	7 days
Identification	On arrival, the goat was arbitrarily allocated a stock number, or supplier's 2
	7 days On arrival, the goat was arbitrarily allocated a stock number, or supplier's number. During the acclimation and testing period an individual animal number
	was allocated.
Husbandry	Conventional hygienic conditions in air-conditioned rooms $\sqrt{2}$
Housing	During the acclimation period, the goat was kept in a raised stall with a metal grid
	as base and straw and haves bedding.
	During the whole testing period, the goat was kept in an electro-polished staintess
	steel metabolism cage for farmanimate (goaf, sheep and pig, supplied by
	. With this cage, an almost separate and quantitative collection of
	urine and faces was possible. The cage was equipped with a cariable-restraining
	device.
Dietary regimen	During the mole residence time, the goat was fed ad libitim with unipant feed
	("Raiffeisen Lamm-Gold" supplied by
). It was supplemented by hay
	(during the acclimation period only), hay pellets and carros. The feed was not a
	cettified diet, i.e. a was not checked for contamination according to current
	standards. The feed consumption was recorded by back-weighing during the
	experiment. 9 & A a b b b b b b b b b b b b b b b b b b
	Tap water from the focal methos supply was given ad libition during the whole
	regidence time.

B. Study Design

Preparation of the Fest Compound for Administration

The radio abelled test compound was delivered in solid form. It was diluted in a ratio of 1:1 with the non-radio labelled test compound. In total five golatine capsules containing the solid test compound were prepared and gored in a freezer at 0-18 °C. The identity confirmation of the test compound was proven by LC-MSMS. In order to demonstrate the stability of the solid test compound in the capsules, a small portion of the test compound was sorred together with the capsules until the last administration Aliquots of the small portion were analysed for stability and purity of the test compound after the first and the last administration by HPLC. In both cases, the purity amounted to >98%.

Dosing

All oral administrations were performed using a capsule applicator once daily for five consecutive days in the morbing after milking. Each gelatine capsule contained an average amount of 89.17 mg, which corresponded to 185 MBq The total administered amount and radioactivity accounted for 445.87 mg and 94 MBq Sespectively.

The total amount of radioact with administered to the animal served as reference-value ($A_0 = 100\%$) for the percentage calculation of the total radioactivity in the biological samples.

Based upon the experimentally determined daily feed consumption during the testing period of 1,974 g dry feedber day (= 2.22% of the body weight), the dose of 1.0 mg a.s./kg bw corresponded to a concentration of 45.19 mg a.s./kg dry feed per day in the diet. This dose was tolerated without any observable toxicological effects.



Sampling of milk, urine and faeces during the in-life phase

The goat was milked in the morning immediately prior to each administration, about eight hours later in the afternoon and directly before the scheduled termination. After weighing, aliquots were taken from each sample for radioactivity measurement by LSC.

Urine and faeces samples were collected in plastic vessels or collecting grifts as quantitatively as possible under dry ice cooling in intervals of 24 hours after the administrations 1 to 4 and 6 hours after the last administration. The vessels were exchanged immediately before the next administration. The vessels were exchanged immediately before the next administration. The vessels were exchanged immediately before the next administration of the collection funnel was rinsed with deionised water into the urine vessels of the respective collection period. After determination of the total volumes, alignots of each urine sample were used for radioactivity measurement by LSC. For collection of faeces, the collecting grid was cleaned prior to was passed several times through a mincing machine in half-frozen spate. Alignots of each faeces fraction were combusted and the radioactivity measured by LSC.

Sacrifice and dissection of organs and tissues

The animal was sacrificed approx. 6 hours after the last administration, a time interval that is consistent with normal slaughtering practices. The animal was at first seclated by an intramuscular mixed injection of Xylazin/Rompun (2%; 0.2 mg/kg bw) and Detamin (10% 5 mg/kg bw) and afterwards anaesthetised by an intravenous dose of about 40 mg/kg bw Pentobarbital-Na (Narcoren®). Under deep anaesthesia, the animal was then exsanguinated by transection the jugubar vein and finally terminated by intracardiac injection with approx. 10 mL of the veterinary drug T 61®. Following exsanguination, the following clible organs and tissues were dissected: muscle (round and loin), fat (omental and perirenal), liver (without gall pladder) and kidneys.

Preparation of Organs and Tissues

The organs or tissue samples were gransferred into tared plastic vessels. After determination and recording of the individual weights, muscle, fat fiver and kidney samples were passed several times through a mincing machine in half-frozen state. Aliquots of the individual organ and tissue samples were combusted and the radioactivity measured by LSC. All samples were stored at \leq -18 °C until the start of metabolite analysis.

For metabolism investigations, peoled camples of mills (collected from 32 h until 101 h), muscle (loin and round muscle) and fat (perficial and omental) were propared Liver, kidney and faeces (0 - 24 h) were homogenised and aliquots were stored frozen until start of extraction. The radioactivity and TRR-values of the complex were calculated from the incline data

C. Analytical Proceedures

Sample Extraction and Analysis of Extracts

Aliquots from milk, fruscle, fat, kiver, kidney and faeces were conventionally extracted three times with a mixture of acetonithe/water (8/2, v/v) using a Polytron homogeniser. Additionally milk was extracted once with THP and once with acetonitrile/water (3/7; v/v). Minor radioactivity could be released by these additional extractions, only. The combined conventional extracts were partitioned against n-heptine.

The aqueous phases were concentrated by rotary evaporation and subjected to HPLC analysis based on reversed phase. Gromatography with an acidic water/acetonitrile/THF gradient.

Solids of muscle from the conventional extraction were exhaustively extracted with acetonitrile/water (1/4; v/v) using microwave assistance. Solids of liver from the first conventional extraction were exhaustively extracted twice with acetonitrile/water (8/2; v/v) followed by acetonitrile/water (1/1; v/v) and by 0.1 M HCl using microwave assistance. The metabolites in the exhaustive extract were further characterised using TLC analysis.



Aliquots of the conventional liver extracts and kidney extracts were incubated for 20 hours at 37°C with a defined amount of β -glucuronidase/arylsulfatase. After incubation, the enzymatic suspensions were purified and analysed by HPLC.

Determination of the Radioactivity in the Cream Fraction of Milk

To evaluate the radioactivity in the cream fraction of milk, an aliquot of the milk sample partitioned against n-heptane.

Radioactivity measurement

The radioactivity measurement in liquid samples was carried out by liquid scine flation country (LSC). The solid samples were either dissolved in BIOLUTE or combusted in an oxygen atmosphere using an oxidiser. The released ¹⁴CO₂ was trapped in an alkaline scintillation cocktail and the radioactivity was determined by LSC.

Metabolite analysis

based on reversed phase Parent compound and metabolites were quartified by the extracts by HPCC chromatography using an acidic water/acetonitrile/ HF gradient

The peaks in the individual HPLC profiles were numbered increasingly in the order of elution in the HPLC-profiling methods. Corresponding metabolites were named with the same peak-ID.

The assignment of parent compound and metabolites was achieved by comparison of HPLC metabolite profiles of the analysed samples among each other and compared to the goat metabolism study with the phenyl label. Furthermore, metabolites were solated from urine by HMLC. They were identified in the isolated fractions by spectroscopic methods. Other metabolites were identified by chromatographic comparison of the metabolic profile of by co-chromatography with radiolabelled test and reference compounds in selected samples. The conventional extracts of liver and kidney were enzymatically digested. The glacurorac acid@onjugates were thereby digested and converted into their corresponding aglycons.

Unknown metabolites were characterised based on their extraction and chromatographic behaviour.

Unknown metabolites were characterised based on their extraction and c An overview of the reference compounds is given in Table 6.2. \$3.



BCS-CN88460 (parent compound) N-(5-chloro-2-isopropy cyclopropyl-3-(difluoro 1-methyl-1H-pyrazole-4 ID: BN4106A1 2-{4-chloro-2-[(cyclopr (difluoromethyl)-5-fluo yl]carbonyl} amino) ID: BN4114B1 methyl]phenyl}programo	methyl)-5-fluoro- I-carboxamide
(parent compound)cyclopropyl-3-(difluoro 1-methyl-1H-pyrazole-4ID: BN4106A11-methyl-1H-pyrazole-4BCS-CN88460-desmethyl- carboxylic acid2- {4-chloro-2-[(cyclopr (difluoromethyl)-5-fluo yl]carbonyl}amino)	methyl)-5-fluoro- I-carboxamide
ID: BN4106A1 BCS-CN88460-desmethyl- carboxylic acid 2-{4-chloro-2-[(cyclopr (difluoromethyl)-5-fluo yl]carbonyl}amino)	opf4{[3- opf4{[3- opf4]{2- ic acid
BCS-CN88460-desmethyl- carboxylic acid 2-{4-chloro-2-[(cyclopr (difluoromethyl)-5-fluo yl]carbonyl}amino)	ic acod
carboxylic acid (difluoromethyl)-5-fluo yl]carbonyl}amino)	ic acod
vl]carbonyl}amino) 🖑	ic agod 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
ID: BN4114B1	ic agod 5 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
ID: BN4114B1 methyl]phenyl}program	ic acod at the second s
BCS-CN88460-desmethyl- N-[5-chloro-2-(Chydro	хургорал-2- vl-3
propanol yl)ber@yl]-N-cycloprop	
(difluoromethyl)-5, tuo	
ID: YK0614E2 carboxamide	
L' & BY A	
BCS-CN88460-carbox fic	
	ro-I metnyl Chi-
ID: BN4114F1	propanor on on
ID. BIN4114F1	jpnenvi}propanorc
O S Acid S S	
	\mathcal{O}
BCS-CN88460-prophol N-[5Chloro 2(1-hydro	F F H_3C OH
ID: BN4183B	© ^z 1-metpyl-1H-
of pyrazote-4-carboxamie	
$A \qquad \bigcirc \qquad $	
	H ₃ C Cl
ID: BN4183B BCS-CN88460-2-propanol M-[5-chloro-2c(2-hydro yl)henzyl]-N-cycloprop (d)fluoromethyl)-S-fluo yl)henzyl]-N-cycloprop (d)fluoromethyl)-S-fluo syrazotS-4-carboxamide (d)fluoromethyl)-S-fluo (d)fluorometh	»"
BUS-K N88460-2-propanol AN-[5-ch1010-262-hydro	v_{1-3}
y O ^y [y])Denzyi]-NecycloBrop	y]-3- ro 1 methyl 1H
ID: YK0614H2	
	N N N
	H ₃ C F
J D A K	rı ₃ c cl
\sim	
Ũ	

Table 6.2.3- 3:List of reference compounds

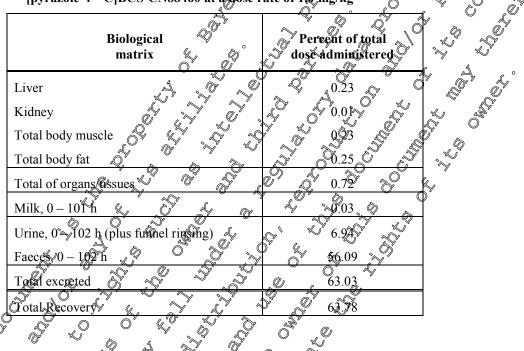


II. Results and Discussion

A. Recovery and Elimination of Radioactivity

The overall recovery in the lactating goat after administration of a mean daily dose of 10 mg [pyrazole-4-¹⁴C]BCS-CN88460 per kg body weight (according to 45.19 mg a.s./kg feed/day) on five consecutive days accounted for 63.78% of the total dose. The remaining apount of radioactivity (approx. 36%) was expected to still be present in the gastrointestinal tract at acrifice, due to the short period between last administration and sacrifice (approx. 6 hours).

Table 6.2.3- 4:Recovery of radioactivity in dissected organs and tissues, milk, and exclusion of a statistic distribution of 5 daily doses of [pyrazole-4-14C]BCS-CN88460 at a dose rate of 1.0 mg/kg



An amount of approx 0.03° of the total dose was secreted with the milk, only. At sacrifice, radioactive residues in the organs and tissues dissorted from the body were calculated or estimated to be 0.72% of the total dose.

Up to the time of sacrifice, 6.44% of the total dose was excreted with the urine and 56.09% with faeces (see table above). The daily renal excretion of the radioactivity started shortly after the first dosing before the daily renal excretion are reached a more or less constant level with round about 1.1% to 1.9%. The daily faecal excretion of the radioactivity started after the first dosing. The daily faecal excretion of the radioactivity started after the first dosing. The daily faecal excretion are exhibited a more or less constant gradient and the faecal excretion reached its maximum after the fifth dosing with 49.4%. The cumulative renal and faecal excretion was characterised by a here are from 4 h until sacrifice

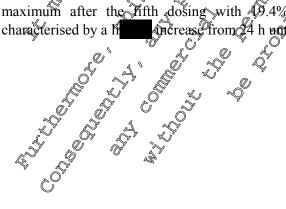




Table 6.2.3- 5:Distribution of residues in liver, kidney, muscle, fat and milk of lactating goats
following oral administration of 5 daily doses of [pyrazole-4-14C]BCS-CN88460 at a
dose rate of 1.0 mg/kg

uose rat	c 01 1.0 mg/kg				, O A
Organ/Tissue	Collection Time	Fresh weight [g]	TRR [mg/kg]	Transfer factor [TF] (****)	Percent of total dese administered
Liver	6 h after last admin.	1,440.86	0.717	<u>4</u> 0.016	5 ^{50.23} 5 ⁵⁷ (2)
Kidney	6 h after last admin.	244.43	0.189	0.004	
Round muscle (sample)	6 h after	3,340.2	0.035	0	
Loin muscle (sample)	last admin.	292	0.041	9°07.	
Total body muscle **)		27,000.00 。	@ 038 ~~	\$ 001 ~	×0.23 ×
Perirenal fat (sample)	6 h after	0778.430	× 0.095	\$\$	
Omental fat (sample)	last admin.	1,145,64	0.4Q0	° -75-	
Total body fat **)	L S	10,800.00	0:102	\$.002 ×	
Total of organs/tissues	Q			Č Č	\$ 0.7 ²
	~~ · · ·	0 [°] [°] [×] [×]			Ş. Ç
Milk, total	day I to 50	100014.26	00.014 O		°≈¥0.03
Milk, plateau-level	agay 324	4,584.403	~~ 0.0 5 ~	<u>≤0.00</u>	0.02
			KN 12		
Feeding level		\$¥5.19 K	_C × ⁴ Umg	g a ŝ. Kg dry fee	ed/day]

*) Percentage values and fresh weights were calculated from the body weight a Cacrifice, assuming 30% and 12% of the kody weight for total body muscle and total body fat, respectively.

**) weighted mean TRR-values from the two types of muscl@and fat

***) The transfer factor was calculated by dividing the TRR value of the respective sample by the feeding level (publigrams of a.s. per kitograms dry feed for each day)

B. Levels and Time Course of Total Radioactive Residues in Milk

The radioactivity levels measured in milk samples and the calculated amounts are shown in the table below. The TRR values in milk samples ranged from 0.009 mg/kg at 24 hours after the first administration to 0.021 mg/kg approx, 8 hours after the third administration and approx. 1 h before sacrifice. The time course of PRR-values of the opening and morning milk indicated a diurnal pattern for the testing period. The radioactive residues increased significantly during the eight-hour period after each administration. A residue plateau-level of 0.015 mg/kg was reached at about day 3-4 after the first administration. This calue was calculated from the evening sample of day 3, both samples of day 4 and the morning sample of day 5.

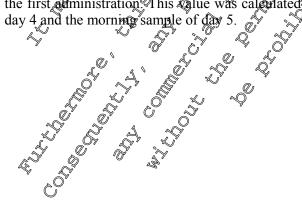
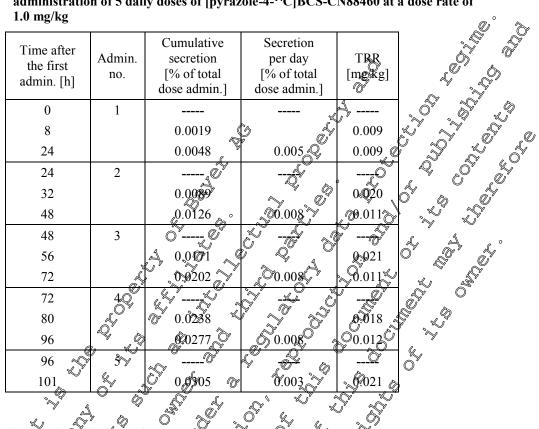




Table 6.2.3- 6:Time course of total radioactivity in the milk of lactating goats following oral
administration of 5 daily doses of [pyrazole-4-14C]BCS-CN88460 at a dose rate of
1.0 mg/kg



C. Total Radioactive Residues in the Dissected Organs and Fissues

The highest TRR-value was determined in liver (0.74) mg/kg; 0.22% of total admin. dose) indicating the significance of this organ for metabolism. The PRR-value for kidney accounted for 0.189 mg/kg (0.01% of total admin. dose) and Demonstrated that test compound related radioactivity partly was eliminated from the animal via urinary exercision. For body far, the TRR-value amounted to 0.102 mg/kg (0.25% of total admin. dose assuming 12% of the body weight for this tissue). The lowest TRR-value was determined in muscle (0.038 mg/kg; 0.23% of total admin. dose assuming a value of 30% of the body weight for this tissue).

D. Extraction Efficiency of Residues

The majority of the residues in the milleas well as organs and tissues were efficiently extracted (89.2% to 98.7% pusing acetonitrile/vater (82; v/v) mixtures. In case of muscle and liver, the solids after conventional extraction were exhaustively extracted using acetonitrile/water mixtures with microwave treatment. Only up to 7.8% of the TRR or 0.036 mg/kg of the residues remained in the post extraction solids (PES) of liver and kidney. For sample preparation the extracts were partitioned against n-heptane. Very low amounts of radioactority were recovered in the organic phase of the extracts amounting to $\leq 1.4\%$ or ≤ 0.001 mg/kg of the TRR. Concentration procedures of the aqueous phases caused no losses so all of the residues in the aqueous phases were quantitatively analysed by HPLC.

A summary of the extraction efficiency is shown in the table below.

-y of the



Extraction efficiency of milk, muscle, fat, liver and kidney samples of lactating goats Table 6.2.3-7: following oral administration of 5 daily doses of [pyrazole-4-¹⁴C]BCS-CN88460 at a dose rate of 1.0 mg/kg

uose rat		m ₆ / n ₅							_@`	
Sample Milk (32 – 101 h			Musele		Fat		Liver		Kioney	
TRR [mg/kg]	0.015		0.036		0.104		W.717		0.189)
	% of TRR	mg/kg	% of TRR	mg/kg	% of ØTRR	mg/kg	TRR	mg/kĝ	% of mg/k	
Conventional extraction	98.7	0.015	89.2	0.032	98.3	0,492	90.1	JØ4646	392.2 D.17	4
Exhaustive extraction			4.3	0.002		: م م	。 4.8 ₀	© _{0.035}		U U
Total extracted	98.7	0.015	93.6	0.034		0.102	94.9	0,681	92.2 Q97	4
Post-extraction solids (PES)	1.3	< 0.001	% 6/:4	0,002	7	0.002	\$ 5.1	0.036	°≫ 7.8 0.01	5
Accountability	100.0	0.015	ں 100.0	0.036	0.00	0.104	100.0	0.767	100-0 0.48	<u>9</u>
		1			1 0	v A	- S			

E. Quantification, Identification and Characterisation of

Quantification of Parent Compound and Metabolites

Parent compound and metabolites wete quantified for the extracts as well as ju the sample of urine (0-24 h) by HPLC-chromatography based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient. Metabolites in the exhaustive extracts from muscle and liver as well as co-eluting metabolites in a fraction of kidner were quantified by DLC.

Metabolites in the extracts as well as in the same of usine (0,34 h) were assigned to each other by comparison of the metabolite proviles and they retention times. Corresponding metabolites were named with the same peak ID. Detailed information can be found in the report.

Isolation and Identification of Parent Compound and Metabolites

The assignment of parent compound and metabolities was achieved by comparison of HPLC metabolite profiles of the analysed samples among each other and by comparison of the metabolite profiles of the current study with the profiles of the goat metabolism study of the phenyl label.

Metabolites were isolated from wrine (24 - 48 h) by HPLE. They were identified in the isolated fractions by specifoscopic methods. In addition parent compound and metabolites were identified in urine (0 - 24 h), in the conventional extracts of wilk, muscle and fat as well as in isolated fractions from milk, muscle, tat, liver and kidner by HPLC co-chromatography with radiolabelled reference compounds taken from the hen metabolism stary with the pyrazole label or from the goat metabolism study with the phenyl label Conjugates were subjected to enzymatic cleavage with an aqueous solution of B-glucuron/dase/sulfatase before HPI-Q-analysis.

F. Distribution of Parent Compound and Metabolites in Milk, Organs and Tissues

The identification rates arounted to 530% of the TRR for milk, 67.7% for muscle, 81.5% for fat, 58.3% for liver, and 65.4% for kidney.

Parent Compoord was detected in milk, muscle, fat, liver and kidney and amounted to 0.005 mg/kg (33.4% of the TRR for milk, 0.008 mg/kg (22.3% of the TRR) for muscle, 0.061 mg/kg (58.7% of the TR(\mathbf{k}) for \mathbf{k} , 0.025 mg/kg (3.5% of the TRR) for liver and 0.005 mg/kg (2.7% of the TRR) for kidney.

Metabolites in milk

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Besides parent compound as the main residue in milk, BCS-CN88460-2-propanol was the major metabolite (20.3% (0.003 mg/kg) of the TRR).



Ô.

Metabolites in muscle

Besides parent compound as the main residue, BCS-CN88460-2-propanol was the major metabolite and accounted for 17.9% (0.006 mg/kg) of the TRR. Other prominent metabolites were BCS-CN88460-propanol (10.2% (0.004 mg/kg) of the TRR) and BCS-CN88460-carboxylic acid (8.1% (0.003 mg/kg) of the TRR). BCS-CN88460-desmethyl-propanol (4.4% 0.002 mg/kg) of the TRR) and BCS-CN88460-propanol-GlucA (isomer 2) (4.8% (0.002 mg/kg) of the TRR) were minor compounds.

Metabolites in fat

Besides parent compound, the major metabolite was BCS-CN88460-2 propanol accounting for 16,8 (0.017 mg/kg) of the TRR. BCS-CN88460-carboxylic acid (3.3% Q0.003 mg/kg) of the TRK and BCS-CN88460-propanol (2.7% (0.003 mg/kg) of the TRR) were minor compounds in fat. Q,

Metabolites in liver

Ż BCS-CN88460-2-propanol-GlucA was the main residue in liver and accounted for 0.099 mg/kg (13.8% of the TRR). Other prominent metabolites were BCS-CN/8460-propanol-Gluc (isomer 1 and 2) accounting for 0.094 mg/kg (13.1% of the TRR) and 0.055 mg/kg (7.7% of the TRR), respectively, BCS-CN88460-carboxylic acid accounting for 8.9% (0.064 mg/kg) of the TRR, as well as BCS-CN88460-propanol accounting for 0.042 mg/kg (3.8% of the FRR). The four metabolites BCS-CN88460-lactic acid, BCS-CN88460-desmethyl-carboxylic acid, BCS-CN88460-desmethylpropanol and BCS-CN88460-2-popanol were minor metabolites and ranged between 0.003 mg/kg (0.5% of the TRR) and 0.019 mg/kg (2.6% of the TRR).

Metabolites in kidney

BCS-CN88460-carboxykic acid was the main metabolite in kidney, accounting for 0.034 mg/kg (18.0% of the TRR). Other prominent metabolites in kidney were BCS-CN88460-N-methyl-pyrazolecarboxylic acid (5.8% 0.01 mg/kg) of the TRR BCS-CN88400-lactic acid 6.1% (0.012 mg/kg) of the TRR), BCS-CS 88460-propagol-GlocA (isomer 2) (7.0% (0.013 mg/kg) of the TRR) and BCS-CN88460-propanol 5.6% (0.01 mg/kg) of the TRR. The two monor co-eluting metabolites BCS-CN88460 Propanol-GlucA (2,6% (0,005 mg/kg) of the TRR) and BCS-CN88460-propenol-GlucA (3.6% (0.007 mg/Rg) of the TRR) were Subquantified by TLC. Four metabolites BCS-CN88460-propanol-GluA (isomer), BCS-CN88460-desmethyl-carboxylic acid. BCS-CN88460-desmethyl-propanol and BCS-CN88460-2 propanol were detected in minor amounts $(\leq 4.2\%$ of the TRR).

W

More metabolites in the matrices may be present as indicated by broad non-resolved zones in the chromatograms. All unknown metabolites in the extracts were characterised by their extraction and chromatographic behaviour and amounted a each 214.3% of the TRR.

The distribution of the patient compound and metabolities in milk, organs and tissues is summarised in

The set of the set of



Table 6.2.3- 8:Radioactive residues of parent compound and metabolites in milk and edible organs
of lactating goats following oral administration of 5 daily doses of [pyrazole-4-
14C]BCS-CN88460 at a dose rate of 1.0 mg/kg

¹⁴ C]BCS-CN88460 at a dose rate of 1.0 mg/kg											
Samp	le	Μ	lilk	Mu	iscle	Fat			Liver		iney 🖌
TRR	[mg/kg]	0.	015	0.	036	0.	104	0.	717	0.	£89 Ø
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TBR	mg Kg
Conve	entional extraction	98. 7	0.015	89.2	0.032	<u>98.3</u>	0.102	z \$90 .1	0.646	y 92.2	♀ 0.174¥
39	parent compound	33.4	0.005	22.3	0.008	\$8.7	0.061	3.5	0.025	2.7	0.605
4	N-methyl- pyrazole- carboxylic acid (M50)					» 		, ? 	, , , , , , , , , , , , , , , , , , ,	₹ ¶ 5.8	90.01 9
25	2-propanol- GlucA* (M20)			-4				.1 . 9.8	(0999 20999	°≈y2.6	ר.005
25	propenol-GlucA* (M25)			<u> </u>	, ~ ··· ~	@	Q			30	0.007
26	lactic acid (M10)			ý <u>-</u> -^	y A	Ĭ ĮÕ		<u>≈1.6</u>	0,011	6.1	0.012
27	propanol-GlucA (isomer 1) (M19, isomer 1)								0.09 £	3	0.006
28	propanol-GlucA (isomer 2) (M19, isomer 2)			4.8	0,602			°7.7	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	≫ ∀ 7.0	0.013
30	desmethyl- carboxylic acid % (M11)	\$						\$9 \$9.9	0.007	4.2	0.008
31	desmethyl- propanol (MQC)	<u>®</u>	22 2 2 2 1 2	Ø 4.4	5 ⁵⁰ .002*		Ψ́φ i	0.5	0.003	1.6	0.003
33	carboxylic and (M12)	ð - ,		8.Y	0.003	3 3.3	Ø 003,	\mathcal{Q}	0.064	18.0	0.034
34	propano (M010)	0	0′	\$10.2	0.004	⊘ 2.7≜	° 0.003	5.8	0.042	5.6	0.011
36	2-propanol (Me02)	20.3	©0.003	17,9		16.8	0.017	2.6	0.019	4.2	0.008
	identified 🕺	J 5 <u>3.7</u>	0.008		0.024	8 ¥.5	~0,085	58.3	0.418	65.4	0.123
Chara	ctensed by HPLC	467	0.006	20.6	£.008	√J 6.1	0.017	31.5	0.226	26.8	0.050
peak		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	50°		5 %	Í A	•		17		16
	est unknow hopeak	14.8	0.002	<u>∿</u> 0%8	4,002	9.5	0.008	4.0	0.029	5.7	0.011
partiti	cterised by Ö ^ÿ on (organic phase)	Q.4	≈0,001,	0.9 0.9	\$0.001	0.8	0.001	0.3	0.002	n.q.	n.q.
	ustive extraction	<u>~</u> "0		× 435	0.002			4.8	0.035		
- ACN	/wder extract	- R		A.3	<i>∘0.002</i>			2.1	0.015		
pear		<u>, </u>			5	-			11	-	
	gest unknown peak	vC	, ; 	/ 10°	0.001			0.9	0.007		
	extract ber of miknown	Č*		~~~~~				2.8	0.020		
peak	s & L	- 10		U -		-			4	-	
	est jinknown peak O							2.3	0.017		
	characterised	44.1	0.006	25.8	0.009	16.8	0.017	36.6	0.262	26.8	0.050
		98.7 №	< 0.001	n.q.	n.q.	n.q.	n.q.	n.q.	n.q.	n.q.	n.q.
Post e	xtraction solids	*	0.015	93.6	0.034	98.3	0.102	94.9	0.681	92.2	0.174
(PES)	8	1.3	< 0.001	6.4	0.002	1.7	0.002	5.1	0.036	7.8	0.015
	Intability	100.0	0.015	100.0	0.036	100.0	0.104	100.0	0.717	100.0	0.189

* BCS-CN88460-2-propanol-GlucA and BCS-CN88460-propenol-GlucA were co-eluting in the kidney and were subquantified by TLC.



The distribution of radioactivity in milk between the cream fraction and the remaining skimmed milk showed that the major portion of the radioactivity was found in the fraction of skimmed milk (see k fractions below).

Table 6.2.3- 9:	Distribution of radioactivity in milk between cream and skimmed milk fractions
1 abic 0.2.5- 7.	Distribution of radioactivity in milk between cream and skinning milk fractions

Sample description	%	6 of TRR	mg/kg
n-heptane phase (cream)		13.3	0.002
aqueous phase (skimmed milk)	Ĉ	, 86.7	\$0.013
Total	R.	100.0	0.015
Å	1) ^v

Conjugates in the liver and kidney like BCS CN88460-2-propanot Gluc A and BCS-CN88460propanol-GlucA (both isomer 1 and 2) could be enzymatically cleaved to their aplycons (see tables below). The cleavage of some unknown conjugates in non-resolved zones resulted in higher amounts of the aglycons. None of the unknown compounds after cleavage of the liver and kidney extracts accounted for more than 9.6% (0.069 mg/kg), of the PRR (mean of all three replicates) or 93% (0.018 mg/kg) of the TRR, respectively. The following main aglycons could be clearly identified after enzymatic cleavage: BCS-CN88460-2-propanol and BCS-CN88460 propanol. \bigcirc

Radioactive zosidues of parent compound and metabolities in live samples of first and Table 6.2.3-10: second conventional extraction and after enzymetic cleavage for 20 h

		la la	×× A.		- Al				
Samu	le L F		er S entional	Liv C	N 16		matic cle juots of li	avage of ver extra	three acts
Samp		extra	tion S	conyer extra	ntional ction	mean	values	stano devia	
peak ID	Compound (Report name) BCS-CN 88460	‰ of ♂RR ‰	ang/kg	¢% of ∼ TR®	mg	% of TRR	mg/kg	% of TRR	mg/kg
Extrac	t used for HPLO	89.8	0:644	90.2	0.647	81.5	0.585	1.2	0.009
39	parent compound	3 .5	0.025	5.0	0.036	6.1	0.044	0.5	0.004
25	Propanol-Gluc (M20)	13.8	≫ [∿] 0.09∮		0,078	0.9	0.007	0.2	0.002
26	lactic acid (MQ0)	10	0.641	2.6	0.019	0.7	0.005	0.1	0.001
27	propanol-ChicA (isomer 1) (M19, isomer 1)	Ø ^{3.1}	× 0.094	> 11 A	0.080				
28	propanof-Gluc $\mathcal{A}(\text{isomer } 2)$ (M19, isomer 2)	~ 1J	0.055	7.0	0.050				
30	despatchyl-carboxylic acid	0.9	£0.007	0.8	0.006	2.2	0.015	0.1	0.001
31 *	desmethyl-propanol (1796)	0 8 .8.9	0,003	0.7	0.005	4.7	0.033	0.2	0.001
33	carboxylic acid (MIQ)	8.9	0.064	8.2	0.059	11.7	0.084	0.5	0.004
34	propanok (M01)	8.9 5.8	Q 0.042	7.4	0.053	20.8	0.149	0.8	0.006
36	2-propanol (M92)	2 @ 58.3	0.019	3.7	0.026	11.9	0.085	0.7	0.005
Total	carboxylic acid (MIQ)	58.3	0.418	57.4	0.412	58.9	0.423	1.1	0.008
Total o	characterized 4	31.5	0.226	32.8	0.235	22.6	0.162	1.2	0.009
	stability of the	89.8	0.644	90.2	0.647	81.5	0.585	1.2	0.009
Br.									



Sample		Kida 1 st convo extra	entional	Kidi 2' conver extra	nd [°] ntional	cleava conver extr exp <u>e</u> ri	matic age of ntional oct -	enzy cleav conver extr experi	ney- mathc age of rtionat act - mart 2
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of	mg/kg	%∛of" JKR	mg/kg	°≈% of ∘, ℃TRR	∀mg/kgy
Extract	used for HPLC	92.2	0.174	91.8	0.173	82.1	0.15	82.1	0,155
39	parent compound	2.7	0.005	3.6	0.00	3.0	00006	Q2.2	0.004
4	N-methyl-pyrazole- carboxylic acid (M50)	5.8	0.010	4.8	Q,009	Ø 1.8	Q0.0030	4	0.004
25	2-propanol-GlucA (M20)	7.3	\$0,014	ຼ¢ົຸ 6.5 ຼ	℃ 0.012×			°~	≪"
26	lactic acid (M10)	6.1	0.012	33	0.006	3.0	0.006	<i>‰</i> , 3.7≟	0.007 ∘
27	propanol-GlucA (isomer 1) (M19, isomer 1)	34.1 2 2 2 7.0	0.0006	3.6	0.007	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	128 84	, M.	
28	propanol-GlucA (isomer 2) (M19, isomer 2)		\$0.013 \$		0.644	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	 2 2 2 2	Ĵ	Õ
30	desmethyl-carboxylic acid (M11)	4.2 4.2	0,008	ۍ 3.5	Q.007	38	0.067	×4.6	0.009
31	desmethyl-propanol (MQC)	× 1.6	0.003	5 1,4	0.003	4.9	0.009	4.3	0.008
33	carboxylic acid (M12)	18.0	0.064	18.3	€,035	23.6	0.044	22.7	0.043
34	propanol (M01)	<u>3</u> .6	0.011	3.2	0.00	10,6	0.020	10.8	0.020
36	2-propanol (M02)	<u>م</u> 4.2	$6^{0.008}$	J 40	0,008	6.6	013	6.8	0.013
Total i	dentified	65A	0.123	60.1	6 .113	[∞] 57.3₄	^(×) 0.108	57.0	0.108
Total c	haracterised 🖉 🔬 🔊	26.8	0.050	V U	©0.060	248	0.047	25.1	0.047
Accour	ntability 🖉 🔨 🎸	» <u>،</u> 92.2	≫0 .174	× 91.8	0,193	×2.1	0.155	82.1	0.155

Table 6.2.3-11: Radioactive residues of parent compound and metabolites in kidney samples of first and second conventional extraction and after enzymatic cleavage for 20 h

Metabolites in Unine and Distribution

The metabolic profile of usine (0, -24) h) and faces (0^{-24}) were similar to the profiles of edible materials, especial pliver and kidney, except that parent compound was not present in the sample of urine. In faeces parent compound was the main residue (8.4% of the first dose). All identified

The distribution of the parent compound and metabolites in urine and faeces is summarized in the table below.



Table 6.2.3-12:Radioactive residues of parent compound and metabolites in non-edible samples of
lactating goat following oral administration of 5 daily doses of [pyrazole-4-14C]BCS-
CN88460 at a dose rate of 1.0 mg/kg

	er too roo at a dose rate or rio mg, ng		
Sample		Faeces	Urine 🖉 🖉
Sample		(0 - 24 h)	(0 – 24 h)⊘
Peak	Compound (Report name)	% of dase	% of dose
ID	BCS-CN88460-	in the	in the same a
39	parent compound	sample	
4	N-methyl-pyrazole-carboxylic acid (M50)	о С С С	0.20 0.20
25	2-propanol-GlucA (M20)	<0.1	
25 25			
23 26	propenol-GlucA (M25) lactic acid (M10) propanol-GlucA (isomer 1) (M19, isomer 1) propanol-GlucA (isomer 2) (M19, isomer 1) desmethyl-carboxylic acid (Mk1) desmethyl-propanol (M06) carboxylic acid (M12) propanol (M01) 2-propanol (M02)		
20 27	propanol-GlucA (isomer 1) (M19, isomer 1) •		
27	propanol-Cluc A (isomer 2) (M10-isomer 1) °		
28 30	propanol-GlucA (isomer 2) (M19) some (2)		
30 31	desmethyl-carboxylic acid (MNI)		
	desineuryi-propanor (MOO)		
33	desmethyl-propanol (M06)		
34	propanol (M01)	ST.3	\$.7 ···
36	2-propanol (M02)		<u> </u>
Sum id	entified	ô 120	3.7
	characterised by APLC	© 0.4	©° 1.7
			2 15
	inknown peak	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.3
	erised by partitioning (n-fleptane Phase) 🖉 😽	\$ 0.1	
Total c	naract@ised	0.5	1.7
Sum of			
Total e	xtracted	× ^v 13.2	
	raction solids (PES)	0.5	
Total		13.8	5.4
\$Q			

BCS-CN88460-2-propanol-GlucA and BCS-CN88460-propenol-GlucA co-eluted in HPLCanalysis with the protiling method BCS460 I. Subquantification in the fraction of the sample of urine resulted in a ratio of 60.6% of BCS-CN884602-propanol-GlucA to 39.4% of BCS-CN88460-propend-Glux.

G. Storage Stability of Residue

e C

During the study, all samples and extracts were stored in a freezer at \leq -18 °C or for a short time in a refrigerator. All samples of milk and entitle organs and tissues were extracted within three months after sample collection. The first metabolite profile was recorded not later than six days after the start of the extraction and sample oreparation.

A second conventional extraction of milk was performed approx. 15 months after sampling, a second conventional extraction of liver was performed approx. 13 months after sampling and a second conventional extraction of kidney was performed approx. 14 months after sampling. From the stored milk sample, the distribution of radioactivity in the fractions of skimmed milk and cream was determined. The extracts of liver and kidney were used for enzymatic cleavage experiments. The storage stability was exemplarily demonstrated for these samples. It was therefore concluded, that the metabolic profiles represent the residues in the matrices and analysed samples at sacrifice.



III. Conclusion

The metabolic behaviour of [pyrazole-4-¹⁴C]BCS-CN88460 in the lactating goat can be characterised by the following observations:

The TRR-values and the transfer factors in milk, organs and tissues were very low compared to the dose level of 45.19 mg a.s./kg feed/day and a dosing period of five days. The highest TRR-value was detected for liver and was caused by the short time period of 6 hours between last dosing and satirfice. It indicates the significance of this organ for metabolism. The significantly lower TRR-value for kidney shows that no residues were retained in this tissue and reflects the low amount of radioactivity, which was excreted by the urine. The TRR-values in the respective opening and morning full satirfies showed a diurnal pattern as they declined slightly pror to the delivery of the next dose for most day. A continuous increase was observed before a residue plateau-level was reached at day three after the first administration.

The elimination of radioactivity was mainly faecal (36.1% of the dose) and only 8.9% were eliminated via urine. This excretion behaviour was similar to the findings in the ADME studies with rate

The radioactive residues were efficiently extracted from milk as well as from edible organs and tissues; extraction rates ranged from 92,2% to 98.7%

The identification rates ranged between 5307% and 81.5% for the TRR in milk, and dible organs and tissues.

Parent compound was detected in milk, muscle, fall liver and komey. Barent compound was a major compound in milk, muscle and fat and a minor compound in fiver and kidney. Overall up to eleven metabolites were identified?

BCS-CN88460-2-propanol (M02) was detected as a major metabolite in milk (92 - 101 h), muscle and fat, BCS-CN88460-propanol (M01) was detected as a major metabolite in muscle, BCS-CN88460-2-propanol-GlucA (M20) and BCS-CN88460-propanol GlucA (isomer 1, M19 – isomer 1) as major metabolites in liver and BCS-CN88460-carboxylic acid rM12 as a major metabolite in kidney. Further abundant metabolites were BCS-CN88460-propanol-GlucA (isomer 2, M19 – isomer 2) in liver and kidney, BCS-CN88460-lactic acid (M10) in kidney, BCS-CN88460-N-methyl-pyrazole-carboxylic acid in kidney (M50), BCS-CN88460-carboxylic acid (M12) in muscle and liver and BCS-CN88460-propanol (M05) in liver and kidney BCS-CN88460-desmethyl-carboxylic (M11) was a minor compound in liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in muscle, liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in muscle, liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in muscle, liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in muscle, liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in muscle, liver and kidney BCS-CN88460-desmethyl propanol (M06) was a minor metabolite in kidney and in urine.

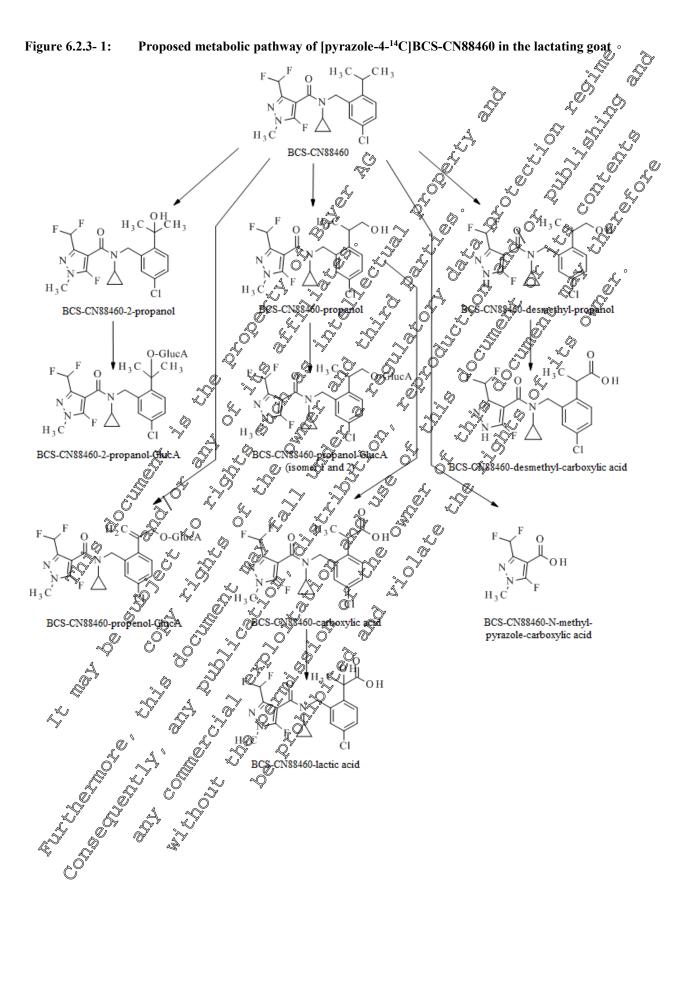
The metabolic profiles of when and faces were similar to the profiles of edible materials, especially liver and kidney, except that parent compound was not present in the sample of urine.

The principal metabolic reactions of [pyracole-4-4]C]BCS-CN88460 in the lactating goat are listed below:

- hydroxylation of position 1 of position 2 of the propyl group in the phenyl ring
- conjugation with glucuronic acid
- oxidation of the & proparol group was leading to carboxylic acid or with a hydroxy group in position 2 to factic, acid
- demethylation of the pyrazole moiety
- Cleavage of the phonyl moiety in combination with cleavage of the cyclopropyl ring
- leading to BCS-CN88460-N-methyl-pyrazole-carboxylic acid
- Achydration after hydroxylation in position 1 and 2 of the propyl group followed by

Based on these results, the metabolism of [pyrazole-4-¹⁴C]BCS-CN88460 in the lactating goat is considered as sufficiently understood and a metabolic pathway is proposed.







Report:	KCA 6.2.3/02; 4 , R.; 4 , AK.; 4 , F.; 2017; M-604286-01-1
Title:	[Phenyl-UL-14C]BCS-CN88460 - Metabolism in the lactating goat
Report No.:	EnSa-17-0308
Document No.:	M-604286-01-1
Guideline(s):	[Phenyl-UL-14C]BCS-CN88460 - Metabolism in the lactating goat EnSa-17-0308 M-604286-01-1 OECD Test Guideline No. 503 Commission Regulation (EU) to 283/2013 in accordance with Regulation (EC) No 1107/2009 US EPA OCSPP Test Guideline No. 860.1300
Guideline deviation(s): GLP/GEP:	none yes

Executive Summary

The metabolism and excretion of [phenyl-UL-9C]BCS-CN88460 was investigated in the lactating goat as a model for ruminants. The test compound was grally administered to a lactating goat in gelatine capsules at a dose of approx. 1 mg per kg body weight. Pased on the daily feed consumption, the dose level corresponded to 20.57 mg and /kg dry feed day. The goat received five doses at 24-hour intervals in the morning after milking and was sacrificed approx. 6 hours after the fast dosing.

Throughout the experiment, the goad was housed in a metabolism case, which permitted separate collection of urine and faeces. The goad was milked in the morating immediately prior to each administration, about eight hours hater is the atternoop and opprox. O hour before sacrifice. The total radioactive residues (TRRs) were determined in each milk cample and in dissected organs and tissues (muscle, liver and kidney) at sacrifice. Omental fat and perirenal tat could not be found. The goat was relatively young and fatless. The total radioactivity (% of total dose administered) were additionally determined in each urine and faeces sample.

Recovery and Elimination of Radioactivity

The overall recovery accounted for approx. 31% of the dotal dose. The remaining amount of radioactivity was expected to still be present in the non-edible part of the animal body and especially in the gastrointestinal tact.

An amount of approx. 0.06% of the total dose was secreted with the milk, only. At sacrifice, radioactive residues in the edible organs and tissues dissected from the body were calculated to be approx 0.27% of the total dose and were very low

Up to the time of acrifice approx. 9.8% of the total dose was excreted with the urine and approx. 40.8% with faces. The daily renal excretion of the radioactivity started shortly after the first dosing before the daily renal excretion rate reached a more or less constant level with 1.2% to 3.6%. The daily faecal excretion of the radioactivity started after the first dosing. After the third dosing, the excretion rate amounted to approx. 17 % and the daily faecal excretion rate exhibited a more or less constant gradient. The cumulative renal and faecal excretion was characterised by a light increase from day 3 until sacrifice.

Total Radioactive Residues in Milk, Organs and Tissues

The TRR-value and transfer actors for mole, organs and tissues were very low compared to the dose level of 20.50 mg as tkg feed/day and a dosing period of five days. The TRR-values in milk samples were very low and ranged from 0.008 mg/kg after the first administration to 0.016 mg/kg after the fourth administration. The time course of TRR-values of the evening and morning milk samples indicated a dornal pattern for the testing period as a whole. The radioactive residues increased significantly during the eight-hour period after each administration followed by a small decrease measured prior to the delivery of the next dose.

Regarding organs and tissues, the TRR-values amounted to 0.011 mg/kg for muscle (composite of round and loin muscle), 0.348 mg/kg for liver and 0.183 mg/kg for kidney.



Metabolism

The majority of the residues in the milk as well as organs and tissues were efficiently extracted (extraction rates between 88.3% and 100.0%) using acetonitrile/water mixtures. In case of liver, the solids after conventional extraction were exhaustively extracted using acetonitrile/water (1/4) v/v) mixtures with microwave treatment. Up to 8.2% of the TRR (0.029 mg/kg) of the residues remained in the post extraction solids (PES).

For sample preparation the extracts of liver and kidney were partitioned against n beptanes The extracts of milk and muscle were purified with SPE cartridges and a subsequent phase separation with NaCl. Very low amounts of radioactivity were recovered in the organige hases amounting to $\leq 0.8\%$ of the TRR. Concentration procedures of the aqueous phases caused minor losses of prdioactivity amounting to $\leq 6.3\%$ of the TRR. \bigcirc

Parent compound and metabolites were identified based on co-promatography with isolated metabolites and reference compounds or by comparison of the metabolite pattern and retention times. Metabolites were isolated from urine and identified by spectroscopic investigations.

The identification rates amounted to 50.4% of the TRR for mile, 64.0% for muscle 47.2% for lifer, and 42.4% for kidney.

Parent compound was detected in milt, mysole, liver and kidness It was a mater compound in milk and muscle and a prominent compound in liver. Overall up to ter metabolites were identified

Metabolites BCS-CN88460-2-propanol@M02) and BCS-CN88460-propanol-Gluc (isomer 2, M19 isomer 2) were detected in all matrices. BCS-CN 8460, 2 propagol represented a major residue in muscle and amounted between 1.4% and 4.2% of the TRR for all matrices, while BCS-CN88460propanol-GlucA (isomer 2) amonted between 2.5% and 8.6% of the ARR Metabolites BCS-CN88460-carboxylic acid (M12) and BCS-CN88469 propagel (M01) were identified in muscle, liver and kidney and ranged between 2.5% and 9.0% of the TRP. BCS CN88460-2 propanol-GlucA (M20), BCS-CN88460-lactic acid (M10) and BCS-CN88460-desmethyl-carboxylic acid (M11) were detected in liver and kidney and accounted for between 0.5% and 13.0% of the TRR BCS-CN88460-propanol-GlucA (isomer 16 M19 \ isomet 1) was identified in milk, liver and kidney and its amount ranged from 2.3% to 8.8% of the PRR. BCS-CN88460 desmethyl-propano (M06) was detected in milk, muscle and liver and amounded between 0.6% and 6.7% of the TRR. BCS (N88460-propenol-GlucA (M25) was detected in kidney and accounted for 6.2 of the TRR Q

More motabolites in the matrices may be present as indicated by broad non-resolved zones in the chromatograms. Albunknown metabolited in the extracts were characterised by their chromatographic behaviour and amounted to <386% of the TRIP but to very tow mg/kg values (0.005 mg/kg).

The metabolic profiles of uppe (0, 24 h) and faces $(0^{\circ}24 \text{ h})$ were similar to the profiles of edible

A summary of the distribution of parent compound and metabolites for edible materials is provided in the following tables



Table 6.2.3-13:Radioactive residues of parent compound and metabolites in milk and edible organs
of lactating goats following oral administration of 5 daily doses of [phenyl-UL-
14C]BCS-CN88460 at a dose rate of 1.0 mg/kg

	CJBCS-CN884								Ĩ.	~
Samp	le	Milk		Muscle		Liver		Kidney		S
TRR	[mg/kg]	0.013		0.011		0.348		0.183		0
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	
Conve	entional extraction	98.5	0.013	100.0	0.011	88,3	0.307	\$ 97.9	Q0.179	Ŗ
38	parent compound	33.9	0.004	213	0.002	5.3	0.018		0.003	
20	2-propanol-GlucA (M20)			<u> </u>	,	Q 13.0	0.043	4.9*	007	6
20	propenol-GlucA (M25)			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	-	·	_0	€ .2*	0.011	
21	lactic acid (M10)			4	<u> </u>	Q1.3	Q0.005	4,2	0.068	
22	propanol-GlucA (isomer 1) (M19, isomer 1)	2.3	<0,001	°		× 8,80	0.084	₹\$.6	÷007	
23	propanol-GlucA (isomer 2) (M19, isomer 2)	2.5	0.001° 1		0,001	05.9	0.021	5 8.6 8	0.016	
27	desmethyl-carboxylic acid (M11)				^ان الم		0.002	3.6	2 0.007	
28	desmethyl-propanol (M06)	6.7	\$0.0014 50.0014 50.0014	≥ 3.0 ≥ 9.0	<0.001	Ç0.6	0.002	<u> </u>		
30	carboxylic acid (M12)	6 ⁽			0.001	ð 4.2	<u>)</u> 0.015	\$6 /8	0.012	
31	propanol (M01)	× 9-	\$	9.0	×0.00K	, 49	0017	2.5	0.004	
34	2-propanol (M02)	ُ∕≫5.0	0.001	° 14.2⁄	0.002	2.8	0.010	o [≫] 1.4	0.003	
Total identified		50.4	0.007	62 *.0	0.007	^م ر 47.2	0.164	42.4	0.078	
Characterised by HPLC 😽 🐧		4 Ø23	0,006	<i>≨</i> √29.8) 37.8	QZ32	54.4	0.100	
Exhaustive extraction (ACN/water)					0.003	3.5 🎡	s 0 2012			
Total characterised		× 47.32	0.066	29 .8	0.003	© [*] 41.3*	§ 0.144	54.4	0.100	
	of losses	×0,8	≪Q.001	ړ∽ې 6.3	\$ 0.00K	, <u>3</u> 02	0.011	1.1	0.002	
Total	extractable	% 98.5	0.013	¢ 100.0	0.01	\$91.8	0.319	97.9	0.179	
Post e	xtraction colids (RES)	0 1.5	¢<0.00	, q.	Ôn.q.	8.2	0.029	2.1	0.004	
Accou	ıntabilây 🔬 🏑	100.0	0.013	P 00.0	7, 0.011	100.0	0.348	100.0	0.183]

* BCS-(1) 88460-2-propanol-Gloc A and BCS-CN88460 properties of local were co-eluting in the chromatography of the extract of kidney and were subjunctified by TLC.

The main metabolic reaction was the Oydrox lation in the propyl group of the phenyl ring. Conjugation with glucurous acid was observed after hydroxylation in position 1 or 2 of the propyl group. Another important metabolic reaction was the carboxylation of the 1-propanol group, leading to a carboxylic acid or with a hydroxy group in position 2 of the propyl group to a lactic acid group. Minor metabolic reactions were the demethylation of the pyrazole moiety, hydroxylation in position 4 of the phenyl moiety and the dehydration after hydroxylation in position 1 and 2 of the propyl group followed by conjugation with glucuronic acid.

Based on the results the metabolism of [phenyl-UL-¹⁴C]BCS-CN88460 in the lactating goat is considered as adequately onderstood and a metabolic pathway is proposed.



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I. Materials and Methods

A. Materials

1 Test Material

1. Test Material	
Chemical structure	F + G + G + G + G + G + G + G + G + G +
	H & Chabel position + C + C + C + C + C + C + C + C + C +
Radiolabelled test material	[Phenyl-UL- ¹⁴ G]BCS&CN88460
Specific radioactivity used	$4 12 \text{ MD} / 0 = \sqrt{9} 40 \text{ s}^{10} 10 \text{ s}^{10} 20 \text{ s}^{10} \text{ MD} \sqrt{10} 108$
for administration	dpm/mg A dpm/mg dpm/mg
	4.13 MBq/mg = 2.48 x 10° 2.06° MBq/mg = 1.24 x 10^8 dpm/mg \rightarrow $(delivered sample before sample after radiodilution) \rightarrow (delivered sample \rightarrow (deli$
Radiochemical purity	>98% (HPLC) 2 2 2 2 2
Non-labelled test material	
Chemical purity	99.4%
Dose level	5 daily oral-doses of 1 mg/kg by
Vehicle	Capsule Of G G G G G G G G G G G G G G G G G G
No.	
2. Test Animals	

2. Test Animals

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B. Study Design

Preparation of the Test Compound for Administration

The radiolabelled test compound was delivered in solid form. It was diluted in a ratio of 1:1 with the non-radiolabelled test compound. An amount of approx. 47.3 mg of this diluted test compound was taken for preparation of each administration capsule. In total, five gelatine capsules containing the solid test compound were prepared and stored in a freezer at \leq -18 °C. A small portion of the test compound was dissolved in acetonitrile from which an abjuot was taken for identity confirmation of the test compound by LC-MS/MS.

In order to demonstrate the stability of the solid test compound in the capsules, small portion of the test compound was stored together with the capsules until the last administration. Alignots of the small portion were analysed for stability and purity of the test compound after the first and the last administration by HPLC. In both cases, the purity amounted to >98%

Dosing

All oral administrations were performed using a capsule applicator once daily for five consecutive days in the morning after milking. Each gelatine capsule contained an average amount of 47.51 mg, which corresponded to 97.7MBq. The total administered amount and radioactivity accounted for 236.56 mg and 488 MBq, respectively.

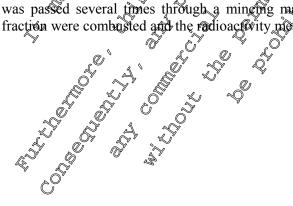
The total amount of radioactivity administered to the animal served as reference value ($A_0 = 100\%$) for the percentage calculation of the total radioactivity in the biological samples.

Based upon the experimentally determined daily feed consumption during the testing period of 2,300 g dry feed per day (= 4.86% of the body weight), the dose of 1.0 mg as kg to corresponded to a concentration of 20.57 mg as kg dry feed per day in the diet. This dose was tolerated without any observable toxicological effects.

Sampling of milk Jurine and faces during the in-life phase

The goat was rolked of the morning immediately prior to each administration, about eight hours later in the afternoon and directly before the scheduled termination. After weighing, aliquots were taken from each sample for radioactivity measurement by LSC.

Urine and faeces samples were collected in plastic vessels or collecting grids as quantitatively as possible under dry ice cooling in interval of 24 hours after the administrations 1 to 4 and 6 hours after the last administration. The vessels were exchanged immediately before the next administration. The collection funnel was ansed with defonised water into the urine vessel of the respective collection period. After determination of the total volumes, aliquots of each urine sample were used for radioactivity measurement by LSC. For collection of faeces, the collecting grid was cleaned prior to each administration. After determination and recording of the individual weights each faeces fraction was passed several times through a minoring machine in half-frozen state. Aliquots of each faeces fraction were combined and the radioactivity measured by LSC.





Sacrifice and dissection of organs and tissues

The animal was sacrificed approx. 6 hours after the last administration, a time interval that is consistent with normal slaughtering practices. The animal was at first sedated by an intramus@lar mixed injection of Xylazin/Rompun (2%; 0.2 mg/kg bw) and Ketamin (10%; 5 mg/kg bw) and afterwards anaesthetised by an intravenous dose of about 40 mg/kg bw Pentobarbital-Na (Nargaren®). Under deep anaesthesia, the animal was then exsanguinated by transection the ugular vein and finally terminated by intracardiac injection with approx. 10 mL of the veterinary drug "T 61®", Following exsanguination, the following edible organs and tissues were dissected: provide (round and loin), liver (without gall bladder) and kidneys. Omental fat and perfrenal fat could not be found. The goat was relatively young and fatless.

Preparation of Organs and Tissues

The organs or tissue samples were transferred atto tared plastic vessels. After determination and recording of the individual weights, muscle, liver and kidney samples were passed several fimes through a mincing machine in half-frozen state. Aliquots of the individual organ and tissue samples were combusted and the radioactivity measured by USC. All samples were stored at \$18 °C until the start of metabolite analysis.

For metabolism investigations, pooled samples of mik (collected from 32 h unf) 101 b) and muscle (loin and round muscle) were prepared. Liver, kidney and faeves (0 - 24 h) were homogenised and aliquots were stored frozen until start of extraction. The radioactivity and TER-values of the samples C. Analytical Procedures of Extracts of Extracts of Aliquots from liver Addrey and from the second from the se

Aliquots from liver and faces were conventionally extracted three times, aliquots from milk and muscle were stracted two times, with a mixture of acconitrile/ wate (8/2; v/v) using a Polytron homogeniser. The combined extracts of liver, kidney and Paeces were partitioned against n-heptane, the combined stracts of mit and muscle were parified using a C18 cartridge. The purified extracts were concentrated by rotary evaporation and subjected to HPLC analysis based on reversed phase chromatography with an acidic water action the THF gradent.

Solids of liver from the conventional extraction were exhaustively extracted twice with acetonitrile/water (DI; v/v) using microwave assistance. The metabolites in the combined exhaustive extracts were further characterised using TLQ analysis.

Aliquots of the conventional liver and kichey extracts were incubated for 20 hours at 37°C with a defined amount of B-gluguronidase/arybulfatase. After incubation, the enzymatic suspensions were purified and analysed by HPLC Ĩ Ŵ

Determination of the Radioactivity in the Crease Fraction of Milk

To evaluate the radioactivity in the seam fraction of milk, an aliquot of the milk sample was partitioned against n-heptane.

Radioactivitomeasurement

The radio retivity measurement in liquid samples was carried out by liquid scintillation counting (LSC). The solid samples were either dissolved in BIOLUTE S or combusted in an oxygen atmosphere using an exidiser. The released ¹⁴CO₂ was trapped in an alkaline scintillation cocktail and the radioactivity was determined by LSC.



Metabolite analysis

Parent compound and metabolites were quantified in the extracts by HPLC based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient. The peaks in the individual HQLC profiles were numbered increasingly in the order of elution in the HPLC-profiling methods Corresponding metabolites were named with the same peak-ID.

The assignment of parent compound and metabolites was achieved by comparison of HPLC metabolite profiles of the analysed samples among each other and compared to the goat metabolism study with the pyrazole label. Furthermore, metabolites were isolated from urine by HPVC. They were identified in the isolated fractions by spectroscopic methods. Other metabolites were identified by chromatographic comparison of the metabolic profile or by co-chromatography will radioabelled test enzymatically digested. The glucuronic acid conjugates were thereby digested and converted into the corresponding aglycons. Unknown metabolites were characterised basedon their extraction and chormatographic behaviour. An overview on the reference compounds its given in Table 6.2.3214. and reference compounds in selected samples. The conventional extracts of liver and kidned wet the owner where the document of the owner where a conner the owner where the o enzymatically digested. The glucuronic acid conjugates were thereby digested and converted into their



Report name / other names/codes	Chemical Name (IUPAC)	Chemical Structure
BCS-CN88460-2- propanol-GlucA	2-{4-chloro-2-[(cyclopropyl{[3- (difluoromethyl)-5-fluoro-1-methyl-1H- pyrazol-4-	F H ₃ C CHC
ID: YK0413E	yl]carbonyl}amino)methyl]phenyl}propan-2- yl beta-D-glucopyranosiduronic acid	
	Ű ^Ŷ	
BCS-CN88460- propenol-GlucA	2-{4-chloro-2-[(cycloprop y] f]- (difluoromethyl)-5-fluoro-Comethyl-1H- pyrazol-4-	F Q F Q Y HOY GO OUT
ID: YK0413F	yl]carbonyl}amino)me@yl]phe@yl}prop#2- en-1-yl beta-D-glucopyranosiduronic acid	
BCS-CN88460-lactic	2-{4-chloro-20 cyclopropyl	
acid	(difluoromethyl)-5-Mioro-1-methyl-1H-	OF OF OF OH
ID: YK0413C	yl]carb@yl}amwo)metfwl]phebyl}-2-0	
*		
BCS-CN88460-	2-{4@hloro22[(cyclopropx6]3- 2)	F F G H ₃ C GlucA
BCS-CN88460- propanol-GlucA (isomer 1)	(dtfluoronothyl) Stluoro-P-methyl-1H-@	
	v][carbony]{againo)methy]]phenyl{propyl	
ID: YK0413B	pyrazol 4 yl]carbonyl} ataino)methyl]phenyl}propyl glucopyranosidurokie acid	
		$\mathcal{C}_{\mathbf{H}_3\mathbf{C}}$ \mathcal{F} $\mathcal{L}_{\mathbf{C}}$ $\mathcal{C}_{\mathbf{I}}$
BCS-CXXX460-	2-{4@iloro-2-[(cyclopropy]@3- (diffuoromethy])-5[luoro-1-methy]-1H-	F GlucA
(isomer 2)	pyrazol-	
	vi]carbonyl}amino)methyl]phenyl}propyl	
ID: YK0413D	glucopyranosiduron@acid	
1 1		H ₃ C I
BCS-CN88460-	2-{4-Qiloro-2-[(cyclopropy]]3-	0
desmethyl-carboxylic	(difluoromethyl)-5-fluoro-11-pyrazol-4-	F F H ₃ C
acid	vgearbors, i} ami@)meth(r]phenyl}propanoic acid	Р ОН
ID: BN4114B		N
	2-{4-Qloro-2-[(cyclopropy) {}3- (difluoromethyl)-5 {}fluoro [PI-pyrazol-4- yfearbonyl] amito)methyl]phenyl} propanoic acid	H F Cl
Table is continued on the	next page.	1
	~	

 Table 6.2.3- 14:
 List of reference compounds



Table 6.2.3-14	continued
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Report name/ other names/codes	Chemical Name (IUPAC)	Chemical Structure
BCS-CN88460-carboxylic acid/ BCS-CY26497	2-{4-chloro-2-[(cyclopropyl{[3- (difluoromethyl)-5-fluoro-1-methyl-1H- pyrazol-4- yl]carbonyl}amino)methyl]phenyl}propanoic	
ID: BN4114F	acid	
BCS-CN88460-propanol	N-[5-chloro-2-(1-hydrox propan-2- yl)benzyl]-N-cyclopropy-3-	C F O O H ₃ C O H
ID: BN4183B	(difluoromethyl)-5-fftuoro-1-methyl-4)1- pyrazole-4-carboxamide	H, CO F
и р		

II. Results and Discussion

A. Recovery and Elimination of Radioactivity

\$ 1

The overall recovery in the lactating goat after administration of a mean daily dose of 1.0 mg [phenyl-UL-¹⁴C]BCS-CN88460 per kg body weight (according to 20.57 mg a.s. Ag feed/day) on five consecutive days accompted for approx. 51% of the total dose . The remaining amount of radioactivity was expected to still be present in the gion-edible part of the animal body and especially in the gastrointestinal tract.

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Table 6.2.3-45:

Recovery of radioactivity in dissected organs and tissues, milk, and excreta of lactating goats following oral administration of 5 daily doses of [phonyl-UD]⁴C[BCS-CN88460 at a dose rate of 1.0 mg/kg

Liver Kidney Total body muscle	0.10
	0.19
Kidney, N OF N W	0.01
Kidney Total body muscle	0.06
Total of organs/tissues	0.27
Milk Q – 10 M	0.06
Urine, 0 - 02 h (plus furfiel rinsing) Faeces, 0 - 102 h	9.81
$\begin{array}{c} & & \\$	40.78
Total excreted	50.59
Total Recovery	50.91



An amount of approx. 0.06% of the total dose was secreted with the milk, only. At sacrifice, radioactive residues in the organs and tissues dissected from the body were calculated to be 0.27% of the total dose.

Up to the time of sacrifice, 9.81% of the total dose was excreted with the urine and 40.78% with faeces (see table above). The daily renal excretion of the radioactivity started shortly after the first dosing before the daily renal excretion rate reached a more or less constant level with round about 1.2% to 3.6%. The daily faecal excretion of the radioactivity started after the first dosing. After the second dosing, the faecal excretion rate exhibited a more or less constant gradient and the faecal excretion reached its maximum with 17.5% after the fourth dosing. The cumulative renal and faecal excretion was characterised by a lime increase from day 3 until sacrifice.

Table 6.2.3- 16:	Distribution of residue oral administration of	es in live®kidne 5 daily doses of	y, muscle and [phenyl-UL-	hnilk of l CBCSC	actating g CN88360 a	oats following at a dose tate of	
	1 0 mg/kg		kĭ k		A V	<i>°</i>	

1.0 mg/kg	5		E S	Nº O	& A c
Organ/Tissue	Collection Time	Frésh weight [2]	ERR fmg/kg	Transfer stactor STF] * (2)	Persent of total dose administered
Liver	6 h atter last admin.		3 48		\$ 0 .19
Kidney	Øh after√ ∑Past admin.	155.38		0.009	0.01
Round muscle (sample)	6 Pafter 🔊	1,922.53	0.011		
Loin muscle (sample)	last autilit.	140,80°	0.040	× ·	
Total body muscle ***		13,659.00	× 0.011	0,001	0.06
Total of organs/tissues			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u></u>	0.27
	4° &		N Q	<i>S</i> ^a	
Milk, total 🔗 🖇	O day 1 to 5	11,231.80	° 6011	0.001	0.06
Milk, plątegu-level	,day 3-4 🕰	\$873.21	0.012	0.001	0.03
Feeding level	× &	20257 K	m کې [m	g a.s./kg dry fee	ed/day]

*) Percentage values and resh weights were calculated from the body weight at sacrifice, assuming 30% of the ody weight for total body puscles.

**) weighted mean TRR-values from the two types of muscle

***) The transfer factor was calculated by dividing the TRR-value of the respective sample by the feeding level (milligrams of a.s. per kilograms dry feed for each day).

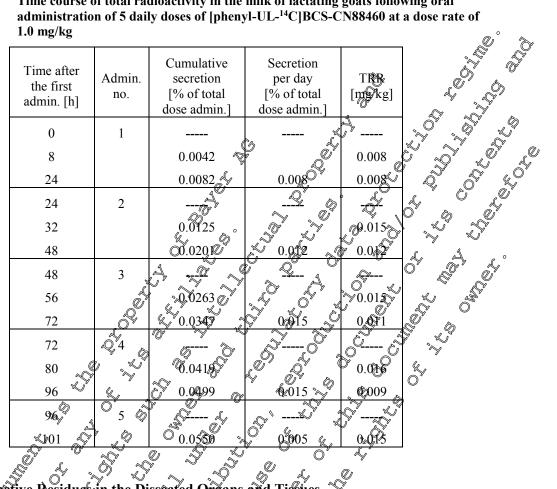
B. Levels and Time Course of Potal Radioactive Residues in Milk

The radioactivity levels measured in milk samples and the calculated amounts are shown in the table below. The DRR-values in milk samples ranged from 0.008 mg/kg after the first administration to 0.016 mg/kg after the fourth administration. The time course of TRR-values of the evening and morning milk indicated a diminal pattern for the testing period. The radioactive residues increased significantly during the eight-hour period after the first three administrations.

A residue plateau-fevel of 0.012 mg/kg was reached at about day 3-4 after the first administration. This value was calculated from the evening sample of day 3, both samples of day 4 and the morning sample of day 5.



Time course of total radioactivity in the milk of lactating goats following oral Table 6.2.3-17: administration of 5 daily doses of [phenyl-UL-14C]BCS-CN88460 at a dose rate of 1.0 mg/kg



C. Total Radioactive Residues in the Dissected Organs and Tissues

The highest TOR-value was determined in liver (0.348 mg/kg 0.19% of total admin. dose) indicating the significance of this organ for metabolism The TRR-value for Fidney accounted for 0.183 mg/kg (0.01% of total admin dose) and demonstrated that test compound related radioactivity partly was eliminated from the drimal the urinary excretion. The lowest PRR-value was determined in muscle (0.011 mg/kg; 0.06% of total admin. dose assuring a value of 30% of the body weight for this tissue).

D. Extraction Efficiency of Residues

The majority of the residues in the miller well as organs and tissues were efficiently extracted (88.3% to 100.0%) using acetoritrile water mixtures. In case of liver, the solids after conventional extraction A summary of the extraction efficiency is shown in the table below. were exhaustively extracted using aceton file/water mixtures with microwave treatment. Up to 8.2% of the TRR (0.029 mg/kg) remained in the post extraction solids (PES). After clean-up and concentration procedure the main portion of the extracted radioactivity was quantitatively analysed by HPLC.

A summa



Table 6.2.3- 18:Extraction efficiency of milk, muscle, liver and kidney samples of lactating goats
following oral administration of 5 daily doses of [phenyl-UL-14C]BCS-CN88460 at a
dose rate of 1.0 mg/kg

	01 100 116/116	•						^	
Sample	Milk (32 – 101 h) Muscle Liver		er 🏷	Kidr					
TRR [mg/kg]	0.0	0.013		0.013 0.011		0.348		0.183	
	% of TRR	mg/kg	% of TRR	_mg/kg	% of FRR	mg/kg	% of TRR	mg/kg	
Conventional extraction	98.5	0.013	100.0	0.011	88.3	0.307		Q179	
Exhaustive extraction			<i></i>		s 3.5	0012	~~	6 [°] -4	
Total extracted	98.5	0.013	100.0	0,011	91.8	Q0.319	97.9	0,1,79	
Post-extraction solids (PES)	1.5	<0.001	" <i>(</i> ") 1		\$ 8,2	0.009	2.1	0.004	
Accountability	100.0	0.093		0.014	109 .0	0 .348	L 1004	0.183	
		A.		/ 🖓	4	C.	<u>, %</u>	Ű,	

E. Quantification, Identification and Characterisation of Residues

Quantification of Parent Compound and Metabolites

Parent compound and metabolites were quantified in the conventional extracts of milk, edible organs, tissues and faeces as well as in urine (0 - 24 h) by HPLC, based on reversed phase phromatography using an acidic water/acetomtrile/THF gradient. Metabolites in the exhaustive extract of liver as well as co-eluting metabolites in an fraction of kidner were quantified by FLC.

Metabolites in the extracts as well as in the sample of urine (0 -424 h) were assigned to each other by comparison of the netabolite profiles and their retention times. Corresponding metabolites were named with the same peak (D. Deviled information can be found in the report.

Isolation and Identification of Parent Compound and Metabolites

The assignment of parent compound and metabolites was achieved by comparison of HPLC metabolite profiles of the analysed samples among each other and by comparison of the metabolite profiles of the current study with the profiles of the goat metabolism study of the pyrazole label.

Metabolites were isolated from trine (24 - 48 h) by HPLC. They were identified in the isolated fractions by spectroscopic methods. In addition parent compound and metabolites were identified in urine (0 - 24 h), in the convertional extracts of milk and muscle as well as in isolated fractions from milk, muscle, fiver and kidney by HPLC co-chromatography with radiolabelled reference compounds taken from the hen metabolism study with the pyrazole label or from the goat metabolism study with the yrazole label label. Conjugates were subjected to enzymatic cleavage with an aqueous solution of β -glucuronidase/sulfatase before HPLC-analysis.

F. Distribution of Parent Compound and Metabolites in Milk, Organs and Tissues

The identification rates amounted to 50.4% of the TRR for milk, 64.0% for muscle, 47.2% for liver, and 42.4% for kidney. 5

Parent compound was detected in milk, muscle, liver and kidney and amounted to 0.004 mg/kg (33.9% of the TRR) for milk, 0.002 mg/kg (21.5% of the TRR) for muscle, 0.018 mg/kg (5.3% of the TRR) for liver and 0.003 mg/kg (1.6% of the TRR) for kidney.



Metabolites in milk

Besides parent compound as the main residue in milk, BCS-CN88460-desmethyl-propanol was the major metabolite (6.7% (0.001 mg/kg) of the TRR). Metabolites BCS-CN88460-2-propanol and BCS-CN88460-propanol-GlucA (isomer 1 and 2) were minor metabolites (all ≤5.0% (0.001 mg/kg) of the TRR).

Metabolites in muscle

Besides parent compound as the main residue in muscle, BCS-CN88460-2-propanol was the major? metabolite accounting for 14.2% (0.002 mg/kg) of the TRR. Other prominent metabolites were BCS-CN88460-propanol-GlucA (isomer 2) (6.5% (0.001 mg/kg) of the TRR) BCS CN88460carboxylic acid (9.0% (0.001 mg/kg) of the TRR) and BCS-CN88460-propanol (9.0% (0.001 rsg/kg) of the TRR). BCS-CN88460-desmethyl-propanol was present in nonor amounts 3.7% (<0.00 cmg/kg) of the TRR).

Metabolites in liver

Metabolites in liver BCS-CN88460-2-propanol-GlucA was the main residue in liver and accounted for 0.045 mg/kg (13.0% of the TRR). Other prominent metabolites BCS_CN88460-propanot ClucA (isomer 1 and 2) accounting for 0.031 mg/kg (8.8% of the TRR) and 0.021 mg/kg (5.5% of the TRR), respectively. The six metabolites BCS-CN88460 dictic & acid BCS-CN88460 diction acid, BCS-CN88460-desmethyl-propanol BCS CN88460-carboxylic acid BCS CN88460-propanol and BCS-CN88460-2-propanol were minor metabolites, amounting between 0002 mg/kg 10.5% of the TRR) and 0.017 mg/kg (4.9% of the TRR).

Metabolites in kidney

Prominent metabolites in adney were BCS-CN88460-carboxylic acid and BCS CN88460-propanol-GlucA (isomer 2). They accounted for 0.012 mg/kg@6.8% of the TRR) and 0.066 mg/kg (8.6% of the TRR), respectively. Two further abundant metabolites in kidne@were identified as BCS-CN88460-2propanol-GlucA (40% (0.007 propenol-GlucA (6.2%) and BCS-CN88460-propenol-GlucA (6.2%) (0.011 mg/kg) of the TRR). The five minor metabolites BCS-CN 88460-Jactic acid, BCS-CN 88460propanol-Gluc (isomer 1), BCS-CN88460-desmethyl-carboxyler acid, BCS-CN88460-propanol and BCS-CN88460-2-propanol/were detected (≥ 0.008 mg/kg or $\le 42\%$ of the TRR).

More metabolites in the matrices may be present as indigated by broad non-resolved zones in the chromatograms. All unknown metabolites in the extracts were characterised by their extraction and

(0.005 mg/kg). The distribution of the parent composition and metabolites of milk, organs and tissues is summarised in the table below.



Table 6.2.3- 19:Radioactive residues of parent compound and metabolites in milk and edible organs
of lactating goats following oral administration of 5 daily doses of [phenyl-UL-
14C]BCS-CN88460 at a dose rate of 1.0 mg/kg

	¹ *CJBCS-CN884	460 at a c	lose rate	of 1.0 mg	/kg				Ŵ
Samp	le	М	Milk Muscle			Liv	ver	Kidney	
TRR	[mg/kg]	0.0)13	0.0	11	0.3	648	0.1	, 8 3
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg	% of TRR	mg/kg
Conve	ntional extraction	98.5	0.013	100.0	0.011	8,8,3	0.307	\$ 97.9	\$0.179
38	parent compound	33.9	0.004	213	0.002	5.3	0.018		0.003
20	2-propanol-GlucA (M20)			<u> </u>	,	Q 13.0	0.043	45 9 *	0.007
20	propenol-GlucA (M25)			"O~	4			% .2*	0.011×
21	lactic acid (M10)				× ×	Q1.3	Q.005	4,2	0.068
22	propanol-GlucA (isomer 1) (M19, isomer 1)	2.3	<0,001	°		× 8,80	0.084	°~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	×0.007
23	propanol-GlucA (isomer 2) (M19, isomer 2)	2.5			0,001	\$5.9	0.021	² 8.6	0.016
27	desmethyl-carboxylic acid (M11)	de la companya de la comp				() () () () () () () () () () () () () (0.002	3.6	0.007
28	desmethyl-propanol (M06)	6.7	\$0.001	× 3.0	<0.001	<u>\$</u> 0.6	0.002	Ő -z	
30	carboxylic acid (M12)	ő ⁽	¢	9.0	0,001	0 4.2		·	0.012
31	propanol (M01)		\$	9.0	0.00K	, 1 9		2.5	0.004
34	2-propanol (M02)	°≈75.0,	0.001	°° 14.2⁄	0.002	2.8	0.010	õ ⁹ 1.4	0.003
	identified	50.4	0.007	62 .0	0.007	<u>م</u> لكم للم	0.165	42.4	0.078
extract	cterised in the conventional	47:3	£006	29.8¢	^{\$*} 0.003	328	00732	54.4	0.100
Num peaks	ber of unknown		3 S			0	\$ ⁷	2	1
	est unknown peak 0° 5	38.6	% 005	25.0	Q 0.003		0.023	9.1	0.017
ACN/1		o«		×	\$	3.5	0.012		
peak)	8		£	, ,	5		
Larg peak	est miknown					1.7	0.006		
Total	characterised N 🔬 🧷	47.3	00006	©29.8	_≫ 0.003	41.3	0.144	54.4	0.100
	f losses	0.8	مُعْرَضَ 🖓		0.001	3.2	0.011	1.1	0.002
Total	extractative C	× 98:5	0.013	100.0	0.011	91.8	0.319	97.9	0.179
	ractable (PES)	428	<0,001	Øn.q.	n.q.	8.2	0.029	2.1	0.004
Accou	intability 🔍 📿	100.0	©0.013	100.0	0.011	100.0	0.348	100.0	0.183

* BC8-CN88460-2-propanol GlucA and BC8-CN88460-propenol-GlucA were co-eluting in the kidney and were subquantified by TLC2

The distribution of radioactivity in mills between the cream fraction and the remaining skimmed milk showed that the radioactivity was distributed evenly between the fractions of cream and skimmed milk (see table below).

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Table 6.2.3- 20:	Distribution of radioactivity in milk between cream and skimmed milk fractions
1 4010 0.2.0 20.	Distribution of fudiouctivity in mink between cream and skinning mink fractions

Sample description	% of TRR	mg/kg
n-heptane phase (cream)	49.7	0.006
aqueous phase (skimmed milk)	50.3	0.007
Total:	100.0	0.013

Conjugates in the liver and kidney like BCS-CN88460-2-propanol GlucA and BCS-CN88460propanol-GlucA (both isomers 1 and 2) could be enzymatically cleaved to their agreens. The cleavage of some unknown conjugates in non-resolved zones resulted in higher appoints of the aglycons. None of the unknown compounds after the aglycons. None of the unknown compounds after the aglycons. aglycons. None of the unknown compounds after cleavage of the liver and kidney extract accounted for more than 9.9% (0.035 mg/kg) of the TRR (mean of all five replicates) of 6.9% 0.012 mg/kg) of the TRR, respectively. The following main aglycons could be clearly dentified after enzymatic cleavage: BCS-CN88460-2-propanol and BCS-CN88460-propanol Ø

Table 6.2.3- 21:	Radioactive residues of parent compound and metabolites in liver samples of first and
	second conventionabextraction and after enzymatic cleavage for 20 h

Samp	_Ø	Liver-O 1 st conventional		Conventional extraction		Enzymaticcleavage of five aliquate of liver extracts					
	Q. (etion 4	extra	action	S mean	yalues?	devi	dard ation		
peak ID	Compound (Report name) BCS-CN88460	‰of ≾₽RR	mg/kg	% of TRR	mgkg	% of TRR	`ngg/kg	% of TRR	mg/kg		
Extra	ct used for HPLC	∑ 85 <u>,</u> €	0.296	\$3.5	@0.298	80.5	0.280	0.2	0.001		
38	parent	5.3	0.018	گې 5.6	y 0.0 20	A Ç7	0.016	0.4	0.001		
20	2-propagol-Glue (M20)	Õ13.0¢	0.045		0,046	1.3	0.005	0.3	0.001		
21	lactic acid (M10)		Q:005	A .2	0.004	0.7	0.002	0.1	< 0.001		
22	propanol-GlucA (isomer 1)	8.8	0.031	C 8.9							
23	propanol-Gluc A (isomer 2) (M19, isomer 2)	5.9	0.1921	\$8.2 0	49.029						
27	desmethyl-carbox the acid	e ^{0.5}	$0^{0.00}$	> 0,6	0.002	1.5	0.005	0.2	0.001		
28	desmethyl-propanol (1906) 🔌	0,6	0.002	@ .7	0.002	4.3	0.015	0.2	0.001		
30	carboxylic acid (M12)	4 2	°, 0 9015	4.3	0.015	9.6	0.033	0.4	0.001		
31	propanol (M01) 🥎	4.9	0.01		0.020	18.4	0.064	0.6	0.002		
34 🕷	2-propanol (M02)	or 2,80	Ó Q.QOÓ	2.5	0.009	13.4	0.047	0.5	0.002		
Total	identified 🔬 💇 👸	47.2	0 .164	50.9	0.177	53.8	0.187	2.7	0.010		
Total	characterised	~\$ 3 7.8	Q*0.132	34.6	0.121	26.7	0.093	2.5	0.009		
Accou	untability / /	~ 85 Ø	0.296	85.5	0.298	80.5	0.280	5.3	0.018		
Let a later of the		34 2-propanol (M02) 2 0.000 2.5 0.009 13.4 0.047 0.5 0.002 Total identified 47.2 0.164 50.9 0.177 53.8 0.187 2.7 0.010 Total characterized 37.8 0.132 34.6 0.121 26.7 0.093 2.5 0.009 Accountability 85.2 0.296 85.5 0.298 80.5 0.280 5.3 0.018									



Sample		convei extra	ney- ntional oction	enzyi cleava convei extr experi	ney- matic age of ntional act - ment 1	enzyi cleava conver extr exp <u>e</u> rii		enzy cleav conver extr experi	ney-@ matic age of rtional act- ment 3	
peak ID	Compound (Report name) BCS-CN88460-	% of TRR	mg/kg	% of TRR	mg/kg	%rof ÆR	mg/kg	°∿% of ∿ ∽TRR	mg/kg	_
Extrac	t used for HPLC	96.8	0.177	94.4	0.173	93.7	0.17	29.5	0.173	Ô
38	parent	1.6	0.003	¢۲ 1.6	0.005	1.2	00002	₽ 1.2	°0.002	×
20	2-propanol-GlucA* (M20)	10.2	0.01	▶ 1.1	0.002	Q 1.5	Q0.003	1.4	0.063	
21	lactic acid (M10)	4.2	0.008	。2.0	<u>@</u> .004	× 1.95	0.004	_ ≪U.7 ~~>	00003	
22	propanol-GlucA (isomer 1) (M19, isomer 1)	3.6	00.007	¢° 0,3	0.001	0 7.5	\$ 001		<0.001 (
23	propanol-GlucA (isomer 2) (M19, isomer 2)	86	0.046	~~	ð ^{~~}	<u>مَ</u>		\$- 		
27	desmethyl-carboxylic acid (M11)	Q 3.6	\$0.007	64	0.602	6.0	Ø.011	6.7	0 0.012	
28	desmethyl-propanol (M06)	y _D	Ĩ Ž	¥.9	0.009	රි 5.0ද්	0.009	ັ ູ ຟ.2	0.010	
30	carboxylic acid (M12)	\$6.8	0,012	12.4	0.023	1898	0.023	13.2	0.024	
31	propanol (M01)	مَحْ 2.5 ا	0.004	¢۲ 20	0,637	20.8	0.038	o [∞] 19.1	0.035	
34	2-propanol (M02)	/ 1. O	0.003	@5.1	. "	5.8	0.011	5.7	0.010	
Total identified		0,078	L 54.0	4	555	0.401	54.2	0.099]	
Total c	characterised 🔬 💭	گې 54.4	0.100	40.0	0.074	ر» 38.3 ۵	0 070	40.3	0.074	
Accou	ntability	968	0.157	.94.4	0.173	© [♥] 93.7Å	0.172	94.5	0.173	1

Table 6.2.3- 22: Radioactive residues of parent compound and metabolites in kidney samples of first and second conventional extraction and after enzymatic cleavage for 20 h

* BCS-CN88460-2-popanof Gluca and BCS-CN88460-popenol fluc A were only detected in kidney in a ratio of 6/4. Office of the second se

Distribution of Metabolites in Urme and Faeces

The metabolic profile of urine (0 - 24 h) and faces (0 - 24 h) overe similar to the profiles of edible materials, especially liver and kidney, except that parent compound was not present in the sample of urine. In faeces, parent compound was the main residue (8.0% of the first dose). All identified

metabolites in urfle and faces accounted for <1.2% of the first dose). All identified metabolites in urine and faces is summarized in the table below.



Table 6.2.3- 23:Radioactive residues of parent compound and metabolites in non-edible samples of
lactating goat following oral administration of 5 daily doses of [phenyl-UL-14C]BCS-
CN88460 at a dose rate of 1.0 mg/kg

Compound (Report name) BCS-CN88460- parent compound	Faeces (0 - 24 h) % of close in the sample	Urine $(0 - 24 \text{ b})$ % of dose in the sample
(Report name) BCS-CN88460-	% of dose in the sample	% of døse in
		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
	لا الا الا	<u>`~</u> ~
2-propanol-GlucA (M20) and propenol-GlucA (M25) (co-elution)	je	
lactic acid (M10)	炎	Q 0.2 0 V
propanol-GlucA (isomer 1) (M19, isomer 1)	\$° -6 ⁷	\$ 0.2 \$ 0.3 \$ 0.7 \$ 0.7
propanol-GlucA (isomer 2) (M19, somer 2)	0.4	×0.7 ~
desmethyl-carboxylic acid (MA)	₩ 0.1 ×	°≫0.2 [√]
desmethyl-propanol (M06)	0.3 ^{0*}	S OF C
carboxylic acid (M12)	<b>9</b> .7	40:8
propanol (M01)	× 1.2 ×	
2-propanol (M02)	Č 0, E	0
2-propanol and hydroxyphenyl (M04) (co-elution)		1.00
	~ ⁰ 11.4	3.6
terised by HRGC 'n a a a a a a a a a a a a a a a a a a	0.50	2.6
own peaks & & & &		19
n peak 2 . O' & &	~~ 0.2 ~	0.3
ised, A & X V V	0.5	2.6
	AQ.5	
	@ 12.4	
solids (PES) 4 & A A A	0.4	
	12.8	6.2
	propanol (M01) 2-propanol (M02) 2-propanol and hydroxyphenyl (M04) (co-elution) terised by HREC own peaks ised ised Solids (PES)	lactic acid (M10) propanol-GlucA (isomer 1) (M19, isomer 1) propanol-GlucA (isomer 2) (M19, isomer 2) desmethyl-carboxylic acid (M14) desmethyl-propanol (M06) carboxylic acid (M12) propanol (M01) 2-propanol (M02) 2-propanol and hydroxyphenyl (M04) (co-elution) <i>acidy for the set of the s</i>

#### G. Storage Stability of Residues

During the study, all samples and extracts were stored in a freezer at  $\leq$  -18 °C or for a short time in a refrigerator. All samples of nork, and edible organs and assues were extracted within four months after sample collection. The first metabolite profile was recorded not later than four days after the start of the extraction and sample preparation.

The storage stability was exemplarity demonstrated for all other matrices. A second conventional extraction of liver was performed approx. 11 months after sampling. The extract was used for enzymatic cleavage experiments.

#### III. Conclusion

The metabolic behaviour of [phenyl-UL-¹⁴C]BCS-CN88460 in the lactating goat can be characterised by the following observations

The FRR-values and the transfer factors in milk, organs and tissues were very low compared to the dose level of 20.57 mg a.s./kg feed/day and a dosing period of five days. The highest TRR-value was detected for liver and was caused by the short time period of 6 hours between last dosing and sacrifice. It indicates the significance of this organ for metabolism. The significantly lower TRR-value for kidney shows that no residues were retained in this tissue and reflects the low amount of radioactivity, which was excreted by the urine. The TRR-values in the respective evening and morning milk samples



showed a diurnal pattern as they declined slightly prior to the delivery of the next dose for most days. A continuous increase was observed before a residue plateau-level was reached at day three after the first administration.

This \$ The elimination of radioactivity was mainly faecal and only 9.8% were eliminated via urines excretion behaviour was similar to the findings in the ADME studies with rats.

The radioactive residues were efficiently extracted from milk as well as from edible organs and tissues; extraction rates ranged from 88.3% to 100.0%.

The identification rates of parent compound and metabolities in milk, edible organs and tissues ra between 42.4% and 64.0% of the TRR. Ì

Parent compound was a major compound in milk and muscle, a prominent compound in lived and minor compound in kidney. Overall up to ten metabolites were identified Ò

BCS-CN88460-2-propanol (M02) was detected as a major metabolite in muscle, BCS-CN88460desmethyl-propanol (M06) as a major metabolite ip milk (32 - 101 h) BCS-CN88460-2-propanol-GlucA (M20) as a major metabolite in liver and BCS-C98846@proparol-GlucA (isomer 2 M19, isomer 2) as a major metabolite in kidney. Further abundant metabolites were BCSCN88460propanol-GlucA (isomer 1, M19 - isomer 1) in liver and ridney BCS CN88460-propanol-GlucA (isomer 2, M19 – isomer 2) in musche, liver and kidney BCS CN88460-carloxylic acid (M12) in muscle, liver and kidney and BCS @N88460-propanol (M01) in muscle and liver BCS @N88460lactic acid (M10) and BCS-CN88460-desmethyl-carboxylic acid (M11) were minor metabolites in liver and kidney. BCS-CN88460-properiol-GlacA (1925) was only detected as Ominor metabolite in kidney and in urine.

The metabolic profile of usine and faeces were similar to the profiles of earble materials, especially liver and kidney.

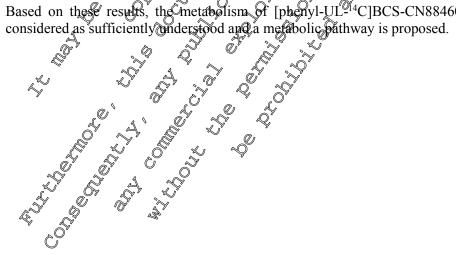
The principal metabolic reactions of [phenyl-UL C]BCS-CNS8460 in the factating goat are listed below:

- hydroxylation n position 1 and position 2 of the propyl group in the phenyl ring
- conjugation with glucuronic acid
- oxidation of the 1-propanol group was leading to a carbox gric acid group or with a hydroxy 1 group in position 2 to factic acid 💍

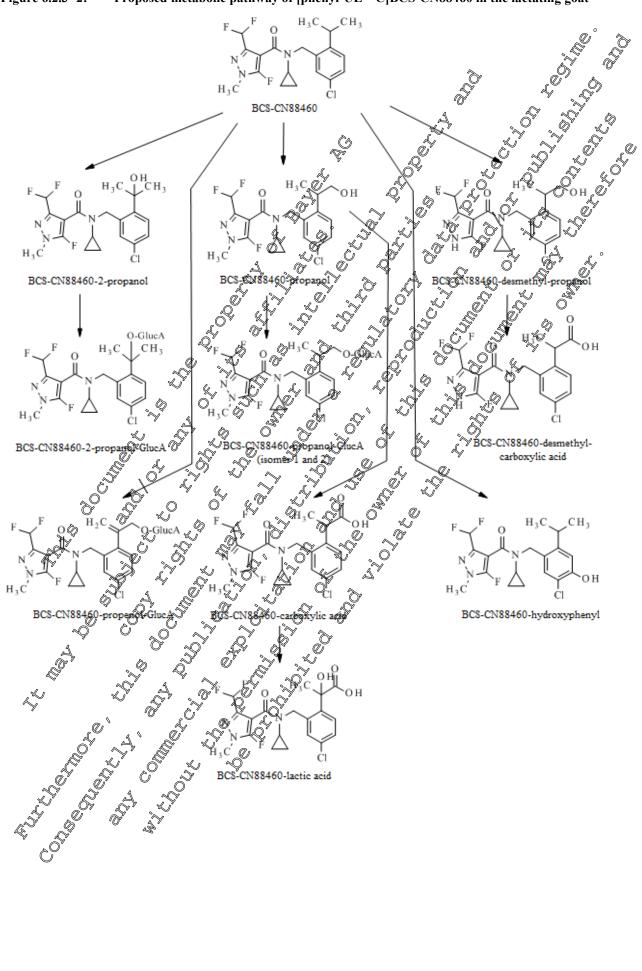
demethylation of the pyrazole moiety

- hydroxylation in position 4 of the phenyl moiety
- dehydrapon after hydroxylation in position 1 and 2 of the propyl group followed by conjugation with glueuronic acid ~

Based on these results, the metabolism of [phenyl-UL214C]BCS-CN88460 in the lactating goat is







#### Figure 6.2.3-2: Proposed metabolic pathway of [phenyl-UL-¹⁴C]BCS-CN88460 in the lactating goat



#### CA 6.2.4 Pigs

As the metabolic pathways in ruminants and hens were similar to the metabolic pathway in rats, no metabolism study in pigs has been submitted.

#### CA 6.2.5 Fish

As outlined in the EU-Directive 91/414/EEC, the EU Aquatic Guidance Document, as well as a EPA and PMRA guidelines, a log  $P_{ow} > 3$  should be used as a general trigger for a fish bioconcentration study. The whole study is summarised under CA 8.2.2.3/01 in MCA, Section 8 The nature of the residue in fish was investigated using [pyrazole-4-¹⁴C]BCS-CN88469 and is summarised here in more detail (Appendix VI of the study report).

Table 6.2.5- 1:	Overview over available fis	s bioco	Reentration	and met	abolism 🔊	udies	Č.

	4			
Fish	Exposure	Concentr		Reference
Bluegill sunfish	continuous exposure for 4 of pyrazole-labeller isoflucypram		S' O D	Mc210008-01-1

< 1	
Report: k	KČA 6 45/01; <b>10</b> , KS <b>T 10</b> , KS, 2017; M-610008-015
Title:	pyragaie-4-sac bes-chapa-oo - Aqueous exposure biocpice intation fish test and
ي لا م	piotransformation in fish (Expomis) macrochirus)
Report No.:	EBLNN359 47 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Document No.: 🖉 🔊	M-610098-0161 ~ (7 2 2 2 2
Guideline(s):	EU Directive 1/414/PEC; Regulation11072009 (Europe); OECD Test Guideline
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	305, US EPA OCSPP 850, 1730 S
Guideline deviation(s):	305 US EPA OCSPP 850 730 According to the guideline and the studg protocol, the measurement of the total
	rgang carbor TOC) will be performed 48 and 24 hours prior to test initiation.
	notes prioc to test initiation. This deviation has no negative impact on the outcome of
tt 🖏	the study since there results of both measurements were reasonable (< 2 mg/L)
GLP/GEP:	However, due to scheduling issues the TOC content was measured 72 hours and 24 notes prior to test initiation. This deviation has no negative impact on the outcome of the study since there results of both measurements were reasonable (< 2 mg/L) were $\sqrt{2}$
	yes at the the the the the the the the the th
×	

Executive summary

The metabolism of BCS1CN88460 in bluegh sunfish was investigated as part of the fish bioconcentration study. The test compound was radiolabelled in the pyrazole-4 moiety.

The analysis of stock solutions of the test compound from all aquariums showed that [pryrazole-4-¹⁴C] BCS-CN88460 was stable in the stock solutions during the exposure phase.

Water samples were collected during the exposure period of 28 days for aquarium C and 14 days for aquarium D. Allowater samples taken after day 28 were not further analysed due to low radioactivity. The radioactive residue was extracted from water samples by solid phase extraction (SPE) with RP18. The residue were fluted with acetonitrile and methanol/tetrahydrofurane, concentrated and analysed by HPLC with radiodetection. The radioactive concentrations in the water ranged from 3.9 to 6.4 µg/C. Parent compound was the main compound in the water samples and amounted to \geq 98.2% in aquarium C and \geq 90.9% in aquarium D. The following minor metabolites were detected in the water samples: conjugate of BCS-CN88460-N-methyl-pyrazole-carboxylic acid, BCS-CN88460-desmethyl-



GlucA (isomer 1), BCS-CN88460-cyclopropyl-pyrazole-carboxamide, BCS-CN88460-desmethylpropanol and BCS-CN88460-propanol. Each of these metabolites accounted to $\leq 0.1 \, \mu g/L$.

Total Radioactive Residues in Edible and Viscera Fish Parts

Edible parts and viscera of fish sampled on Day 7 and 14 from aquarium D (metabolism test with 5 μ g/L) were conventionally extracted with acetonitrile/water mixtures. The T&Rs were moderate for edible fish parts and amounted to 0.565 mg/kg for day 7 and 0.567 mg/kg for day 14. In viscera fish parts the TRR was 3.955 mg/kg on Day 7 and 3.365 mg/kg on Day 14. The extraction rates amounted between 92.8 and 98.7%. The post extraction solids (PES) amounted to \$.8% (0.033 mg/kg) of TRE for edibles on Day 7, 7.2% (0.041 mg/kg) of TRR for edibles on Day [4, 1.3% (0.05) mg/kg) of TRR for viscera on Day 7 and 1.7% (0.058 mg/kg) of TRR for viscera on Eavy 14.

Metabolism

Parent compound and metabolites were analyse and quantified in the Concentrated extract by HELC with radiodetection. They were assigned to each other in the profiles based on the metabolite pattern and their retention times. Parent compound and metabolites were identified in solated fractions by HPLC- and TLC-co-chromatography with radiolabelled reference compounds, which were ordentified by structure elucidaton in the ADME studies with rats

Parent compound was a prominent compound in edible parts of fight and amounted to 16.7% (0.095 mg/kg) of TRR for day 7 and 19.2% (0.109 mg/kg) of TRR for day 14 In viscera parts of fish parent compound was detected with 5.1% (0.201 mg/kg) of TRR for ay 7 and 9.7% (0.326 mg/kg) of de la construcción de la constru Ŭ) TRR for day 14. N A I Ì

The main metabolite in etable fish parts was BCS-CN88460-cyclopropyl-pyrazole-carboxamide (M58) and amounted to approx of 1% of the TRR for day 7 and 4. At day 14 the conjugate of BCS-CN88460-N-methyl pyrazole-carboxylic acid was detected with 15,1% (2086 mg/kg) of TRR and BCS-CN88460-propanok (M01) with 90.0% (0.05) mg/kg) of the TRR. The conjugate of BCS-CN88460-N-methyl-pyrazole-carboxylic acid could be cleaved to its aplycon with hydrochloric acid at elevated temperatures. Further metabolites in edible ish parts were BCS-CN88460-N-methylpyrazole-carboxylic acid (M50), BCS-CN88460-desmethyl (M13), BCS-CN88460-desmethyl-propanol (M60) and conjugates like BCS-CN88460-desmethyl-propanol-GlucA (isomer 1, M31), BCS-CN88460-propanol-GlucA (isomer 1 and 2 M19) and BCS-CN88460-desmethyl-GlucA (isomer 1, $\sqrt{135}$). They appounted to $\leq 50\%$ (0028 mg/kg) of TRR %

Beside parent compound the major part of radioactivity in viscera of fish was represented by the two metabolites BCS-CO8846@propagol-GlocA (isomer K and 2, M19) and amounted to in sum approx. 40% of the TRR Other metabolites in viscera fish tissues were BCS-CN88460-N-methyl-pyrazolecarboxylic acid (M50), Sonjugate of BCS-CNS8460-N-methyl-pyrazole-carboxylic BCS-CN88460-cyclopropy-pyrazore-carboxamide (M58), BCS-CN88460-desmethyl-prop acid, BCS-CN88460-desmethyl-propanol-GlucA (isomer 1, M31), BCS-CD88460 desmethyl-propanol (M06), BCS-CN88460-propanol (M01), BCS-CN& 460-desmethyl-Gluck (isomer 3/ M35) and BCS-CN88460-desmethyl (M13). These metabolites amounted to $\leq 6.6\%$ (0.262 mg/kg) of TRR.

Unknown metabolites in all fish issue were characterised by their extraction and chromatographic behaviour and amounted to 3.4% (0.04) mg/kg) of TRR for edible fish parts and $\leq 5.4\%$ (0.213 mg/kg) of TRR for viscera fish parts. Details of the distribution of parent compound and metabolites in fish thesues are presented below:

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Table 6.2.5- 2:	Radioactive residues of parent compound and metabolites in edible and viscera tissues
	of fish after 14 days exposure of [pyrazole-4- ¹⁴ C]BCS-CN88460 to bluegill sunfish

	edible parts of fish				viscera of fish 🖉			
	da	y 7	day	day 14		day 7		r t
TRR [mg/kg] =	0.5	65	0.5	567	3.9	55		65
Compound/fraction	% TRR	mg/kg	% TRR	mg/kg	% TRR	≥mg/kg	% TRR	mg/kg
Conventional extract	94.2	0.532	92.8	0.527	98.7	3.901		3/307
BCS-CN88460-N-methyl-pyrazole- carboxylic acid (M50)	3.3	0.019			3.4	0.135	× 4,5	0.152
BCS-CN88460-cyclopropyl-pyrazole- carboxamide (M58)	30.9	0.175	30.4	0.133	5.8	0.029	\$5.9	0.197
Conjugate of BCS-CN88460-N-methyl- pyrazole-carboxylic acid **	7.3	0;041	15.1	9 .086	©° 1.2	√0.049	2.F	0.072
BCS-CN88460-desmethyl-propanol-GlucA (isomer 1) (M31, isomer 1))	2@	, 0.014	° bê		S .2	©204	× 5.9	×0.198
BCS-CN88460-propanol-GlucA (isomer 1) (M19, isomer 1)	4.6	¢.026		<i>с</i> " «	S V	0.909	2805	0, 1 92
BCS-CN88460-propanol-GlucA (isomer 2) (M19, isomer 2)	\$.0 4	0.098	× 3.0	0017	x)16.3	0.643	//	0.580
BCS-CN88460-desmethyl-propanol (1996)	071.9	0.011				0.137	_√.1 ^≫	0.037
BCS-CN88460-propanol (M01)	* 6 0 *	0,096	Ø.0	B Ø57	© 3.1	0 .123¢	4.0	0.135
BCS-CN88460-desmethyl-Gluc	۶°1.8	<u>, 0</u> .010	[∼] √ 1.4	€ € 0.008	\$ 	0.262	2.6	0.086
BCS-CN88460-desmethyl (2013)	6 1 (0.0 1 0	3.8	0:019	\$0.5	0 .018	1.2	0.039
Parent compound	10.7	0.095		\$0.109		©) 0.201	9.7	0.326
Total identified	_{@1} 81.6	9.46 1	ر [¥] 87.3	[©] 0.495	73.6	2.910	77.8	2.616
Number of unknown compounds	× ·		t joi			-	1	
Amount of the largest unknown compound	3.4	0:019	2 .5	014	~~ 5.4		4.2	
Total characteriged * 🔊 🧴	\$2.6	0:071	🔊 ັ5.5			0.991	20.5	
Total extracted	∛94.2	Q0.532	Y		98.7	3.901	98.3	
Post extraction solids (PES)	58	0.039		02041	1.3	0.053	1.7	
Accountability O N &	100.0	Ø \$ 5 65	\$90.0	Ø.56 7	100.0	3.955	100.0	3.365

* Unknown metabolites were characterised based on their extraction and chromatographic behaviour.

** The aglycon BCS-CN\$8460.0 methy pyrazole-carboxylic acid could be clearly identified after acidic cleavage of the conjugate acidic cleavage of the cleavage of

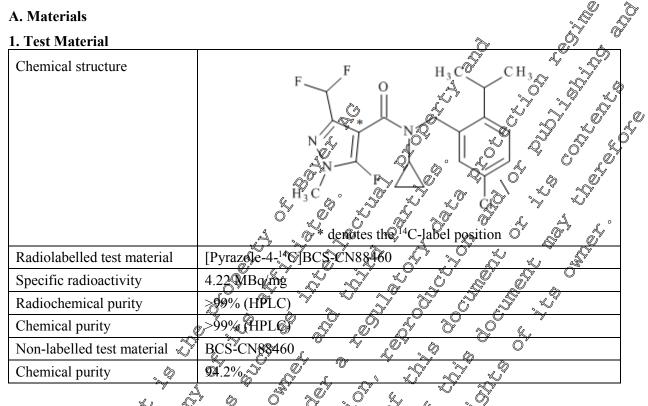
The principal metabolic reactions of $[pygzole_2]^4C]$ CS-CN88460 in fish are listed below:

- demethy lation of the pyrazole moilery was reading to desmethyl compounds
- hydroxylation in position 1 of the propyl group was leading to propanol compounds
- conjugation with glucoronic acid after hydroxylation in position 1 of the propyl group or via nitrogen was leading to several glucuronic acid-conjugates
- cleavage of the phonyl projecty was leading to the cyclopropyl-pyrazole-carboxamide compound
- cleavage of the pheny moiety in combination with cleavage of the cyclopropyl ring and further followed by exidation was beading to a N-methyl-pyrazole-carboxylic acid compound
- conjugation of BCS-CNS8460-N-methyl-pyrazole-carboxylic acid was also observed

On the basis of the results of this study it was concluded that [pyrazole-4-¹⁴C]BCS-CN88460 was stable in water and intensely metabolised in fish and a pathway of [pyrazole-4-¹⁴C]BCS-CN88460 in fish is proposed.



I. Materials and Methods



B. Study Design

Preparation of the Test Compound for Administration

For the experiments, the radiolabelled test compound was dillied with appropriate amounts of nonradiolabelled test compound, yielding 24L of stock solution for each of aquarium B and C and 1.4 L of stock solution for aquarium D. The stock solution for each of dividual aquarium was prepared by using dimeth dormamide (IDMF) as solvent.

The purity of the test compound in the stock solutions was checked before application by HPLC. In addition, an aliquot of stock solution **B** and **C** were taken on Day 28 after application and an aliquot of stock solution **D** on Day 4 after application After storage period of the aliquots for approx. 2 months at approx. 18°C the sability of the jest compound was checked by HPLC. In all cases the purity of the test compound was 99.29%.

Water samples

Water samples were taken from day 0, 1, 28 and 29 for aquarium C, and from day 7 and 14 for aquarium D.

Fish samples

For analysis of parent compound and metabolites from aquarium D (nominal test concentration of $5.0 \ \mu g$ [paraole 4-14C]BCS-GN88460 / L water) a number of 15 fishes were sampled after an exposure period of 7 and 14 days, respectively. Fishes were dissected into edible tissues (fillet, body muscle, skip and speleton) and viscera / non-edible parts (viscera = head, fins and internal organs). The coarse pieces of the edibles or viscera of each day were combined and homogenised with a high speed bender. From these samples, a sub-sample was taken for extraction and analysis of parent compound and metabolites.



C. Analytical Procedures

Sample Extraction and Preparation for Chromatographic Analysis

Preparation of water samples

Each individual water sample (1000 mL) were applied to a pre-conditioned RP18 solid phase extraction (SPE) cartridge (to concentrate the radioactive compounds from the water sample). The aqueous flow through was collected and the retained radioactivity on the RPT8 phase was eluted with, approx. 500 mL acetonitrile followed by approx. 250 mL methanol/tetrahydrofurane. (9/1; v/s). The acetonitrile eluates were concentrated to an aqueous comainder using a rotary evaporator (bath temperature approx. 35 °C). Each remainder was diluted with acetonin le/water $(1/\sqrt[3]{v/v})$ gelding the final extracts. The final extracts and the other eluates were stored in a freezer (≤ 1 S°C).

The radioactivity in the flow through fraction, elustes, concentrates and distillates was determined by LSC. The total radioactive residue (TRR) of each water sample was determined by summing up the radioactivity measured in the flow through fraction and the chates based on the volume of the sample Ź and the specific radioactivity of the test compound $\mathcal{A}_{\mathcal{A}}^{(\mathcal{A})}$

Extraction and Preparation of Fish Samples 🌤

Samples of the edible parts of fish@and_viscera were extracted successively three times with acetonitrile/water (8/2; v/v) using a firgh speed homogeniser. Splids and extracts were separated by centrifugation. Extracts were comprined and concentrated to an aqueous remainder using a rotary evaporator (bath temperature approx. 30°C). The remainded was diffuted with accontrile/water (1/1; v/v) yielding the final extract. Radioactivity in the extracts was determined by LSS after volume measurement. Radioactive residues in the remaining solids were determined by combustion of aliquots followed by LSC.

The TRR (Total Radioactive Residue) in fishsamples was alculated by summing up the radioactivity measured in the extracts and PES (post extraction solids) based on the used sample amount and the specific radioactivity of the test compound.

Radioactivity measurement

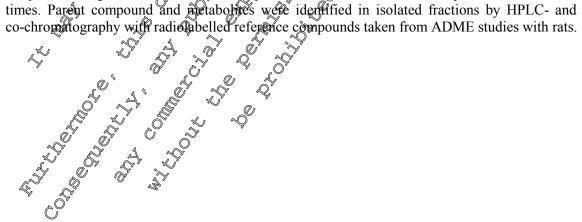
The radioactivity measurement in liquid samples was carried out by liquid scintillation counting (LSC). The solid samples combusted in an oxygen atorosphere using an oxidiser. The released ¹⁴CO₂ was trapped in an alkaline scincillation cocktail and the radioactivity was determined by LSC.

Metabolite analysis

Parent compound and metabolites were quantified in the extracts by HPLC based on reversed phase chromatography using an acide water acetomitrile THF gradient.

Q

They were assigned to each other in the profiles based on the metabolite pattern and their retention times. Parent compound and metabolites were identified in isolated fractions by HPLC- and TLC





Report name/	Chemical name (IUPAC)	Chemical Structure
Parent compound (BCS-CN88460)	N-(5-chloro-2-isopropylbenzyl)- N-cyclopropyl-3- (difluoromethyl)-5-fluoro-1-	F F H ₃ C CH ₃
Sample ID: PP01SSV	methyl-1H-pyrazole-4- carboxamide	
BCS-CN88460-N-methyl- pyrazole-carboxylic acid	3-(difluoromethy) 3-fluoro-1- methyl-pyrazol	
(BCS-AB72918 or BCS-CR73065)	acid a a a a a a a a a a a a a a a a a a a	
Sample ID: HF7708I		
BCS-CN88460-cyclopropyl- pyrazole-carboxamide (BCS-CX99798)	N-exclopropyl-3-	
Sample ID: HF7708J		
BCS-CN88460-desmethyl- propanol-GlucA (isomer.1)	2-{4-chloro-2-/(cycleoropyl{[3- (diffuoromethyl)-5-fluoro-11- pyrazol-4	Free Office Contractions of the contraction of the
Sample ID: HF76B36	yi]carbonyl}anano)metbyl]pheny l}propyl glucopyranosiduronic acid	
BCS-CN88460 propanol-GlacA (isomer 1)	#-{4-ehtoro-2-(cyclopropyl}] (difluoromethyl)-5-Horo-1- methyl-1HOpyrazol 4-	F H ₃ C GlucA
(isomer 1) Sample ID. HF76B37	Acid A A A A A A A A A A A A A A A A A A A	
BCS-CN88460-propanel-GlucA (isomer 2)	2-{4-chloro-2-Keyclopsopyl{[3- (diflacoomethyl)-5-fluoro-1- methyl-1H-pyrazol/4-	$F \xrightarrow{F} O \xrightarrow{H_3C} O \xrightarrow{GlucA}$
Sample IBTHF76B38	ydearbonyl amino)methyl]pheny	$\begin{array}{c c} N & & \\ N & & \\ N & & \\ H_3C' & F & \\ \end{array}$
BCS-CN88460 desmethyl-	₹ ¶4[5-chtoro-2-(1-hydroxypropan-	F H ₃ C
(BCS-DC22055)	2-yl)benzyl]-N-cyclopropyl-3- (difluoromethyl)-5-fluoro-1H- pyrazole-4-carboxamide	N N OH
Sample D: HE59F21		$\begin{array}{c c} H & F & \\ \hline & & \\ & & Cl \\ \end{array}$

Table i $\widehat{C}_{ontinued}^{\nu}$ on next page.



Table 6.2.5-3continued

Report name/	Chemical name	Chemical Structure
	(IUPAC)	
BCS-CN88460-propanol	N-[5-chloro-2-(1-hydroxypropan-	F H ₃ C
(BCS-CY24813)	2-yl)benzyl]-N-cyclopropyl-3-	F COOH
	(difluoromethyl)-5-fluoro-1-	
Sample ID: HF8614M	methyl-1H-pyrazole-4-	N N N N N N N N N N N N N N N N N N N
1	carboxamide	
		HC L A G
BCS-CN88460-desmethyl-GlucA	N-(5-chloro-2-isopropylbenzyl)- N-cyclopropyl-34	F FOO CH3
(isomer 1)	(difluoromethy @-5-fluoro-1-	
Sample ID: HF76B49A	(beta-D-glucopyranuronosyl) IH-	
1	pyrazole-4 earbox anide	
		Souch O' A all a
BCS-CN88460-desmethyl	N-(5 chloro-2-isopropylben yl)-	F F F F F H C FH 3
	Novclopstopyl-3-	
Sample ID: KM9413K	Orfluoromethy 195-fluoro-1H-0	
Å	pyrazofe-4-carboxamide	
Ŵ		
· · · ·		
L ST	VII. Results and Discussion	
~~ °O* .	San Discussion	

Water Samples

The radioactive concentrations in the water samples collected during the exposure period of 28 days for aquarium O and 54 days for aquarium O ranged from 3.9 6 6.4 µp/L. All samples taken after day 28 were not further analysed due to low radioactivity.

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Parent compound was the main component in the water samples and amounted to \geq 98.2% in water samples of aquarium C and \geq 90.9% in water samples of aquarium D. The following minor metabolites were detected in the water samples: conjugate of BCS-CN88460-N-methyl-pyrazole-carboxylic acid, BCS-CN88460-desmethyl-GlucA (isomer 1), BCS-CN88460-cyclopropyl-pyrazole-carboxamide, BCS-CN88460-desmethyl-orpanol and BCS-CN88460-propanol. Each of these metabolites accounted to \leq 0.1 ugA.

The second design of the secon



Table 0.2.3- 4. Analyses of water sa	inpres of uq					1
wa	ter in aquai	rium C				
	day	0	da	y 1	day	28 🚀
TRR $[\mu g/L] =$		3.9		4.lg	<i>V</i>	500
Compound	% TRR	μg/L	% TRR	μg/L 🔍	% TRR	μg(L
BCS-CN88460 (parent compound)	100.0	3.9	98.2	4.1	98.2	4.9
Conjugate of BCS-CN88460-			1.8	0.1		<u>Ŏ</u> Ĭ <u>-</u> ĠĬ
N-methyl-pyrazole-carboxylic acid *		Ì		Â,	L.	
BCS-CN88460-desmethyl-GlucA		V	-0	§	¥.8	≫0.1 ¥
(isomer 1) (M35, isomer 1)		1	03		×,	Q. A
Total identified	100,0	3.9	-Q00.0			\$.0
Extracts analysed	190.0	3.9	√ 100.0	4.R	1,00.0	
Extracts not analysed	6	° -		· @	ð	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Accountability	0 10000	3.9	190.0	4.1	\$100.0	5.0
Wat	ter in aquai	ain D	Q,	O"	Ŭ O V	
			× A		~	
		day 74	0 ^y		day 14	
$\frac{\text{TRR}\left[\mu g/L\right]}{\sqrt{2}} = \frac{\sqrt{2}}{\sqrt{2}} \frac{1}{\sqrt{2}}$			×4.2	<u> </u>	ž 01°	6.4
Compound & O		<u>ه</u>	₩µg/I			rg/L
BCS-CN88460 (parent compound))*9 <u>6</u>	39		7.0	گن ونگ
BCS-CN88460-cyclopropy opyrazote- carboxamide (M58)		.3 🎸	0.1	è î	ð.6	/ <0.1
$\frac{\text{carboxamide (M58)}}{\text{Conjugate of BCS-CN88460}} \qquad $		1 million	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u>, </u>		
Conjugate of BCS-CN88460- N-methyl-pyrazole-carboxylic acid BCS-CN88460-desmethyl-propanol		3.0	Q.F		1,7	0.1
BCS-CN88460-desmethyl propanol		70	\$ ~ 0 1		<u>S</u>	
		J. 14	0.1	5 °N	/	
BCS-CN88460 Bropanol (M0)		DĂ 🕡	, 0.1	· · · · · · · · · · · · · · · · · · ·		
BCS-CN88460-desmothyl-GhucA		.0 \$	Ø.1	Å.	0.4	< 0.1
(isomer 1) (M35, jsomer 1) & &		~	<u> </u>			
Total identified O	98	Ê (5 ⁵ 4.b	, 10	0.0	6.4
unknown	U I	9.6	<0 <u>4</u>			
Total characterised).6	~0.1			
Extracts analysed		3.9° s	4.2	10	0.0	6.4
Extracts not analysed 4		21	<0.1			
Accountability A &).0	4.2	10	0.0	6.4

Table 6.2.5- 4: Analyses of water samples of aquarium C and D

* The aglycone BCO CN88460-N-methyl Dyrazol carbo ylic acid could be clearly identified after acidic cleavage of the conjugate.

Distribution of Radioactivity in Fish Samples

Edible parts and viscerar of fish sampled on Day 7 and 14 from aquarium D (metabolism test with $5 \mu g/L$) were conventionally extracted with acetonitrile/water mixtures. The TRRs were moderate for edible fish parts and amounted to 0.565 mg/kg for day 7 and 0.567 mg/kg for day 14. In viscera fish parts the TRR was 3.955 mg/kg on Day and 3.365 mg/kg on Day 14.

The extraction rates amounter between 92.8 and 98.7%. The post extraction solids (PES) amounted to 5.8% (9033 mg/kg) of TRR for edibles on Day 7, 7.2% (0.041 mg/kg) of TRR for edibles on Day 14, 1.3% (0.053 mg/kg) of TRR for viscera on Day 7 and 1.7% (0.058 mg/kg) of TRR for viscera on Day 14.

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Distribution of Parent compound and Metabolites in Fish Samples

Parent compound was a prominent compound in edible parts of fish and amounted to 16.7% (0.095 mg/kg) of TRR for day 7 and 19.2% (0.109 mg/kg) of TRR for day 14. In viscera parts of the second se parent compound was detected with 5.1% (0.201 mg/kg) of TRR for day 7 and 9.7% (0.326 mg/kg) of TRR for day 14.

BCS-CN88460 was intensely metabolised in the fish. The main metaboliteon edible fish parts was BCS-CN88460-cyclopropyl-pyrazole-carboxamide and amounted to approx. 31% of the TRR for day 7 and 14. At day 14 the conjugate of BCS-CN88460-N-methyl-pyrazole earboxylic age was detected with 15.1% (0.086 mg/kg) of TRR and BCS-CN88460 propanol with 10.0% (0.057 mg/kg) of the TRR. The conjugate of BCS-CN88460-N-methyl-pyrazole-carboxyfic acid could be cloaved to its aglycon with hydrochloric acid at elevated temperatures. Further metabolites in edible fish parts were BCS-CN88460-N-methyl-pyrazole-carboxylic acto, BCS-CN88460-desmethyl, BCS-CN88460-desmethyl-propanol and conjugates like BCS-CN88460-desmethyl-propanol-ClucA (isomer 1), BCS-CN88460-propanol-GlucA (isomer 1 and 2) and BCS-CN88460-desmethyl-GlucA (isomer 1). They P amounted to \leq 5.0% (0.028 mg/kg) of TRR. * (C Ô

Besides parent compound, the major part of radioactivity in viscera of fish was represented by the wo metabolites BCS-CN88460-propanol-GhrcA (isomer) and 20 and approx. 40% of the TRR. Other metabolites in viscer of ish tissues were BCS-CN88460-N-meth@-pyrazole-carboxylic acid, conjugate of BCS-CN88460 N-methyl-pyrazole-carboxylc acid, BCS CN88460-cyclopropylpyrazole-carboxamide, BCS-CN88460-desmethyl-propanol OlucA (isoper 1), BCS-CN88460desmethyl-propanol, BCS-CN88460-propanol@BCS-CN88460-desprethyl@lucAQisomer 1) and BCS-CN88460-desmethyl. These metabolites amounted to $\leq 6.6\%$ (0,262 mg/kg) of TRR.

Unknown metabolites in all fish ossues were draracterised by the Extraction and chromatographic

Unknown metabolites in all fish of sues were characterised by the extraction and chromatographic behaviour and amounted to <3.4% (0.019 mg/kg) of TRR for edible fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for viscera fish parts and <5.4% (0.213 mg/kg) of TRR for vis



Table 6.2.5- 5:Quantitative distribution of parent compound and metabolites in the edible and
viscera tissues of fish after 14 days exposure of [pyrazole-4-14C]BCS-CN88460 to
bluegill sunfish

bluegill sunfish								
	edible parts of fish				viscera of fish			
		y 7		/ 14	day 7		day	3 4
TRR [mg/kg] =	0.5	565	0.5	567	3.0	55	3.3	65
Compound/fraction	% TRR	mg/kg	% TRR	00		mg/kg	%TŔR	mag∕kg
Conventional extract	94.2	0.532	92.8	0.527	98.7	3.901	98.3	3.307
BCS-CN88460-N-methyl-pyrazole- carboxylic acid (M50)	3.3	0.019	÷		3.4	0.135		0,532
BCS-CN88460-cyclopropyl-pyrazole- carboxamide (M58)	30.9	0.153	30.4	0(173	5.8	ð.229	Q 5.9	6 ⁹ 0.19 %
Conjugate of BCS-CN88460-N-methyl- pyrazole-carboxylic acid **	7.3	2 0.041		y 0.086		0.049	2 .1	00072
BCS-CN88460-desmethyl-propanol-GlucA (isomer 1) (M31, isomer 1))	D	0,001	×1.0	02006	\bigcirc	<i>6</i> 0.204	5,9 /	0.198
BCS-CN88460-propanol-GlucA (isomer 1) (M19, isomer 1)	4.6 ×		× 38	0.022		0,909	23.5	0.792
BCS-CN88460-propanol-GlucA (isomer 2) (M19, isomer 2)	\$5.0	028	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ð 0 .017	© 16.3	0.64	17.3	0.580
BCS-CN88460-desmethyl-propanol (M06)		0.010			~ ^{3.5}		°≫ 1.1	0.037
BCS-CN88460-propanol (M01)	6.3	0.036	,	Ø.057	3.1	0.12	^v 4.0	0.135
BCS-CN88460-desmethyl-GlucA (isomer 1) (M35, isomer 1)	ۍ ۱.8	¢0.010		0.608	×0.6	Q.262		0.086
BCS-CN88460-desmethyl (M13)	ð.7	0.010			0.5	6 0.018	1.2	0.039
Parent compound	<i>¶</i> ,16.7	0.095	\sim	00.109		0.201	9.7	0.326
Total identified	T 81.6	™ 0.464	873		73.6	2.910	77.8	2.616
Number of unknown compounds		8			~~ 1	-	1	
Amount of the largest unknown compound	<u>_</u> @3.4	0,019		\$0.014	🖉 5.4	0.213	4.2	0.142
Total characterised * S	· **	ŶŎ.071				0.991	20.5	0.691
Total extracted	942	0.532			98. 7	3.901	98.3	3.307
Post extraction solids (PES)	5.8	<u>s</u> v	\$7.2	% .041	1.3	0.053	1.7	0.058
Accountability	400.0			0.567	100.0	3.955	100.0	3.365

* Unknown metabolites were characterised based on their extraction and chromatographic behaviour.

** The aglycone BCS-CN88460 &-methyl-pyrazole-carboxylic acid could be clearly identified after acidic cleavage of the conjugate a start of the conjugate acid.

H. Conclusion

The metabolism of BCS CN88460 in bluegh sunfish was investigated as part of the fish bioconcentration study. The set compound was radiolabelled in the pyrazole-4 moiety. BCS-CN88460 was stable in the fish water during the testing period.

After exposure of the fishes for 2 days and for 14 days with [pyrazole-4-¹⁴C]BCS-CN88460 at a concentration of $5/0 \mu g/L$ the total radioactive residues (TRRs) in the edible parts (0.565 mg/kg for day 14) were moderate. In viscera parts the TRRs amounted to 3.955 mg/kg for day 7 and 3.65 mg/kg for day 14.

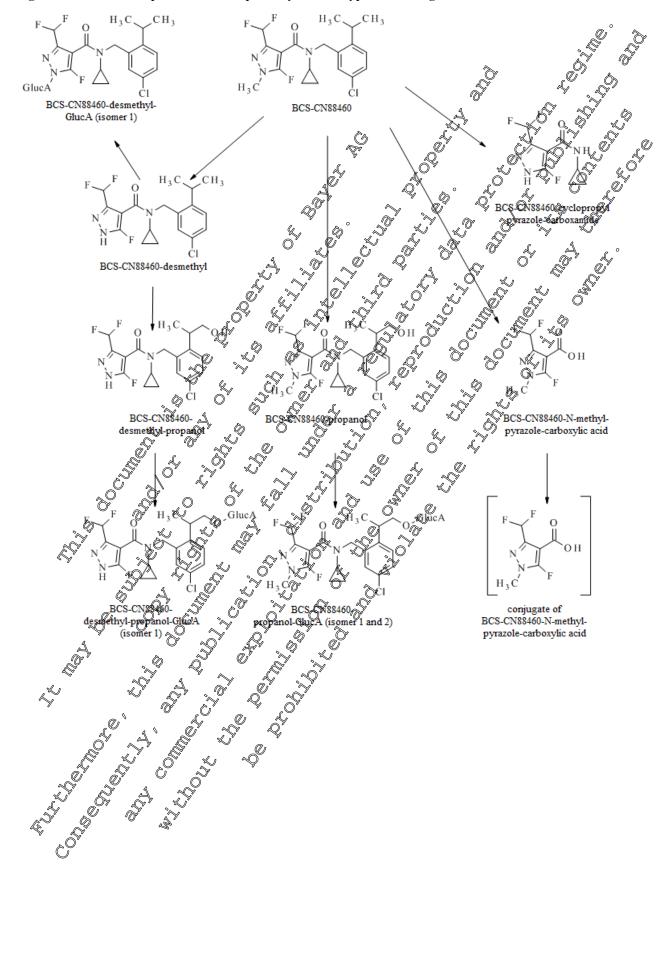
Residues from edible and viscera fish parts could be sufficiently extracted with conventional methods. BCS-CN88460 was intensely metabolised in the fish.

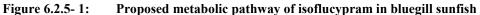
Parent compound was detected in edible and viscera fish parts. Besides parent compound as a major compound in edibles, the metabolite BCS-CN88460-cyclopropyl-pyrazole-carboxamide (M58) was



found with higher amounts. Metabolites BCS-CN88460-propanol-GlucA (M19, isomer 1 and 2) were found as main compound (in sum approx. 41% of TRR) in viscera fish parts.









CA 6.3 Magnitude of residue trials in plants

CA 6.3.1 Barley

BCS-CN88460 (common name: isoflucypram) is to be registered in Europe for use in barley and oat European residue data in barley are therefore presented below to support the intended "representative uses".

As allowed by the EU Guidance document on comparability, extrapolation, group tolerances and data requirements for setting MRLs (SANCO 7525/VI/95 rev. 10.2 of 23 September 2016), the extrapolation of the barley residue data to oat is requested.

Information on the intended use pattern (GAP) is sumparised in Table 6.3.1-1.

Table 6.3.1- 1:	Use patterns (critical GA) formulations in/on barley	P) for the spi and oat in H	ray applicati Jurope m fiel	on of BCS-C ds/northerr	N88469-conta 1 and southern	ining 🖉
	regions)					s

	·5·0·115)		0',0'	N.	Z NO	a s	1
Description	F/G	at a	with stage pplication (H Code)	Applicati rate pe treatme (g a.s./h	r () ⁷ volu nt () a) (L/I	Or Interva me (Gays)	(days)
Barley, oat *			30-61	75	2 100-	400	NA

* agricultural use based on EC formulations (BCS-CN88460 EC 50) ** uses in both the northern and southern residue regions (EU-N and EU-S) NA: not applicable. The application mining is defined by the growth stagg at application.

In order to support the EK, "representative use" of BCS-CNS8460, sets of GLP trials were conducted in northern and southern European fields in 2015 and 2006. In northern and in southern European field-grown basely, BCS-CN88460 was applied once at the latest intended growth stage of BBCH 61.

Three EC formulations containing BCS_CN88400 were tested with similar application rates:

- BCS-CN88460 EC 050 containing 50 g BCS-CN88460 for Tested application rate: 75xg BCS-CN88460 /ba.
- Prothiocomozole & BCS-EN88460 EC 150 containing 50 g BCS-CN88460 /L Tested application rate 75 g BCS-CN88460 /ha.
- Prothiceonazole & Tebuconazole & BCS ©N88460 EC 250 containing 50 g BCS-CN88460 /L
 Tested application rate 62.5 g BCS-CN88460 /ha (within + or 25% of the 75 g as/ha application rate).

In some cases the BC 050 and the EC BO formulations were tested in side-by-side plots at the same location so that these trials cannot be considered all as independent trials.

The number of independent frials conducted (incl. information on geographical region and vegetation period) is symmarised below in Table 6-91-2.

period) is summarised below in Table 6 9.1-2.



Table 6.3.1- 2:	Overview of European residue trials conducted in barley per geographical "residue
	region" and vegetation period

		ion [®] and v	8	I	•						
		No. of in	dependen	t trials		-					
Crop	Region	Veget.	period	-	Report No.	Document	Refererence				
		2015	2016	Σ	(Formulation)	number					
	EU-N	9	4	13	15-2110 (EC 050) 15-2113 (EC150) 15-2118 (EC250) 16-2051 (EC150)	M-585588-02-1 M-580046-02-1 M-583909-02-1 M-589582-02-1	KCA 6.3:4 01 KCA 6 3 1/02 KCA 6 3 1/03 KCA 6 3.1/03				
Barley	EU-S	8	4	12	15-2066 (EC 050) 15-2114 (EC150) 45-2117 (EC250) 16-2052 (EC\50)	M-584388-024	KCA 6.3, 205 KCA 6, 01/06 KCA 6, 01/06 KCA 6.3.1/07 KC& 6.3.1/07				
EU-N = northern FL : formulation EC 050: BCS-CN EC 150: Prothioc EC 250: Prothioc			uthern EU fie 50 g BCS-CN EC 150 conta a BCS-CN88	× .	× °C °C						
Northern Eu	rope (resi	due regio	n) Ő	S.	S S N		V ^v D				
	• F (• • • •			"O" - "O" -							
Report: Title:		KCA 6 3 Amendri	21/01; ienţ no. 1 t	, G.; ź oxtinal re	2015, M-589588-02-1 port - Determination	of the residues of B	لار S-CN88460				
	FL : formulation EC 150: BCS-CN88460 EC 050 containing 50 g BCS-CN88460 /L EC 150: Prothioconazole & BCS-CN88460 EC 150 containing 50 g BCS-CN88460 /L EC 250: Prothioconazole & Tebuconazole & BCS-CN88460 EC 250 containing 50 g BCS-CN88460 /L Morthern Europe (residue region) V KCA 6 41/01; Title: KCA 6 41/01; Menoment no. 1 to the part of the residues of BCS-CN88460 EC 050 in the										
Dan ant Ma				any, north	hern France and the	nited Kingdom					
Report No.: Document No		15-2110 M-58588	8-02-1	Õ		«, »,					
Guideline(s):		Regulation	on (EC) Ne 2009 const	erning the	09 of the European F e placing of plant pro- sting of Chemicals on Crop fyeld Trial	tection products on	the market				
Guideline des GLP/GEP	lation(s):	pone *			Crop Field Trial 2017; M-580046-02- ation of the residues	-					
Report: Title:	¢°°	CN8846			2017; M-580046-02- ation of the residues after pray application her ands, Germany, n	on or province on all	ole & BCS-				
Report No		October	on@ÉC) N 2009 conce	ernin@the	09 of the European F e placing of plant prot	tection products on	the market				
Guideline dev GLP/GEN:	iation(s):	in Contor	-h	, ^r ¥	sting of Chemicals on No. 860.1500 on Crop		G 509 published				



Report:	KCA 6.3.1/03; G.; 2017; M-583909-02-1
Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460,
	prothioconazole and tebuconazole in/on winter barley and spring barley after spray.
	application of prothioconazole & tebuconazole & BCS-CN88460 EC 250 in the
	United Kingdom, northern France, Hungary and Czech Republic
Report No.:	15-2118
Document No.:	M-583909-02-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21
Ouldefine(3):	October 2009 concerning the placing of plant protection products on the marker and $\sqrt{2}$
	repealing Council Directives 79/117/EEC and 91/414/EEC
	OECD 500 Adopted 2000 00 07 OFCD Chideline Wir the Testing of Chamilton and
	OECD 509 Adopted 2009-09-07, OECD Guideline for the Testing of Chemicals,
	Crop Field Trial US EPA OCSPP Guideline No. 600.1500
Cuidalina deviation(a):	US EPA OCSPP Guideline No 860.1500
Guideline deviation(s): GLP/GEP:	repealing Council Directives 79/117/EEC and 91/414/EEC OECD 509 Adopted 2009-09-07, OECD Guideline for the Testing of Chemicals, Crop Field Trial US EPA OCSPP Guideline No 660.1500 none yes
GLP/GEP:	yes Q a A A A A
Report:	US EPA OCSPP Guideline No. 860.1500 none yes KCA 6.3.1/04; Amendment no. 140 final seport Determination of the certification of the
Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460
THU.	and prothioconatole in on winter barley and spring barley after spray application of
	prothioconazofe & B&S-CN8&460 E&150 in the United Kingdom, Cermany, northern
	France and the Netherlands
Report No.:	
Document No.:	M-5895@2-02.1 ~ ~ ~ ~ ~ ~ ~ ~
Guideline(s):	Regulation (EC) No Ch07/2009 of the European Parkament and of the Council of 21
Suideline(5).	October 2009 concerning the placing of plant protection products on the market
	QECD Guideline for the Cesting of Chemicals on Crop Deld Trial (TG 509 published
	in September 2009)
	USERY OCSPE Guideline NO 860 2000 or Tron Kield Tright
Guideline deviation(s)	
GLP/GEP:	
Ĩ, Ĩ	ver f
Thirtoon independent	field residue trans were conducted on barrey (with both spring and winter
rinneen widependent	inclu restance uppers were conducted con gamey (with both spring and winter

Thirteen independent field residue trials were conducted on hadey (with both spring and winter varieties) in the northear European residue region as follows:

In 2015, 4 supervised residue trials (the Netherlands, Germany, France and the United Kingdom) were conducted to support the use of <u>BCS-CN88460 EC 050</u> if on winter and spring barley (**1999**, G.; 2017; M-585588-02-1 KCA 6.3.1). One spray application was made at a nominal growth stage of BBCH 61 and at a nominal rate of 1.5 b ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 200-400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application tuning, except in the trial 15-2110-02 where the application was done at growth stage BBCH 59 instead of 61. This is considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

4 additional supervised residue trials (Netherlands, Germany, France and the United Kingdom) were conducted with the formulation <u>Prothioconazole & BCS-CN88460 EC 150</u> in/on winter and spring barley (**1999**) 2017; M-580046-0201; KCA 6.3.1). One spray application was made at a nominal growth state of BBCH 69 and at a nominal rate of 1.5 L/ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 200-400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing, except in the trial 15-2113-02 where the application was done at growth stage BBCH 59 instead of 61. This is considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

Trials 15-2113-02, 15-2113-03 and 15-2113-04 were located side by side with trials 15-2110-02, 15-2110-03 and 15-2110-04. Thus, for the studies 15-2110 and 15-2113, only 5 trials are considered as independent trials.



Four further supervised residue trials were carried out in 2015, in the United Kingdom, France, Hungary and Czech Republic with the formulation <u>Prothioconazole & Tebuconazole & BCS-</u> <u>CN88460 EC 250</u> in/on winter and spring barley (**100**, G.; 2017; M-583909-02-1; KCA 6.3.1). One spray application was made at a nominal growth stage of BBCH 61 and a nominal rate of 1.25 C/ha, corresponding to 62.5 g/ha BCS-CN88460 a.s.; the water rate was 200- 300 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing.

Four further supervised residue trials were carried out in 2016 with the formulation Prothioconazole & BCS-CN88460 EC 150 in/on spring and winter barley, in the United Kingdom, Germany, France and the Netherlands, to complete the data package (2017, 2017, M-589582-02-1; KCA 6.3.1). One spray application was made at a nominal growth stage of BBCH 6 k and a nominal rate of 1.5 L/ha, corresponding to 75 c/ha BCS- CN88460 a.s.; the water rate was 200 400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing.

In all these trials, samples of green material (whole plants withour roots) were taken interediately after the application and at several intervals thereafter up to 28 days after treatment). It was ensured that one of these samplings be taken at BBCH 75. Furthermore, samples of grain and straw were collected at the commercial harvest (BBCH 89)

Each field sample was placed in doubled abeled bags and stored deep-frozen within 24 hours after sampling and until dispatch to the Laboratory for Sampling, Proparation Technique and Sample Logistics (PVTL), Bayer AG - @rop Science Division in the sample and Rheim Germany. All field samples were shipped at a temperature of -18°C or below under monitored conditions during shipment and arrived at PVTL in good condition. The field samples were stored in a freezer at -18°C or below until preparation of the examination samples

For the trial 15-2118-09, the maximum temperature during the two shiftments of samples to PVTL was -13°C and -7°C. Since the shipments were sufficiently short (less than 24th) this deviation is not expected to adversely impact the quality of the study results for further information see Appendix 8 of the respective report.

For the preparation of examination samples, the deep-frozen field samples were shredded and homogenized with dry ice in a cutter. Representative parts of the hredded samples were transferred into polystyrene boxes and stored at 28°C or below until analysis.

The samples were analysed for the parent compound using analytical method 01475 (**1990**); 2016; M-558986-01-1; referenced in MCA Section 4 under Point 4.1.2) which was validated prior to the residue analysis of the samples. Additional validation recoveries were conducted for barley (grain, straw and green material) in the study 5-2066. The samples of grain and straw were analyzed according to the procedure described in the method for dry matrices (with a soaking step with water before extraction) and the green material samples were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The LOQ was 0.01 mg/kg for parent.

QII. Findings

In each study, corcurrent recoveries were obtained from samples of green material, grain and straw. The recovery samples were spiked at levels of 0.01 mg/kg and up to 4 mg/kg, in order to adequately cover the residue levels found in the treated samples. Details of concurrent recovery data are shown in Table 6.3.1 $^{\circ}$. The average recoveries were within the acceptable range of 70 – 110%. The RSD values were below 20%.

No residues above the LOQs were found in the control samples. The detailed results obtained for barley treated samples in northern Europe are summarised below in Table 6.3.1-4. The results were not corrected for concurrent recoveries.



The analyses were done after a maximum storage period of 390 days. In most of the cases, the time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours. If not the case, the maximum storage period of extracts (30 hours for green material and 55 hours for straw) was covered by stability experiments conducted in the course of the residue study 15-206 . G.; 2017; M-584388-02-1; KCA 6.3.1). See Table 6.1-8.

III. Conclusions (barley, northern Europe)

In order to support the use in the EU of BCS-CN88460 in barley 13 independent trials were conducted in the northern European residue region in the years 2015-2016. BCS-CN88460 was applied once at an active substance rate of 62.5 or 75 g/ha per treatment. All applications were at the required rates, and all trials were conducted according to GLP.

Samples were analysed for the residues of BCS_CN88460 parent compound. The results of the trails presented above demonstrate that:

- Residues of BCS-CN88460 dissipated rapidly in green material, from levels of 0.87 • mg/kg on Day 0 after the treatment to 0.051-0.560ng/kg@n Day 28.
- ng kg and tesidues in straw At harvest, residues in grain ranged from <0.01/mg/k@to 0 • ranged from 0.049 to 1.2 mg/kg

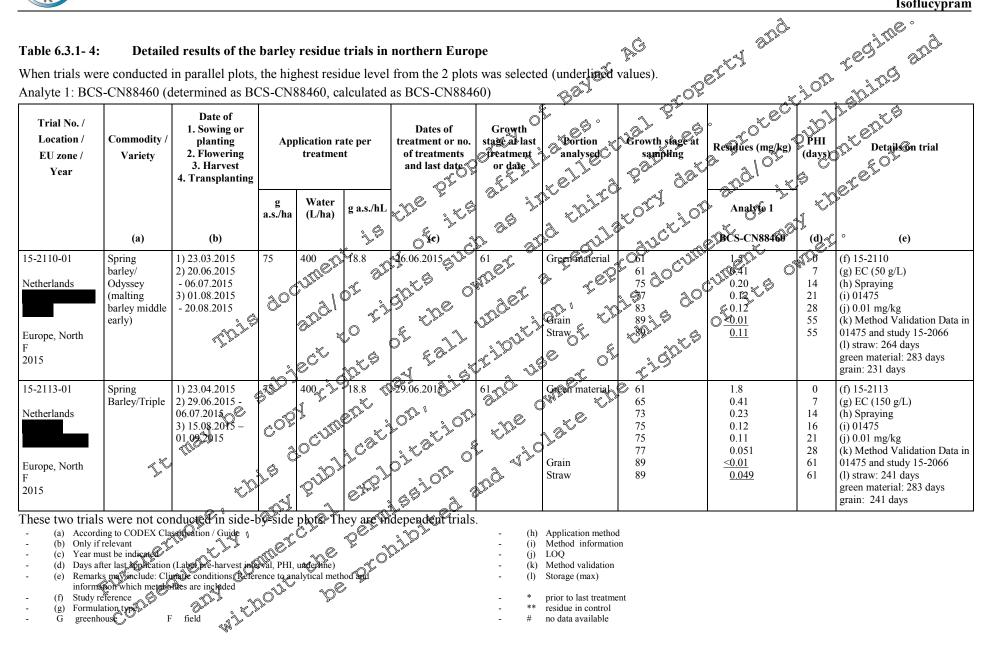
	D (1		E C.	ŇY . a		×-	and the second s	Ro	<u> </u>
Study	Portion	n	Fortifica		Re	covery	(%) _{>}	<u>Q</u>	
	analysed		tion level		Becoveries	Min	Max	Mean	RSD
		2/	(mg/kg)	9		<u></u>	₩J'		~~~~
15-2110	green	1	0.01	96 ⁽¹⁾	× ·	O″ -	Ky -	· - ·	<u> </u>
	material	Ŷ	0.9 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	97 ⁽²⁾	\$ \$	/ (- (5 - 4	¥ -
		1	\$2.5 °	940	, <u>`</u>	D-	Å	<u></u>	-
	<u>o</u>	3	8			~>94	9 7	\$96	1.5
	grain	Ŷ	201 C	92 ⁽¹⁾ ,96 ⁽¹⁾	<u>\$ 2</u>	° 92	° 96 _ℓ	, 94	-
	, Ô	1	0.1	94)	y "0"		<i>w</i>	-	-
Ê.		3 Ù	overall	Č,		§ 92	9 6	94	1.9
« ¥	straw	Ŋ	I 10M01 .⊿.,	114	X W	T.	- 1	-	-
		1	0.1	1,00(2)	y O'	- ⊘	-	-	-
	Ŵ	10	2.65	P 3 ⁽²⁾	St d	Ş -	-	-	-
	~	3	overall		× ×	93	114	102	10.9
15-2113	green	2	0.010	98,99 0		98	99	99	-
	material	<u>1</u>	0.0	96	<u>~~</u>	-	-	-	-
L.	~	Ç r	2.5	93 93 93 0	<u>~</u>	-	-	-	-
\sim		4	overally	<u>~</u>	Y Y	93	99	97	2.7
	grain	1	0.61	(9 7 0 ⁴		-	-	-	-
	gram Straw	₽.	1 √	101-102		101	102	-	-
		3	ðveræll/	~\$		97	102	100	2.6
-C	Straw	1	0.01	104		104	-	-	-
			×0.1	97		97	-	-	-
	No Co	1		99		99	-	-	-
Č 🔬	Ň	3	overall			97	104	100	3.6

Table 6.3.1- 3:	Concurrent	recovery	data for I	BCS CN88	8 460 in	bayley	8
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Study	Portion	n	Fortifica	Re	ecovery	· (%)		
-	analysed		tion level (mg/kg)	Individual recoveries		Max	Mean	RSD - - - - - - - - - - - - -
15-2118	green	1	0.01	98(2)	_	_	-	-
	material	1	0.1	106 ⁽²⁾	-	-	_	s
		1	2.0	98 ⁽¹⁾	-	_	- «	Ç -
		1	2.5	94(1)	-	-		-
		4	overall		94	106		5.1
	grain	2	0.01	95 ⁽²⁾ ;111 ⁽²⁾	9 5 🖓	111	©103	چ -
		2	0.1	111(1);107(2)	107	116	109	Ŵ
		4	overall		95	H M	106	07. 1
	straw	1	0.01	93 ⁽²⁾	-~	× -	d ^a - A	¢* - c
		1	0.1	101 ⁽²⁾	, S		<u>~</u>	ð
		1	2.0	$\frac{101^{(2)}}{85^{(1)}} \bigcirc 0^{\circ} \bigcirc 0^{\circ}$	&-	<u> </u>	<u>~</u> 0-	\$°-
		3	overall	<u> </u>	ر 85 🗸		⁰ 93	8.6 C
16-2051	green	4	0.01	94:86;79,85	707	94	≥ <u>86</u> 0'	X 2
	material	2	0.1	8,95 4 2	°∼93	×95	<i>3</i> 94	Ĵ
		1	1.0	94 × ×) - ~	0°-	ð - <u>(</u>	-
		1	4.0 🖓	95	- Å	Ő		Ĝ
		8	overall		A 79	05	9 ð	
	grain	3	0%01	83; 90 94	⁷ 83 "	<i>y</i> 4	© 89	6.3
		2	<i>©</i> 0.1 <i>O</i> ″	94, 001	94	101	98°) 192	3 37.1
	-1	5	overall	196 N	83	(101	'92	\$ ^{7/.1}
	straw				7 - (<u>- 4</u>	¥ -
	, and the second se	<u>7</u> 1	1 % & ~ //	84	\$ \$ ³ -	ő-	~(? <u>-</u>	-
	Č.		1.0,		~~~~~- 84	97	92	7.8
SD: relativ	ve standard de	R iatio						7.0
	conducted w	vith sp	ring barley co	ntral sample	Ø	No.		
: recovery	conducted w	ith Wi	nter barley co	Strol sample	5.	0 ^Y		
~ 2	~0		ring barley con nter barley con	ntrol sample	S	1		
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BAYE



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting		ication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyse	Growth stage at sampling	Hestdues (mg/kg)	PHI (dave)	Tegilme Details on trial
				Water (L/ha)	g a.s./hL		O PUT	ates.	1. C. L. C.	Anatyte 1	PULOI	ot entre
	(a)	(b)				(c)			Odit of	©BCS-CN88460	(d))	
15-2110-02 Germany Europe, North F 2015	Spring Barley/Streif	1) 13.03.2015 2) 12.06.2015 - 22.06.2015 3) 01.08.2015 - 31.08.2015		300 JINETA	25 25 01 01	05.06.20150		Green material		BCS-CN88960	0 7 14 19 21 28 68 68	(f) (13-2110 (f) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 272 days green material: 304 days grain: 239 days
15-2113-02 Germany Europe, North F 2015	Spring Barley/Streif	1) 13.03.2015 2) 12.06.2015 22.06.2018 3) 01.08.2015 31.08.2015	e Ou		25 F1 0 10 20 5 20 5 7 7 20 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	at fail	NA JADOUT JADUT JADUT JADUT JADUT JADUT JADUT JA		61 75 75 77 86 1 9 1 1 9 1 9 1 9 1 1 1 1 1 1 1 1 1 1 1 1 1	$ \begin{array}{c} $	0 7 14 19 21 28 68 68 68	 (f) 15-2113 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 258 days green material: 307 days grain: 258 days
These 2 trials w	ere conducte	d 🔞 side-by-side	e plots	The sam	ae cocatio	m, K ^{or}	Í i) ///				
 (a) Accordi (b) Only if (c) Year mi (d) Days af (e) Remark informátion (f) Study roles (g) Formula G greenhout 	Germany 22.06.2018 C browning 22.06.2018 C browning 0 14 (h) Spraying Europe, North F 31.08.2015 0 0 0 10											



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	lication ra treatmen	1	Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyse	Growth stage at sampling	ALCON	PHI (daws)	TE Details on trial
			g a.s./ha	Water (L/ha)	g a.s./hL			ates.	. J. J	AnaQte 1	20201	
	(a)	(b)				(c)			and the st		(d)	
15-2110-03 France Europe, North F 2015	Winter Barley/ Etincel	1) 14.10.2014 2) 27.04.2015 – 05.05.2015 3) 25.06.2015 – 05.07.2015		300		28.04.2015 2000	61 E T il	Græn materia Grain Straue 9 2	$ \begin{array}{c} $		14	grain: 283 days
15-2113-03 France Europe, North F 2015	Winter Barley/ Etincel	1) 14.10.2014 2) 27.04.2015 05.05.201 3) 25.06.2015 05.07.2015	\$ \$	300 J. L 202 x 202 x			ridduitd	Grain Stract	69 1 73 75 0 75		0 7 14 21 28 62 62 62	(f) 15-2113 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 302 days green material: 345 days grain: 302 days
These 2 trials w	vere conducte	d in side-by-side	e blots a	t the an	ne locatio	n K	the s	10				0 5
Europe, North F 0.20												



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арг	olication ra treatmer		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyse	Growth stage at sampling	Arcsidues (mg/kg)	PHI (dave)	TE Deteris on trial
			g a.s./ha	Water (L/ha)	g a.s./hL		O LEAN	AT CS . CT	NON SEP	Analyte 1	20201	Atente Atente
	(a)	(b)				(c)		~ 200	all of	0-BCS-CN88460	(d))	
15-2110-04 United Kingdom	Winter Barley/ Glacier	1) 12.11.2014 2) 21.05.2015 - 01.06.2015 3) 01.08.2015 - 15.08.2015	75	200	37.5	21.05.2015T	61 E I JI	Græn material	73 73 73 75 75 75 75 75 75 75 75 75 75 75 75 75	BCS-CN88960 01.2 0.59 0.30 0.22 0.18 0.00 0.18	14 √ ″ ¶ 20	(1) (1) (2) (1) (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2
Europe, North F 2015			900	JITU BI	n L		. der	-0-1 V	6 AO	CONDO UNREODO OS		green material: 319 days grain: 245 days
15-2113-04 United Kingdom	Winter Barley/ Glacier	1) 12.11.2014 2) 21.05.2015 01.06.2015 3) 01.08.2015 – 15.08.2015	75		B5 T		VIL US	Green material			0 7 14 20 28 33 77 77	(f) 15-2113 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 264 days
T		and y	COF	CUIN								green material: 322 days grain: 264 days
- (a) Accordi - (b) Only if (- (c) Year mu - (d) Days af - (e) Remark information - (f) Study re - (g) Formula - G greenho	ere conducte ng to CODEX Cla elevant ist be indicated er last appreciation indivinci metabolic for which metabolic for which metabolic for which metabolic for the formation of the formation for the formation of the formation of the formation for the formation of the formation of the formation for the formation of the formation of the formation of the formation for the formation of the	d m side-by-side	e plots?	the san	ret location	niton 1991, con 1991, con 1991, con	- (h) - (i) - (i) - (k) - (l) - ** - **	Application metho Method informatic LOQ Method validation Storage (max) prior to last treatm residue in control no data available	on			



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	lication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyse	Growth stage at sampling	Aresidues (mg/kg)	PHI (days)	TEGILTIC GLOC
			g a.s./ha	Water (L/ha)	g a.s./hL		OTT I	at es .		AnaQte 1	(dC)	atent -
	(a)	(b)				(c)			Loan at	0°BCS-CIN88460	(aC)	
15-2118-01 United Kingdom PE12 9PQ	Winter Barley/Cassia	1) 02.09.2014 2) 20.05.2015 – 01.06.2015 3) 23.07.2015	62.5	200	31.3			Græn material	61 65 75 83 83 84 9 10 10 10 10 10 10 10 10 10 10 10 10 10	BCS-CN88960	136 121 28	(f) (15-2118 (f) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066
Europe, North F 2015			_ <u>20</u> Ć	JIRCI.	0.T 9.D	ant ^e o	ALL .	ð ₁ e ^g			63C >	(l) straw: 320 days green material: 368 days grain: 306 days
15-2118-02 France Bourgogne	Winter Barley/ Esterel	1) 03.10.2014 2) 29.04.2015 06.05.2016 3) 23.06.2015	62.5	30001 2 ²⁰ 2 ¹⁰			And us	Gieen materials	61 68 109 85 87 86 89 89	© 1.2 0.12 0.14 0.095 0.094 <u>0.020</u> <u>0.51</u>	0 7 14 21 28 55 55	(f) 15-2118 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 350 days
Europe, North F 2015		-24 De	COB	Z CUIN	×.	10 ^{2.} 10 ²	the .	Jate				green material: 390 days grain: 336 days
These two trials	were not con	nducted in side-l	oy-side	plots. Th	by are in	dependent tri@	i at i	<i>y</i> ·	•			
 - (a) Accordi - (b) Only if n - (c) Year mu - (d) Days aft - (e) Remarks - informag - (f) Study re - (g) Formula - G greenhor 	ng to CODEX Cla elevant st be indicated er last appreation in monoclude: Cli son which means lerence use F	nducted in side-l	and y and y wal, pHI, y ence to ano	C 2 Q 2 C 2 Q 2 alytical method	Petro	or 19910 101 101 101 101	- (h) - (j) - (k) - (l) - * - ** - #	Application metho Method informatic LOQ Method validation Storage (max) prior to last treatm residue in control no data available	d on			



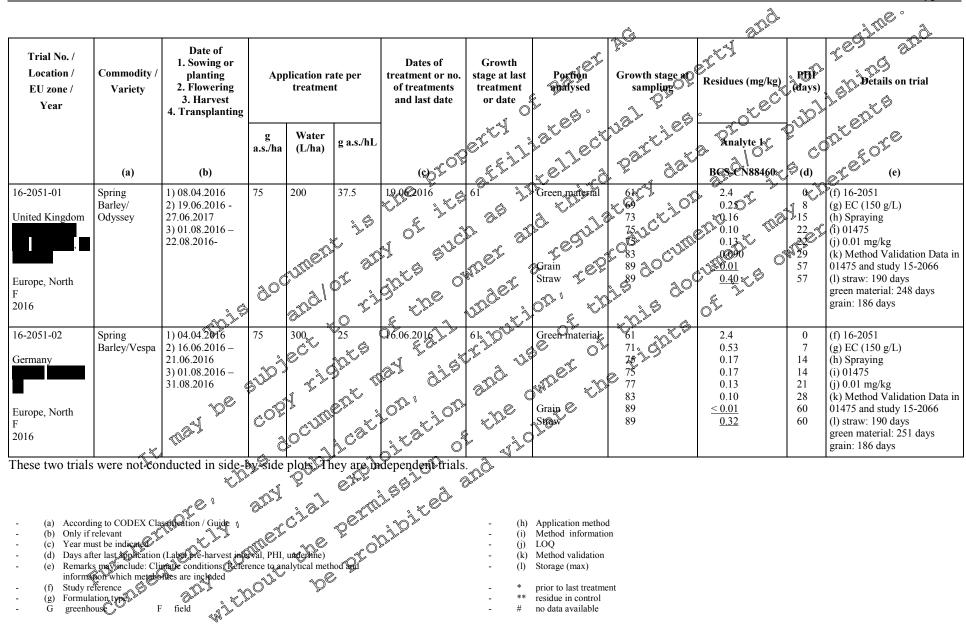
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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion Portion Portion		e C °	, PGP (days)	TES OF ALL
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(C) I OF			val jes Parties	Reserver	€ ^{0,42} € ⁰ (d)	Citer (c)
15-2118-03 Hungary Europe, North F 2015	Spring Barley/ Mandolina	1)13.03.2015 2) 30.05. 2015 – 15.06.2015 3)10.07.2015	62.5	300 Juner		A ANT B O	a der dr	Grafa Straw TEP	2 - 75 83 J.C.C. J. 89 J.O.C. J.M. 89 J.O.C. J.M. 1		0 1 1 1 1 2 1 2 1 3 5 3 5	 (f) 15-2118 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 333 days green material: 353 days grain: 319 days
15-2118-04 Czech Republic Europe, North F 2015	Spring Barley/ Kangoo	1) 18.04.2014 2) 12.06.2015 - 19.06.2015 3) 05.08.2015	62.5			on it at i on	The up	Green traterial	2 89 89 89	$ \begin{array}{c} $	0 7 14 20 28 55 55	(f) 15-2118 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 306 days green material: 346 days grain: 292 days

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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting		ation rate reatment	per	Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyse	Growth stage at sampling	ALC Residues (mg/kg)	PHI (days)	Tegit me and Details on trial
				Vater L/ha) g a	a.s./hL			lates.	Val jes	AnaQute 1	(qC) 5.70)	otentre.
	(a)	(b)				(c)			all at	© BCS-CN88460		
16-2051-03 France Europe, North F 2016	Winter Barley/Obit	1) 01.10.2015 2) 06.05.2016 - 13.05.2016 3) 25.06.2016 - 10.07.2016	75 300	0 25	5 19 19	06.05.20165		Strawer -	2012 2012		0 7 14 121 27 53 53	(f) (16-2051 (f) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 238 days green material: 292 days grain: 234 days
16-2051-04 The Netherlands Europe, North F 2016	Winter Barley/ Quadrigo	2) 31.05.2016 15.06.2016 3) 07.07.2016 – 15.07.2016			jt ^o	at 1,9 ¹		Graie Straiv Straiv	61 65 71 83 86 89 89	$ \begin{array}{c} & 1.6 \\ \bigcirc & 0.97 \\ 0.83 \\ 0.54 \\ 0.39 \\ 0.41 \\ \underline{0.041} \\ \underline{0.44} \end{array} $	0 7 14 21 28 34 37 37	(f) 16-2051 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 229 days green material: 267 days grain: 229 days
These two trials	were not con	nducted in side-l	side pla	#SThev	/ are in	dependent trials	- Ele	100				<u> </u>
F 2016 These two trials - (a) Accordi - (b) Only if - (c) Year m - (d) Days af - (e) Remark informå - (f) Study re - (g) Formula - G greenho	ng to CODEX Cla relevant ist be indicated ter last application s navinclude: Cli por which metabo iference pusc F	(Labor pre-harvest information / Guide 1) (Labor pre-harvest information conditions (Ceremony) (Here are included field with the same conditions (Ceremony))	And		er m		- (h) - (i) - (j) - (k) - (l) - * - ** - **	Application method Method informatic LOQ Method validation Storage (max) prior to last treatme residue in control no data available	m			



Southern Europe

<u>*</u>	0
Report: Title:	KCA 6.3.1/05; G.; 2017; M-584388-02-1 Amendment no. 1 to final report - Determination of the residues of BCS-CN88460 in/on barley after spray application of BCS-CN88460 EC 055 m Portugal, southern of
Report No.: Document No.: Guideline(s):	France and Spain 15-2066 M-584388-02-1 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 2 October 2009 concerning the placing of plant prototion products on the tharket
Guideline deviation(s):	OECD Guideline for the Testing of Chemicals on Crop Field Trial (TG 09 published) in September 2009) US EPA OCSPP 860.1500. Goop Field Trial none
GLP/GEP:	in September 2009) US EPA OCSPP 860.1500, coop Field Trial none yes KCA 6.3.1/06; 2017 M-580022-021
Report: Title:	KCA 6.3.1/06; KC
Report No.: Document No.:	CN88460 BC 150 in Portogal, southern France and Spain C γ 15-2114 Q χ Q
Guideline(s):	Regulation (FC) Nov107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market OECD Quideline for the Testing of Chemicals on Crop Field Trial (TG 509 published
Guideline deviation(S). GLP/GEP:	In September 2009) US EPA OC SPP Gradeline No. 860 1500 on Crop Pield Trial None Yes
Report:	KCA 63.1/07. G.; 2017, M-583692-05 f Amendment no. 1 to final report - Determination of the residues of BCS-CN88460, province and tebugenazole in/on barley after spray application of
Report No.: Document No.: Guideline	Brothlocenazole & BCS CN88460 EC 250 in southern France, Italy, Spain and Portugal 15-2417 Mos83692-02-1 Regulation (EC No 1107/2009 of the European Parliament and of the Council of 21
Å Å	October 2009 concerning the placing of plant protection products on the market and repealing Conncil Directives 79/117/EEC and 91/414/EEC
Guideline deviation(s)	VOS ECA OCSPP Guraeline No. 860.1500
	OCD 509 Adopted 2009-07, OECD Guideline for the Testing of Chemicals, Crop Field Trial US ECA OCSPP Guideline No. 860.1500 note



Report:	KCA 6.3.1/08; ; 2017; M-589554-02-1
Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460
	and prothis consists in (on horizon offer arrow application of prothis consists) $\mathcal{E} \mathbf{P} \mathcal{O}^{(1)}$
	CN88460 EC 150 in Portugal, southern France and Spain
Report No.:	16-2052
Document No.:	M-589554-02-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliamen@and of the Council of 21
	October 2009 concerning the placing of plant protection products on the market
	OECD Guideline for the Testing of Chemicals on Crop Field Trial (TG 509 published)
	in Sentember 2009)
	US EPA OCSPP Guideline No. 860.1500 on Crop Field Trial
Guideline deviation(s):	yes, see report
GLP/GEP:	yes A Q A A O

I. Materials and Methods

Twelve independent field residue trials were conducted on barley (with both spring and winter varieties) in the southern European residue region as follows:

In 2015, 4 supervised residue trials (Portugal, Spain and southern Prance) were conducted to Support the use of <u>BCS-CN88460 EC 050</u> inton barley (**1997**, 6.; 2017; M-54388892-1; KCA 63.1). One spray application was made at a nominal growth stage of BBCH 61 and at a nominal rate of 1.5 L/ha, corresponding to 75 g/ha BCS-CN88469 a.s.; the water rate was 300 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing except for the trial 15-2066-03 where the application was done at BBCH 53 instead of 61. This deviation is considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

4 additional supervised residue trials (Portugal, Spain and southern France) were conducted with the formulation Prothieconazele & BOS-CN88460 EC 150 in/or/barley (1997) ; 2017; M-580022-02-1; KCA 6.3.1) One spray application was made at a nominal growth stage of BBCH 61 and at a nominal rate of 1.5 L ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 300 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing except for the trial 15-2114-02 where the application was done at BBCH 53 instead of 61. This deviation is considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

Trials 15-2066-01 15-2066-02 25-2066-03 and 15-2066-04 were located side by side with trials 15-2114-01, 15-2114-02, 45-2114-03 and 15-2414-04 pespectively. Thus, for the studies 15-2066 and 15-2114, only 4 trials are considered as independent trials.

In trial 1522066-02 and 15-21 4-02 & rainfall hardened within 6 hours after application. Day 0 sampling in the treated plot was collected before rainfall in trial 15-2066-02 and after rainfall in trial 15-2114-02. An impact on the residue levels cannot completely be excluded. On the other hand, this rainfall event reflects what can happen in practice. Therefore these trials are considered acceptable for MRL setting.

Four further supervised residue trials were carried out in 2015, in southern France, Italy, Spain and Portugal, with the formulation Prothioconazole & Tebuconazole & BCS-CN88460 EC 250 in/on barley (1997), G-2017, M-583692-02-1; KCA 6.3.1). One spray application was made at a nominal growth stage of BBCH 61 and a nominal rate of 1.25 L/ha, corresponding to 62.5 g/ha BCS-CN88460 a.s.; the water rate was 300-400 L/ha, reflecting local practice in the trial regions. Again, all treatments were made at the scheduled rates.

Four further supervised residue trials were carried out in 2016 with the formulation <u>Prothioconazole &</u> <u>BCS-CN88460 EC 150</u> in/on barley, in Portugal, southern France and Spain, to complete the data package (**Description**); 2017; M-589554-02-1; KCA 6.3.1). One spray application was made at a



nominal growth stage of BBCH 61 and a nominal rate of 1.5 L/ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 300 L/ha, reflecting local practice in the trial regions. Again, all treatments were made at the scheduled rates.

In all these trials, samples of green material (whole plants without roots) were taken immediately after the application and at several intervals thereafter (up to 28/27 days after treatment). It was ensured that one of these samplings be taken at BBCH 75. Furthermore, samples of grain and straw were collected at the commercial harvest (BBCH 89).

In the trial 16-2052-03 the grain sample weight was 0.96 kg instead of A kg required in the protocol and OECD guideline 509. Nevertheless, the sampling was done randomly over the protocol and the deviation from the targeted sample weight is low (4%). The confected sample is stol considered representative of the plot and this deviation is deemed acceptable.

Each field sample was placed in doubled labeled bags and stored deep-frozen within 24 hours after sampling and until dispatch to the Laboratory for Sampling, Preparation Technique and Sample Logistics (PVTL), Bayer AG - Crop Science Division in the sample and Rhein, Germany. All field samples were shipped at a temperature of 48°C or below under monitored conditions during shipment and arrived at PVTL in good condition. The field samples were stored in a freezer at 48°C or below until preparation of the examination samples.

During the storage of the samples of the trials 15 2117-03 and 15-2117-04 the temperature rose above -18°C, reaching a maximum of -18.8°C and -15.3°C respectively. During the samples storage of the samples of the trial 16-2052-00 the temperature rose above -18°C for a short period, reaching a maximum of -9°C. Nevertheless, it was considered unlikely that these deviations have a negative impact on the quality of the study for further details see Appendix & of the respective reports.

For the preparation of examination samples, the deep tozen field samples were shredded and homogenized with dry ice in a cutter. Representative parts of the shredded samples were transferred into polystyrene boxes and stored at -18°C or below until analysis.

The samples were analysed for the parent compound using analytical method 01475 (2016; M-558986-01-O referenced in MCA04 Point 4.1.2) which was validated prior to the residue analysis of the samples. Additional validation recoveries were conducted for barley (grain, straw and green material) in the study 15-2066. The samples of grain and stow were analyzed according to the procedure described in the method for dry matrices (with a soaking step with water before extraction) and the green material samples were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The OQ was 0.01 mg/kg for parent.



In each study, concurrent recoveries were obtained from samples of green material, grain and straw. The recovery samples were spiked at levels of LOO (0.01 mg/kg) up to 5 mg/kg in order to adequately cover the residue levels found in the treated samples. Details of concurrent recovery data are shown in Table 6.3.1- 5. The average recoveries were within the acceptable range of 70 - 110%. The RSD values were below 20%.

No residues above the LOO's were found in the control samples. The detailed results obtained for barley treated samples are summarised below in Table 6.3.1- 6. The results were not corrected for concurrent recoveries.

The analyses overe done after a maximum storage period of 390 days. In most of the cases, the time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours. If not the case, the maximum storage period of extracts (80.4 hours for green material and 76 hours for straw) was covered by stability experiments conducted in the course of the residue study 15-2066 (1997), G.; 2017; M-584388-02-1; KCA 6.3.1). See Table 6.1-8.



III. Conclusions (barley, southern Europe)

In order to support the use in the EU of BCS-CN88460 in barley, 12 independent trials were conducted in the southern European residue region in the years 2015-2016. BCS-CN88460 was applied once at an active substance rate of 62.5 or 75 g/ha per treatment. All applications we at the required rates, and all trials were conducted according to GLP.

Samples were analysed for the residues of BCS-CN88460 parent compound. The results presented above demonstrate that:

- Residues of BCS-CN88460 dissipated rapidly in green materia, from levels of 0.8 • on Day 0 after the treatment to 0.048 - 1.4 mg/kg on Day 28/07.
- At harvest, residues in grain ranged from <0.01 mg/kg to 6037 mg/kg and residues in straw ranged from 0.021 to 3.1 mg/kg. •

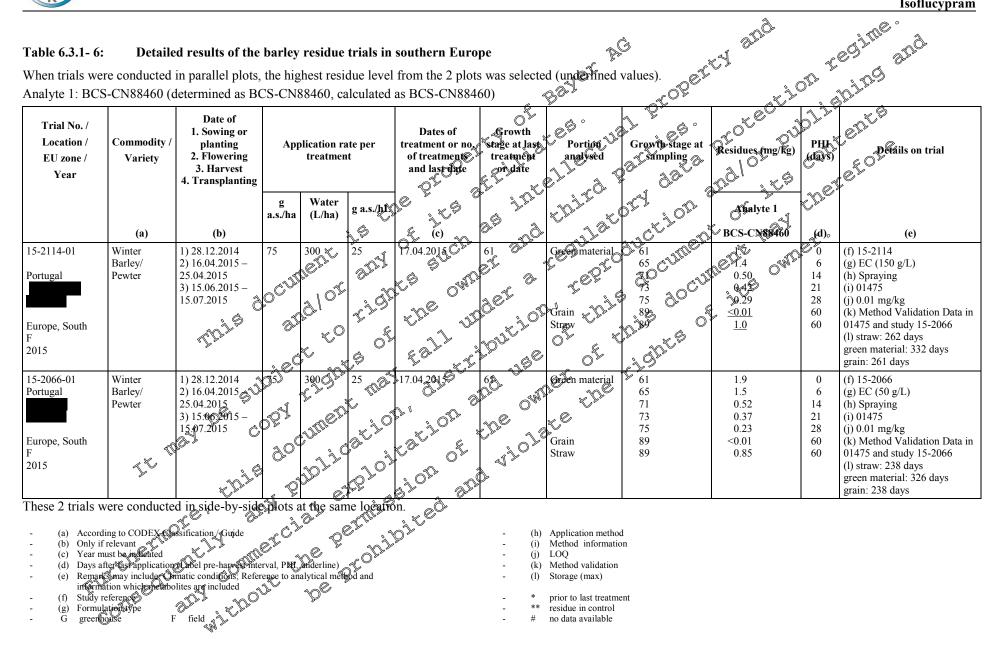
Study	Portion	n	Fortifica	<i>w</i> *	~~~~	Ban	ory (0/5	Ô	*	1
Study	analysed	11	tion level		\sim	~ /	f e e `			<u>~~</u> ,	S
	anaryseu		(mg/kg)	Individ	ial reco	veries	Min		Mean	FRSD	9
15-2114	green	2	0.01	97; 98	- N	- 1	27	B	9 8		\$
	material	1	0.10	950		â	5-	£ ⁰⁻ -	~ .	Ô.,	°~ .
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		5 °/	overall	92 0		\$ £	_≫ ∿ 92	×100	~ ⁹ 96 ~	3.2	
	grain	3	0.0	Ø); 95; 🕅			9¢ ⊘	98	94	4.3	
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		4 (øverall		×	<u>Ş</u>	90	€₇ 98	@95	3.6	
	straw		0	91		<u>~~</u>	Ś	~	× -	-	
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L.		<u>3</u> Û	overall				<u>_9</u> b>	96	94	2.8	
15-2066	green materia	Ŋ	0.01	81; \$5; 91	5% //	<u> </u>	Å 81	102	90	10.2	
	inateriary	4	0.10	80,781;92	\$ 0 *98	<u> </u>	, 80	98	88	10.1	
	-« (7)		1.65	9 6 ~	<u> </u>		-	-	-	-	
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	4	10	overal			Ű	80	98	90	8.9	
, M	grain	49	0.0	94; 95	· . @ *		94	98	96	1.8	
L.	Å.) 4	<u>4</u> 0.10	100 100;	10) ; 10)4	100	104	101	1.9	
			overall				94	104	99	3.4	
	stræv	3	0.01	97; 986Y			97	121	105	12.9	
		3	9 .10 V	89;100;1	101		89	101	97	6.9	
6		1	2.0 쓫	1097			-	-	-	-	
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Table 6.3.1- 5: Concurrent recovery data for BCS-CN88



Study	Portion	-	Fortifica	D	NOME (0/_)		
Study	Portion analysed	n	fortifica tion level	Reco Individual recoveries	overy (Min	%) Max	Mean	RSD - - - - - - - - - - - - - - - - - - -
	unuiyseu		(mg/kg)	Individual recoveries	IVIIII	wax	Mean	кы
15-2117	green	1	0.01	103	-	-	-	-
	material	1	0.10	105	-	-	- 2	- *
		1	2.0	96	-	-	Ø	-
		1	2.5	84	-	-	<u> </u>	-
		4	overall	Ò	84	105	97	9.8
	grain	2	0.01	95; 100	95	100	98	
		1	0.10	105	-	¢'-	-	% -
		4	overall	A	95 ^Q		° 100 🖓	5.0
	straw	1	0.01	102	<i>~</i> -		-~	<u>, °</u>
		1	0.10	96 & &	р -	ď-	K -	Ç ⁹ -
		1	2.0	92	j j	<u>5- "</u>	· - · 0	Íð
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		4	overall		77	ð í 02	ِ ⁶ 92	×
16-2052	green	5	0.01	\$\$3; 87\$;98; 98;000 ~~~	82	100		80
	material	2	0.10	95; 9	395	Ø	Ø	<u>j</u>
		1	1.0 2	26 ² 7 ² 5 ²	P) -	<u> </u>	8 - ₂	م آر
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		1	A.0 0	96 J O O	-	~~-	N.	<u></u> ĝ-
		10 [%]	overall		» 83	100	\$ 94 ~	ў 5. 7
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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmer		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	G Growth stage at sampling	Residues (mg/kg)	PHI Gearys)	egil fall guld guld fall guld huld fall guld guld guld guld guld guld guld gu
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) 0 8 ©		re ^g		BES-CR88460		ED ^L e E ^{OL} (e)
15-2114-02 France Europe, South F 2015	Baraka	1) 16.10.2014 2) 15.04.2015 – 20.04.2015 3) 20.06.2015 – 30.06.2015	75 0C ^{UI}	300 Alent	25 10 5 2011	DE jts	er and	Grain ULA Straw	61, 010 071 75, 1, 10 089 89 000 000 000 000 000 000	0.24 0.10 0.074 0.074 0.074		(f) 15-2114 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 254 days green material: 356 days grain: 253 days
15-2066-02 France Europe, South F 2015	Baraka	1) 16.10.2014 2) 15.04.2015 20.043045 3) 20.06.2015 - 30.06.2015	75 8 9) e ⁽ 0 9 1	t t zight		Eall BE	DUTIO	GENER	619 71 75 75 75 75 75 75 75 75 75 75 75 75 75	▶ 1.6 * 0.28 0.14 0.091 0.076 <0.01 0.14	0 7 14 21 27 69 69	(f) 15-2066 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 230 days green material: 327 days grain: 230 days

 These 2 trials were conducted in side-by-side plots at the same location although rainfall occurred after application, these trials are considered acceptable for MRL setting.

 * sample collected before the rainfall after application
 *** sample collected after the rainfall after application

 - (a) According to CODEX consistication/Guide
 (b) Application method

 - (b) Only if relevant
 (b) Only if relevant

 - (c) Year must be inflated
 (b) Application method

 - (c) Days after the rainfall occurred after the rainfall after application
 (c) Wethod information

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 - (f) Study reference
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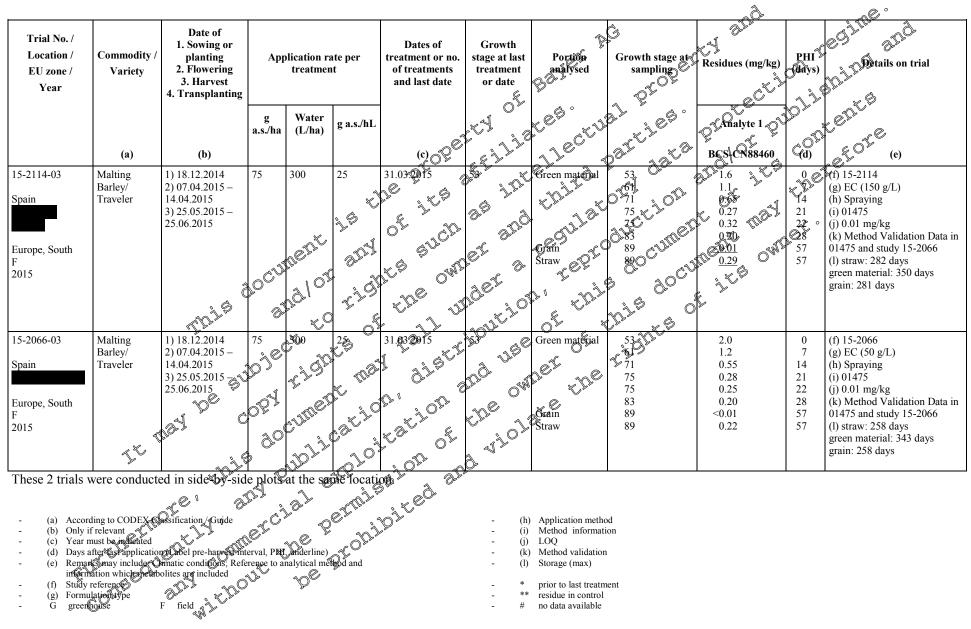
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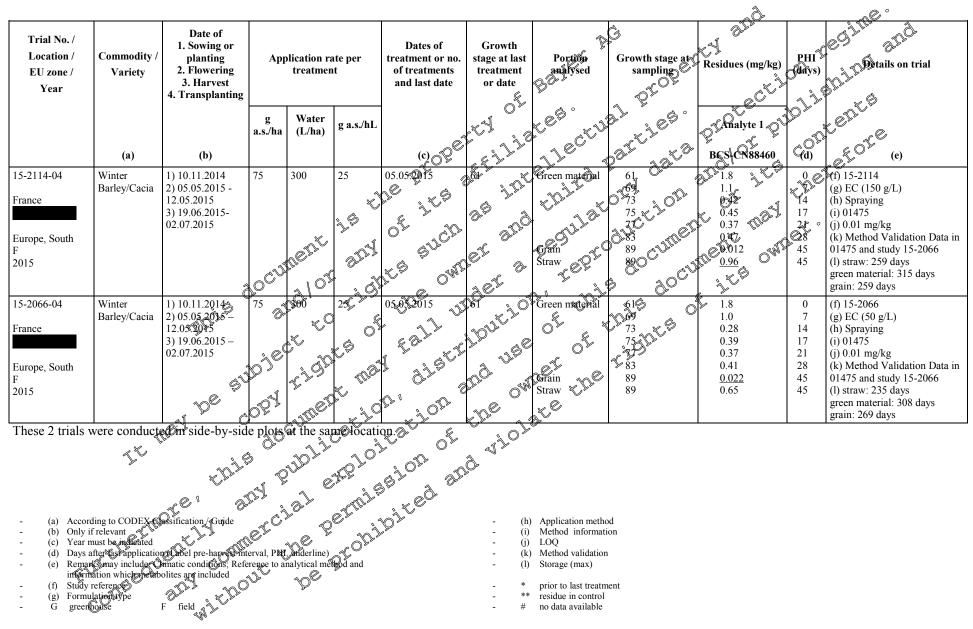


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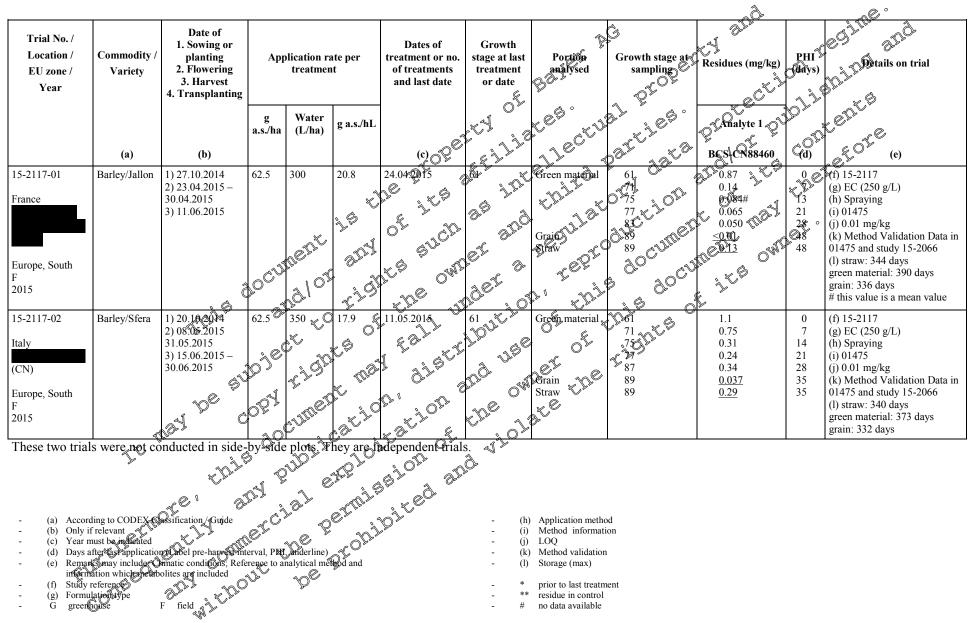


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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmer		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage ato sampling	Ct J	PHI Gaays)	egilitus guli postails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	w.o [©]	FTY J'2	re ^{\$}		BESIC N88460		FO ^{TE} ()
	. ,	. ,				(C)02	e f "			Di StC1100400	ુલ્લ)	(e)
15-2117-03 Spain (Albacete) Europe, South F 2015	Barley/ Shakira	1) 28.01.2015 2) May 2015 3) 30.06.2015	62.5			OF SUCH	er ges Jrs	Graios Jul at Show PTC	075 77 37 075 0189 89 00 00 00 00 00 00 00 00	0.20 0.20 0.054 0.054 0.048 0.048 0.048 0.041 0.041 0.041 0.041 0.041 0.041 0.041 0.041 0.041 0.054 0.05		 (f) 15-2117 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 326 days green material: 370 days grain: 318 days
15-2117-04 Portugal (Ribatejo) Europe, South F 2015	Barley/ Pewter	1) 09.03.2015 2) May 2015 3) July 2015		TOP TOP			and and		610 77 83 789 89 89	1.7 0.83 0.83 1.4 1.4 <u>0.027</u> <u>3.1</u>	0 8 14 20 27 41 41	(f) 15-2117 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 334 days green material: 372 days grain: 316 days

- These two trials were not conducted in side-by-side plots. These are independent trials. During the storage of the samples of the trials 19-2117-03 and 15-2017-04 the temperature rose above -18°C, reaching a maximum of -15.8°C and -15.3°C, respectively. This deviation was considered acceptable (see Appendix 8 of the respective reports). (a) According to CODES classification (Guide (b) Only if relevant (c) Year must endeated (d) Days after represented interval, PH underline) (e) Remark Samy includer Omatic conditions. Refereave to analytical method and information (f) Study refereave (g) Formulation whice preshouse F field (g) Formulation whice Preshouse F field (h) Application method (f) Study refereave (f) Represent (f) Study referea



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	lication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	G Growth stage at $rac{1}{2}$ sampling	Residues (mg/kg)	PHI (Gays)	C9 ¹¹⁰⁰ and hill D ^D tails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) 0 0 0°.	1.6 j 2 j 2	re ^g	at ies.	BES-CR88460		E C C (e)
16-2052-01 Portugal Europe, South F 2016	Barley/ Pewter	1) 11.12.2015 2) 07.04.2016 - 17.04.2016 3) 15.06.2016 - 15.07.2016	OCUS	REAT	25 26 E	08.04216 2 0 1 5 1 1 1 5 1 1 1 1 1 1 1 1 1 1 1 1 1	er ard	Green material LULL Graio ULL Braw LEP	$\begin{array}{c} 61 \\ 0 \\ 71 \\ 73 \\ 70 \\ 70 \\ 70 \\ 70 \\ 70 \\ 70 \\ 70$	DIL 1.4 0.37 0.16 0.079 0.16 0.079 0.16 0.079 0.16 0.079 0.16 0.079 0.16 0.079 0.16 0.079 0.16 0.079 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.16 0.07 0.07 0.07 0.16 0.07 0	0 14 28 67 67	(f) 16-2052 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 188 days green material: 251 days grain: 118 days
16-2052-02 France Europe, South F 2016	Winter Barley/ Augusta	1) 17.11.2015 2) 25.04 2016 3) 0.04.2016 3) 15.06.2016 20.06.2016	75 3 2 2 5 6 2 4 0 2 4	righ righ	235 200 5 100 5 100 5 100		ADON OW	Green material	616 71 73 73 89 89	$ \begin{array}{c} 1.8 \\ 1.3 \\ 0.69 \\ 0.30 \\ 0.23 \\ \underline{<0.01} \\ 0.31 \end{array} $	0 7 12 20 27 54 54	(f) 16-2052 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 187 days green material: 237 days grain: 117 days

I hese two trials were not candidicted in side-by side plots. They are independent trials.
* samples affected by a temperature deviation during the shipment from the field to PVTH. This deviation was nervertheless considered acceptable (see Appendix 8 of the report)
(a) According to CODEX sustification (Guide
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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	lication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage at sampling	Residues (mg/kg)	PHI Gerays)	egitte ° and hippotails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c)	0 ^f	re ^{\$}		GAnalyte 1 BCS- O\$88460	CO D	COLC (c)
16-2052-03 Spain Europe, South F 2016	Malting Barley/ Odyssey	1) 10.12.2015 2) 14.04.2016 – 20.04.2016 3) 25.05.2016 – 30.06.2016	75	300	25 25 25 20	14.04.2000 P 14.04.2000 15 15 15 15 15 15 15 15 15 15 15 15 15	as int	Grain Strace T	0 71 0 75 0 75 0 75 0 77 1 0 75 0 77 1 0 75 0 75		0 7 21 28 57 0	(C46-2052 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 192 days green material: 246 days grain: 122 days
16-2052-04 France Europe, South F 2016	Winter Barley/Cacia	2) 03.05.2016 10.05.2016 3) 2006 2016 - 01.07.2016	e D ^{je}	2001 02 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	25 j. 9 2 j. j. 9 C B C B C B C B C B		ind use	Steam	61 719 77 83 14 83 15 89	$ \begin{array}{c} 0.94 \\ 0.55 \\ 0.30 \\ 0.23 \\ 0.091 \\ \underline{< 0.01} \\ 0.18 \end{array} $	0 8 14 21 28 49 49	(f) 16-2052 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2066 (l) straw: 181 days green material: 232 days grain: 111 days

These two trials were not conducted in side by-side ptors. They are independent trials

- These two trials were not conducted in side by side abox. The ware independent trials the standard side by side abox. The standard side by side ab

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Comparison of the barley results for the three formulations tested

Since residues in grain at harvest are often <0.01 mg/kg, the comparison of the results for the different $\overset{\circ}{\sim}$ formulations used was done using the results in straw at harvest. The data sets 1, 2 and were compared to each other's using the statistical tests: Kruskal-Wallis H-Test and Mann-Whitney U-test, $\alpha = 0.05$. The same approach was done for the data sets 4, 5 and 6.

	**			×,	
Dataset 1	Dataset 2	Dataset 3	Dataset 4	Dataset 5	
EC050 EUN	EC150 EUN	EC250 EUN	EC050 EUS	€C150 EUS	Dataset 6 0 EQ250 EQ8 0.25 25
0.11	0.049	0.16	4.0	0.85	Ø.13 Č
0.12	0.24	0.51	0.16 .	Ď14 or >	0.29
0.18	0.20	0.96	Q29 & 6	0.23 0	@ .021 🗳
0.60	0.94	1.2 5		0%5	3.1
	0.40				
	0.32			0.24 5 031 5	
	0.13			0.85	
	0.13				0 [×]
EUN: northern H	Europe 🔊 F	US: southern Fa	irone 🖉 🐴	0.148 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u>.</u> ົາ

The results of these statistical tests indicate that the populations from the data sets 1, 2 and 3 are not Ð significantly different from each other s. The same applies for the datasets 4, 5 and 6.

The residue data for the different d MRLs. When tright were conducted in side-by-side plots, the highest residue level from the 2 plots was selected. The selected data are compiled in Table 6.3.1-Ø1

	102			No.	× *
Table 6.3.1-Ø:	Summa	rv of BCS-(CN88460 xesidı	ue'data føi	barley trials
0, V	SK /	• *		V.)	

Crop	Northern/ @ TriaDresults relevant to the critical GAP Southern field of glasshouse	STMR (a)	HR (b)
Barley	Northern 10 × 0.01; 0.913; 0.920; 0.941	< 0.01	0.041
Grain	Southern $9 \times 0.0139.022$; 0.027 ; 0.0037	< 0.01	0.037
Ŕ	Northern 0.049; 011; 0.13; 0,16; 0.20; 0.24; 0.32; 0.40;	0.32	1.2
Barley	0.44 2 9.51; 0994; 0.9671.2		
Straw	Southern $0.021; 0.03; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 1.05; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 1.05; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 0.10; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.24; 0.29; 0.29; 0.31; 0.24; 0.24; 0.29; 0.24; 0.29; 0.24; 0.29; 0.24; 0.24; 0.29; 0.24; $	0.29	3.1

(a) Supervised Trans Mediany Residue e. the median regulate level estimated on the basis of supervised trials relating to the critical GAP (b) Highest residu

The results of the statistical tests Kruskal-Wallis H-Test and Mann-Whitney U-test, $\alpha = 0.05$ indicate that the straw residue data from northern Europe are not significantly different from the straw residue data in southern Europe.



CA 6.3.2 Wheat

BCS-CN88460 (common name: isoflucypram) is to be registered in Europe for use in wheat, Durum wheat, rye, spelt and triticale. European residue data in wheat are therefore presented below to support the intended "representative uses".

As allowed by the EU Guidance document on comparability, extrapolation, group tolerances and data requirements for setting MRLs (SANCO 7525/VI/95 rev. 10.2 of 23 September 2016), the extrapolation of the wheat residue data to rye, spelt and triticale is requested.

Information on the intended use pattern (GAP) is summarised in Table 6.3.2

Table 6.3.2- 1:	Use patterns (critical GAP) for the formulations in/on wheat, Durug	he sp ray applica wheat, rve, spe	tion of BCS-	CN38460-6	containing pean fields
	(northern and southern residu				

Description	F/G	annle	Growth stage at application (BBCH-Code)
Wheat, Durum wheat, rye, spelt and triticale *	F**		2 30 2 09 7 7 7 100-400 7 7 NA

* agricultural use based on EC formulations BCS-CN83460 EQ030 and Prothioconazole & BCS-CN88460 EC 450) ** uses in both the northern and southern residue regions (EU-20 and EU-5)

NA: not applicable. The application timing is defined by the growth stage at application.

In order to support the EU "representative use" of BCS-CN88460, sets of GLP trials were conducted in northern and Southern European fields in 2015 and 2016. In southern and in southern European field-grown wheat, BCS-CN88460 was appred once at the lates intended growth stage of BBCH 69.

O

Three EC formulations containing BCS_CN88460 were tested with similar application rates:

- BCS-CN88460 CC 050 containing 50 g BCS-CN88460 A Tested application rate: 75 g BCS CN88460 /ba.
- Prothioconazole & BCS CN88460 EC 150 containing 50 g BCS-CN88460 /L Tested application rate 75 g BCS-CN88460/ha.
- Prothic onazoe & Tebucorazole & BCS@N88460 EC 250 containing 50 g BCS-CN88460/L
 Tested application rate 82.5 g BCS-CN88460/ha (within + or 25% of the 75 g a.s./ha application rate).

In some cases the EC050 and the EC 150 formulations were tested in side-by-side plots at the same location so that these trials cannot be considered as independent trials.

The number of independent mals conducted (incl. information on geographical region and vegetation period) is summarised below in Table 6 22-2.

period) is summarised below in Table 6 22-2.



Table 6.3.2- 2:	Overview of European residue trials conducted in barley per geographical "residue	3
	region" and vegetation period	0

1					1		
		No. of in	idependen	t trials	Deres Ale	D	
Crop	Region	Veget. period		Σ	Report No. (Formulation)	Document number	Reference
		2015	2016		(1 01		4
Wheat	EU-N	8	4	12	15-2111 (EC 050) 15-2115 (EC 150) 15-2120 (EC 250) 16-2053 (EC 150)	M-586570-02-1 M-578221-03-1 M-584680-03-1 M-593778-02	KQA 6.3.204
wheat	EU-S	8	5	13	15-2069 (EC 050) 15-2116 (EC 150) 015-2119 (EC 250) 16-2054 (EC 150)	M-584384-62-1 M-580537-03-1 M-584690-02-6 M-594320-02-1	KCA 6 5 2/05 4 KCA 6 5 2/06 KCA 6 3 2/06 KCA 6 3 2/07 KCA 6 3 2/08
EU-N = northerr FL : formulation EC 050: BCS-Cl EC 150: Prothio EC 250: Prothio			uthern EU fie 50 g BCS-CI EC 150 conta 2 BCS-CN88	`	BCS-CN88460 /L containing 50 (BCS-CN8 2015 M-586570-02 1 port - Determination o at after spray application	460 /4 0 ⁵ 20 27 5 ⁵ 20 27 5 ⁵ 20	
<u>Northern Ei</u>	irope (resi	due regio	<u>n)</u> Ő ⁵				
Report:		KCA 6.3	2/01;	, G .; 1	2015, M-5, 86570-021	ð _n ð .	, Ka
Title:		Amendu	hent no. 1 t	o final re	port - Determination o	f the residues of R	©S-CN88460
		in/on spr	ing and wi	nter whe	at after spray application	prof BCS-CN884	60 EC 050 in
Report No.:		northern 15-2111	France, m	United	Kingdom, the Nether a	nds and Germany	
Document No.).:	M-5865		Õ		«. »»	
Guideline(s):	s			Ø1107/2	09 of the European Pa	and of th	e Council of 21
Guideline de	ation(s):	VECD 🤅	uideline fo	or the Tes	e placing of afant prote sting of Chemical on (Crop Rield Trial	Crop Field Trial (T	G 509 published
GLP/GEP		Ques and			Crop Kield Tria 2017; Me 78221-03- ation of the residues o		
Report:	Q [~]	CA 68		57	; 20 17; M 78221-03-1	l	
Title:	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	CN8846	mazole in (on wheat	@tion of the residues o ℓafter spray application n France, United King	i of prothioconazo	le & BCS-
Report No	<u>م</u>	Ø3-210° ¥M-5787∕	21_03_1				
Guidefine(s):	I) O	Resultation October OECD	on@ÉC) Ne 2009 conce iuidelfre fo	ernin@the or the Tes	009 of the European Pa e placing of plant prote sting of Chemicals on C	ction products on Crop Field Trial (T	the market
Guideline de	viation (s):	VasePA Ales (see	Feport)	aideline	No. 860.1500 on Crop	Field I rial	
Guideline de GLP/GRO?		yes O	z • /				



Report:	KCA 6.3.2/03; G.; 2017; M-584680-03-1
Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460,
THO.	prothioconazole and tebuconazole in/on spring wheat and winter wheat after spra \mathcal{Q}°
	application of prothioconazole & tebuconazole & BCS-CN88460 EC 250 in United
	Kingdom, Hungary, northern France and Poland
Report No.:	15-2120
Document No.:	M-584680-03-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliament and of the Council 21
	renealing Council Directives 79/117/0FC and 91/414/FEC
	OFCD 509 Adopted 2009-09-07 OFCD Guideling for the Testing of Chebricals Trop
	Field Trial
	US EPA OCSPP Guideline Nov 860.1500
Guideline deviation(s):	ves. see report
GLP/GEP:	ves ves ve
D	
Report:	KCA 6.3.2/04;
Title:	October 2009 concerning the placing of plant protection products on the marker and repealing Council Directives 79/117/EEC and 91/414/EEC OECD 509 Adopted 2009-09-07, OECD Guideline for the Testing of Chapricals Orop Field Trial US EPA OCSPP Guideline No. 860.1500 yes, see report yes KCA 6.3.2/04; 50/7; M-593778-02-1 Amendment no. 10 final report Determination of the residues of BCS-CN88460 and prothioconcole inform winter wheat and spring wheat after spray application of prothioconcole inform winter wheat and spring wheat after spray application of prothioconcole & BCS-CN88460 EC 150 information France, Belgium, the
	and prothioconazole in on winter wheat and spring wheat after spray application of
	prothioconazofe & BCS-CN88460 EC 150 in northern France, Belgum, the
Report No.: Document No.:	
Guideline(s):	M-593778-0225 Regulation (EC) No 107/2009 of the European Parthament and of the Council of 21
Guidenne(s).	October 2009 concerning the placing of plant projection products on the market
	OFCD Guideline for the Pesting of Chemicals on Crop Pield Total (TG 509 published
	χ in Sentember 2000 Λ
4	US EPA OCSPP Gradeline No. 8601300 on Crop Freld Trual
Guideline deviation	note of s
GLP/GEP:	Nes in the in the internet internet in the internet internet in the internet in
ð A	I. Materials and Methods
.0	
Twelve independent	field restrice totals were conducted on wheat (with both spring and winter
varieties) in the northe	en European residucategion as follows:
In 2015, 4 supervise	d residue trials (northern France, the United Kingdom, the Netherlands and
Germany) were condu	cted to support the use of <u>BCS-CN89460 EC 050</u> in/on spring and winter wheat
(, G.; 2017; A	$a^{-5}86570-02-4$, KCO 6.3.2. One spray application was made at a nominal
growth stage of BBC	1 69 and at monipal rate of 1.5 L/ha, corresponding to 75 g/ha BCS-CN88460
a.s.; the water rate wa	s 200-400 L/ha, reflecting local practice in the trial regions. All treatments were
made at the scheduled	fates and scheduled application timing.
1 additional supervise	ed residue Gals (Borthern) France, the United Kingdom, the Netherlands and

4 additional supervised residue (rails (forthern France, the United Kingdom, the Netherlands and Germany) were conduced with the formulation <u>Prothioconazole & BCS-CN88460 EC 150</u> in/on spring and winter wheat (**Theorem**, 2016, M-578221-03-1; KCA 6.3.2). One spray application was made at a nominal growth stage of BBCH 69 and at a nominal rate of 1.5 L/ha, corresponding to 75 g/ha BQS-CN88460 c.; the water fate was 200 - 400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing.

Trials 15-2107-01, 53-2110-02, 15-2111-03 and 15-2111-04 were located side by side with trials 15-2115-04, 15-2115-03 and 15-2115-04. Thus, for the studies 15-2111 and 15-2115, only 4 trials are considered as independent trials.

Four further supervised residue trials were carried out in 2015, in the United Kingdom, Hungary, France and Poland with the formulation <u>Prothioconazole & Tebuconazole & BCS-CN88460 EC 250</u> in/on spring and winter wheat (**1999**, G.; 2017; M-584680-03-1; KCA 6.3.2). One spray application



was made at a nominal growth stage of BBCH 69 and a nominal rate of 1.25 L/ha, corresponding to 62.5 g/ha BCS-CN88460 a.s.; the water rate was 200-300 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing.

Four further supervised residue trials were carried out in 2016 with the formulation Prothiocons ole & BCS-CN88460 EC 150 in/on winter and spring wheat (northern France, Belgiun, the Netherlands and Germany) to complete the data package (**Section 1997**; 2017; M-593778 02-1; KCA 6.3.2). One spray application was made at a nominal growth stage of BBCH 69 and a nominal rate of 15 L/ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 300 - 400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled cates and scheduled opplication timing, except in the trial 16-2053-02 where the application was done at growth stage BBCH 65 or instead of 69. This deviation is considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

In all these trials, samples of green material (whole plants without roots) were taken immediately after the application and at several intervals thereafter on to 28/29 days after treatment). Furthermore, samples of grain and straw were collected at the commercial harvest (BBCH 89).

Each field sample was placed in doubled labeled bags and stored deep-frozen within 24 hours after sampling and until dispatch to the Laboratory for Sampling, Preparation Technique and Sample Logistics (PVTL), Bayer AG - Crop Science Division in the sample and Rhen, Germany. All field samples were shipped at a temperature of -18°C or below under monitored conditions during shipment and arrived at PVTL in good condition. The field samples were stored in a freezer at -18°C or below until preparation of the examination samples.

For the preparation of examination samples the deep-frozen field samples were shredded and homogenized with dry ice in a cutter. Representative parts of the shredded samples were transferred into polystyrene boxes and stored at 48°C or below until analysis

The samples were analysed for the parent compound using analytical method 01475 (2016; M-558986-01-1; referenced in MCA Section A under Point 4.1.2), which was validated prior to the residue analysis of the samples. Additional valuation recoveries were conducted for wheat (grain, straw and green material) in the study 45-2069. The samples of grain and straw were analyzed according to the procedure described in the method for dry matrices (with a soaking step with water before extraction) and the green material samples were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The LOQ was 0.01 mg/kg for parent.

parent.

In each study, concurrent recoveries were obtained from samples of green material, grain and straw. The recovery samples were spiked addevels of 0.01 mg/kg and up to 4 mg/kg, in order to adequately cover the residue levels found in the treated samples. Details of concurrent recovery data are shown in Table 6.3.2- 3. The average recoveries were within the acceptable range of 70 - 110%. The RSD values were below 20%.

No residues above the LOC's were found in the control samples. The detailed results obtained for wheat treated samples in borthern Europe are summarised below in Table 6.3.2-4. The results were not corrected for concurrent recoveries.

The analyses were done after a maximum storage period of 381 days. In most of the cases, the time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours. If not the case, the maximum storage period of extracts (38.5 hours for green material) was covered by stability experiments conducted in the course of the residue study 15-2069 (**1999**), G.; 2017; M-584384-02-1; KCA 6.3.2). See Table 6.1-8.



III. Conclusions (wheat, northern Europe)

In order to support the use in the EU of BCS-CN88460 in wheat, 12 independent trials were conducted in the northern European residue region in the years 2015-2016. BCS-CN88460 was applied once at 4 an active substance rate of 75 g/ha per treatment. All applications were at the required rates and all trials were conducted according to GLP.

Samples were analysed for the residues of BCS-CN88460 parent compound. The results presented above demonstrate that:

- Residues of BCS-CN88460 dissipated rapidly in green material, from levels of 0.9 • 2.1 mg/kg on Day 0 after the treatment to 0.065 - 0.87 mg/kg on Day 28/29
- At harvest, residues in grain were all <0.01 mg/kg and residues in straw ranged from 0054 to 154 . 27 27 27 27 27 • 3.6 mg/kg.

	1	1			ô	-01	~~~~	<u> </u>	f.
Study	Portion		Fortifica	Ø	Recover			<u>, C</u>	<u>م</u> ′
	analysed		tion level	Individual recover	ies Min	Max	Mean	RSD	
17 0111		2	(mg/kg)	(1); k1 (2); 10 (2)	<u>/ _ ~ 99</u>	0		S 1	
15-2111	green material	3	0.01			M7	005	9.1	
	material	2	0.10	97 ⁽¹⁾ ;98 ⁽¹⁾	97	y 98 (چ 98 ک		
		1	2.5 👻	9999 63 6	, 6,	A T	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u>_0</u> _	
		6	overcall		∛ 97	Å ¶7	أ02	[©] 7.4 (Ĵ [×]
	grain	2	0.01	101 @ 104 2		104	y 103 🍕		
		1 %	≥0.10 0		, _C ,	Ś	<u> </u>	, Z	
		3	overall	\$ Õ &	. Q01	\$ 407	104 🔬	<u>ڳ</u> 2.9	
	straw	A	0.01	92 ⁽²⁾	× -	- (5 - 4	-	
		1	\$ 0.10 S	989 ~ ~		Å	<u></u>	-	
	Ő	A	2.0 9	80(1)	. * -	<i>.</i> -	÷,	-	
	ð í	Ŷ	overall C		806		, 90	10.2	
15-2115	green	1 🔬	0.01	86 ~ ~ ~	× @-		-	-	
le Ine	material	10	0.20	§\$5 5	- \$	~ -	-	-	
* *		75	225 L	97 5 27	i i	7 -	-	-	
	, S	3	overal	X O C	≫ გ85	97	89	7.5	
	grain	20	0.6	@1;92~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	\$91	92	92	-	
		βŶ,	\$.10 ×	102 2 2 2	102	-	-	-	
	A	3	over#0		91	102	95	6.4	
	Ø straw	10	0.00	98 Ja in	98	-	-	-	
×.,	~	Ş r	Q.10	105	105	-	-	-	
\sim		1	2.0	96%	96	-	-	-	
	, O	3	overall	\$ ²	96	105	100	4.7	
15-2120	geen ~		£01 √	81 ⁽²⁾ . 98 ⁽²⁾	81	98	90	-	
	materiak	2 ្(0.10	1 ⁽¹⁾ ; 112 ⁽²⁾	111	112	112	-	
~	Ų ₍ Č	10	2.0	83 ⁽¹⁾	83	-	-	-	
	, Si a		\$3.0	95 ⁽²⁾	95	-	-	-	1
C. S.	Q O	6	overall		81	112	97	13.7	1
Ďa 🥙	grain	2	0.01	99 ⁽²⁾ ; 100 ⁽²⁾	99	100	100	-	1
U		3	0.10	95 ⁽¹⁾ ; 113 ⁽¹⁾ ; 116 ⁽¹⁾	95	116	108	10.5]
		5	overall		95	116	105	8.6	

Concurrent recovery data for BCS_ON88460 in wheat Table 6.3.2- 3:



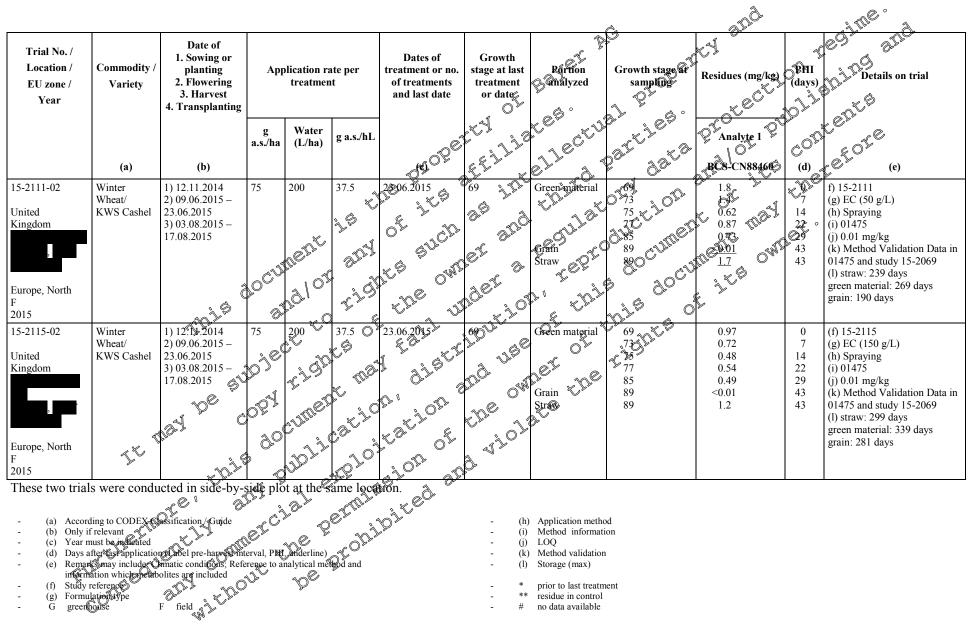


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Table 6.3.2- 4	Detail	ed results of the	e wheat residue tri	als in northern Euro	ре	A.	Ĝ	ty and	Ś	egilme ond		
	When trials were conducted in parallel plots, the highest residue level from the 2 plots was selected (underlined values). Analyte 1: BCS-CN88460 (determined as BCS-CN88460, calculated as BCS-CN88460)											
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Application rate p treatment		O [™] Srowth	analyzed		Residues (Ing/kg)	PHIC (days)	CELO Details on trial		
	(a)	(b)			as and	the gulat	ory on a		CTA)°	(e)		
15-2111-01 France Europe, North F 2015	Winter Wheat/ Rubisko	Thile Thile	320101 1			Green material	69 31 5 77 83 5 5 5 5 5 6 5 77 5 6 6 77 5 6 77 5 6 77 5 77 5 6 7 7 7 7 7 7 7 7 7 7 7 7 7	0.4.6 N	0 7 14 21 28 45 45 45	 (f) 15-2111 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 269 days green material: 300 days grain: 220 days 		
15-2115-01 France Europe, North F 2015	J. T	1) 17.10.2014 2) 15.05.2015 22.05.2046 3) 01.072015 - 007.2015		22.05.2015 The 22.05.2015 22.05.2015 22.05.2015 22.05.2015 2010 20	the ow the ow	Green material Straw	69 71 75 77 83 89 89	$\begin{array}{c} 1.0 \\ 0.61 \\ 0.79 \\ 0.46 \\ 0.49 \\ < 0.01 \\ 0.84 \end{array}$	0 7 14 21 28 45 45	 (f) 15-2115 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 329 days green material: 371 days grain: 311 days 		
- (e) Remar intern - (f) Study	Smay include O ation which netwo reference lation type	structed in side-by assification / Guide assification / Guide by abel pre-harge with matic conditions, Refe olites are included F field	side plot of the same erval, Plot, inderline) prease to analytical method is		- (h) - (i) - (j) - (k) - (l) - * - ** - **	Method informati LOQ	on					

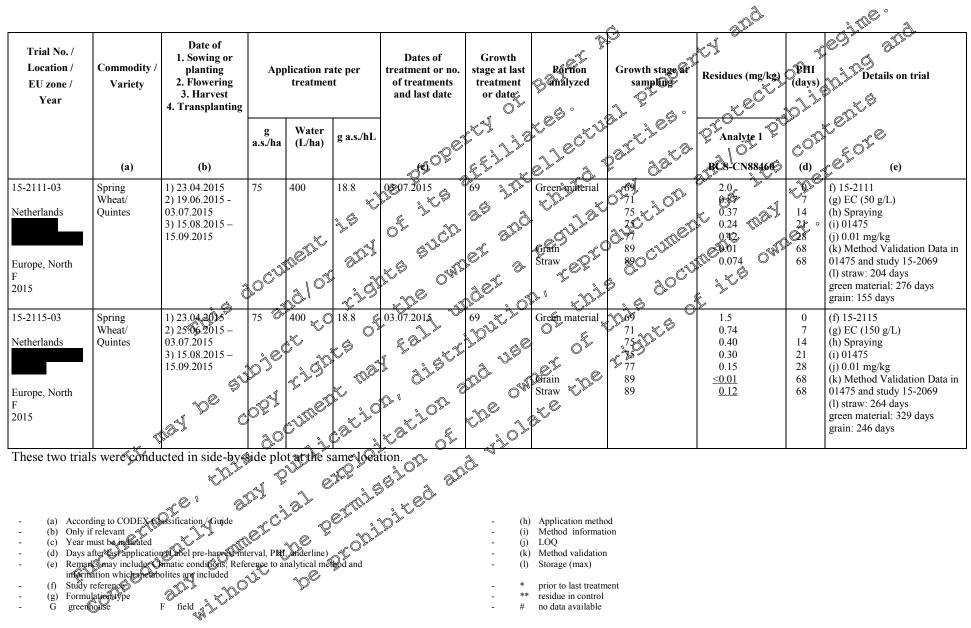


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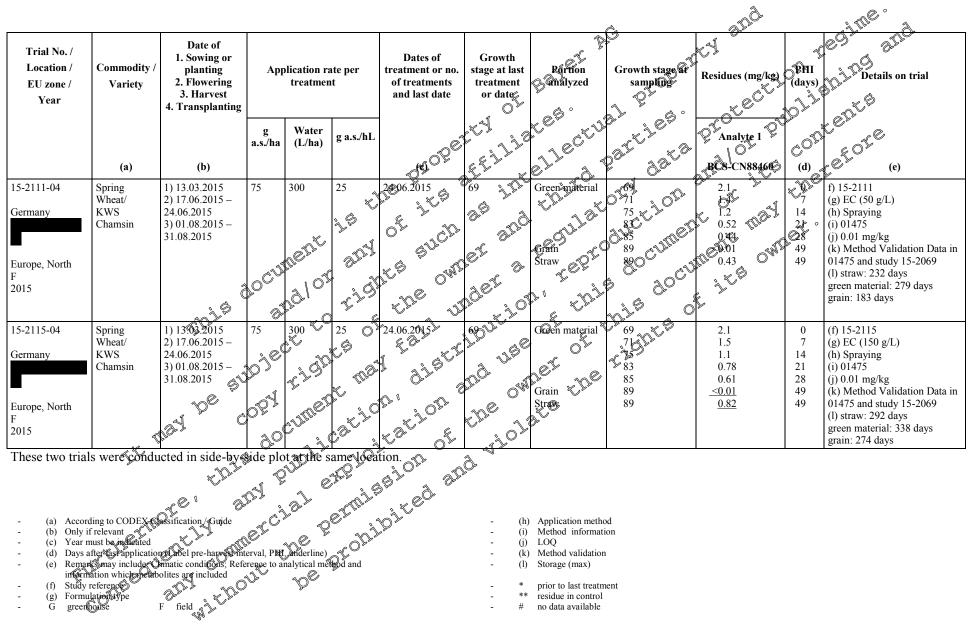


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									Â.	a Dê		A. The of A
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Apŗ	olication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Rártion Ganalyzed	Growth stage of	Residues (mg/kg)	Eni (days)	Control of the second s
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	WODE.	EE 222	ellectu	al tes.	PAnalyte 1 BOS-CN88460		Cer (e)
15-2120-01 United Kingdom Europe, North	Winter Wheat/ Skyfall	1) 06.10.2014 2) 09.06.2015 - 24.06.2015 3) 14.08.2015	62.5	ent	31.3 2.9 2.07		du ad	Grain Straw			**************************************	 (f) 15-2120 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 309 days green material: 362 days
Europe, North F 2015	Winter Wheat/ GK Szala	1) 15.10.2014 2) 15:05.2015 - 30.05.2015 3) 09.07.2015	62.50	300 EC			LOUS OF TOT	Green material Green material OF OF OF OF OF OF OF OF OF OF	2000 75 .835 DU 285	$ \begin{array}{c} 1.3 \\ 0.95 \\ 1.2 \\ 1.3 \\ 0.70 \\ \underline{<0.01} \\ 3.6 \end{array} $	0 7 14 21 28 34 34 34	grain: 309 days (f) 15-2120 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 343 days green material: 381 days grain: 343 days
- (a) Accord - (b) Only if - (c) Year n - (d) Days a - (e) Remar inform - (f) Study n - (g) Formu - G green	La La Bally av De	advisible in side-	by State	plots: J plots: J plot	hey are h		- (h) - (i) - (j) - (l) - (l) - ** - **	LOQ	ion 1			



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									Â.	and.		in the o
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Application rate per treatment			Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Rártion Banalyzed	Growth stage of sampling	Residues (mg/kg)		COLLED Details on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	MODE.	EEDDE	ellectu	al E data	Analyte 1 Analyte 1 BCS-CN88460		C ^{C⁵} (e)
15-2120-03 France Europe, North F 2015		A	LOCUS	all ^{ox}	19 204 204	OL SUCH	er and	Graio	0169 81, t 101 89, c 1111 89, c 1111 89, c 1111 8, g 0, c 11	2.0 1.5 2.5 <u><0.80</u>	E P	(f) 15-2120 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 343 days green material: 372 days grain: 343 days
15-2120-04 Poland Europe, North F 2015		2) 3096.2015 - 03.07.2015 3) 04.08.2015	62.5 0 2 2 2 2 2 2 2 2 2 2 2 2 2	TI JUNEI			L ^a USE	Green material	775 La	$ \begin{array}{r} 1.4 \\ 0.91 \\ 0.58 \\ 0.66 \\ 0.84 \\ \underline{<0.01} \\ \underline{1.5} \end{array} $	0 7 14 21 28 36 36 36	(f) 15-2120 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 317 days green material: 358 days grain: 317 days
 (a) Accord (b) Only it (c) Year n (d) Days a (e) Remarking information (f) Study (g) Formation G green 	ding to CODEX f relevant nust be infracted if er Kust application (Smay include O ation which are ab reference lation type house	inducted in side- biducted in s	erval, Pbt.	pros: »	Colding and		- (h) - (i) - (j) - (k) - (l) - (k) -	LOQ Method validation	ion 1			

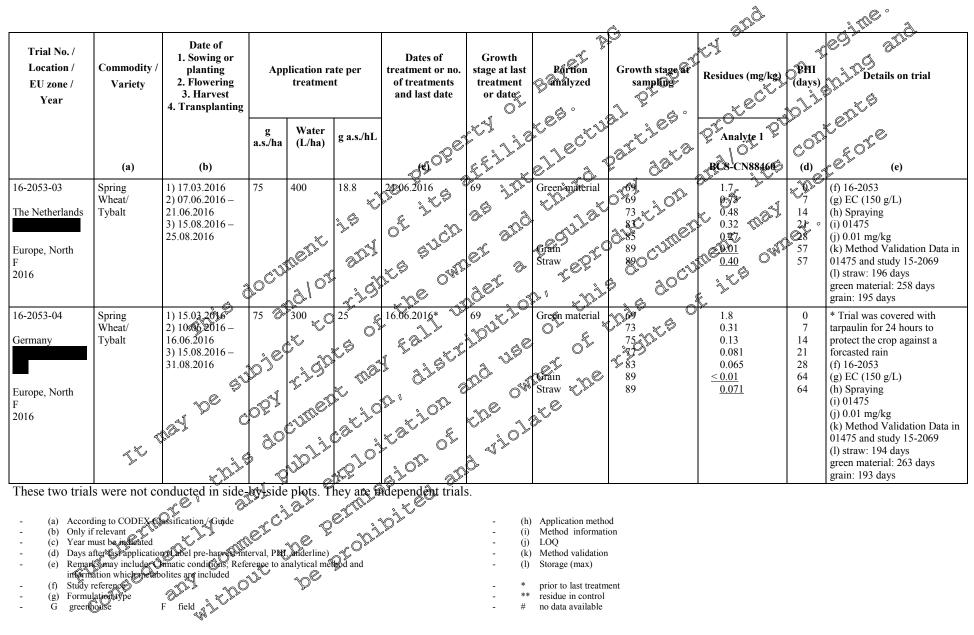


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									Ĉ.	and		A THE SA
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Application rate per treatment			Dates of treatment or no. of treatments and last date	Rártion Ganalyzed	Growth stage at	Residues (mg/kg)		e9 difference of the second se	
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	MODE.	et li	ellectu	al to data	Analyte 1 P Analyte 1 P	(d)	CEL (c)
16-2053-01 France	Sy Moisson	1) 20.10.2015 2) 13.05.2016 – 20.05.2016 3) 10.07.2016 – 20.07.2016	75	300	25 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		der and		0 71 0 1 1 0 1 1 1 0 1 1 1 0 1 1 1 0 1 1 1 0 1	1.7 02 1	2000 13 2000	(f) 16-2053 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in
Europe, North F 2016			10CJ	9101 101	2102 219	L S OW		Gram Straw	80	11. C <u>0.19</u> j. ^{r.G}	52	01475 and study 15-2069 (1) straw: 233 days green material: 291 days grain: 232 days
16-2053-02 Belgium Europe, North F 2016	Winter Wheat/ Rubisko	1) 07.11 2015 2) 05.00 2016 – 15.06.2015 3) 08.08.2016 – 15.08.2016	75 8 0 ¹)e 0 ^{2¹}	it zigh			LL ^C USC M	Green material	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	$ \begin{array}{r} 1.2 \\ 0.38 \\ 0.16 \\ 0.12 \\ 0.087 \\ \underline{< 0.01} \\ 0.054 \end{array} $	0 7 14 21 28 60 60	(f) 16-2053 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 204 days green material: 269 days grain: 203 days
- (a) According to CODEX classification / Guide - (b) Only if relevant - (b) Application method - (c) Year must be inflicated - (b) Only if relevant - (c) Hardware inflication - (d) Days aftersase publications for effective to analytical method and information which phenologies are included - (k) Method validation - (e) Remark smay include Commute conditions. Reference to analytical method and information which phenologies are included - (k) Method validation - (f) Study reference - (l) Study reference - (l) Study reference												
 (a) Accord (b) Only if (c) Year m (d) Days a (e) Remanding (f) Study r (g) Formul G greeth 		assification / Guide Babel pre-happen int imatic conditions, Refe olites are included F field	erval, PM, rense to ar	anderline) halytical met	C ^T		- (h) - (i) - (j) - (k) - (l) - * - **	LOQ	ion 1			



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Southern Europe (residue region)

Donart	KCA 6.3.2/05; G.; 2017; M-584384-02-1
Report: Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460
THU.	in/on wheat and durum after spray application of BCS-CN8800 EC 050 in Portugal
	southern France and Spain
Report No.:	15-2069 M-584384-02-1
Document No.:	M-584384-02-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21
	October 2009 concerning the placing of plant protection products on the market
	OECD Guideline for the Testing of Chemicals on Orop Field Tran (IG 509 published, O
	IN September 2009)
Guideline deviation(s):	ves see report
GLP/GEP:	October 2009 concerning the placing of plant protection products on the market OECD Guideline for the Testing of Chemicals on Orop Field Trial (TG 509 published O in September 2009) US EPA OCSPP 860.1500, Grop Field Trial yes, see report yes
	KCA 6.3.2/06; 2017 M-580 07-03 d Amendment no 2. Determination of the residue of BCS-CN85460 and prothioconazofe in/on/wheat after spisy application of prothioconazofe & BCS-
Derrort	VCA 6 2 2/06
Report: Title:	KCA 6.3.2/06; 2017 M-580 7-03 4 Amendment no 2. Determination of the residues of BCS-CN85460 and
T IIIC.	prothioconazofe in/or wheat after spiny application of prothioconazofe & BCS-
	CN88460 EC/150 in the field in Portugal, southern France and Span
Report No.:	
Document No.:	$M-5805$ G -03 π G
Guideline(s):	Regulation (EC) No 4007/2009 of the European Parliament and of the Council of 21
	October 2009 concerning the placing of plant protection products on the market
	QECD Guideline for the Desting of Chemicals on Crop Deld Trial (TG 509 published in September 2009)
*	IS ERA OCSPP Guideline NO 860 2500 or Cron Keld Tright
Guideline deviation(s)	US ERA OCSPP Guideline Ve. 860 1200 or Crop Field Triat
GLP/GEP:	Ver a so a co co co
Ô &	
	KCA 6.3, 2007; , G. 2017; No 584690-02-1
Report:	KČA 6.3, 2007; , G. 2017; MD 584690-02-1
Title N	Amendment no to final report - Determination of the residues of BCS-CN88460
A . C	prothio onazole and tebucon zole in on wheat and durum wheat after spray
í "Ô	application of prothoconazole & ebucon a cole & BCS-CN88460 EC 250 in southern
	Erance, Spain, Portugal and Italy
Report No.:	55-2119 M-583690-921 0 0 0 0
Document No.: Guideline(s):	NI-584090-1221 0 0 0 C
ourderine(3). »	Reculation (EC) No 1107/2009 of the European Parliament and of the Council of 2 October 2009 concerning the placing of plant protection products on the market
J. J	and representing (Valuncia) The twees (9/11/2) EC and 91/414/EEC
	OECD 509 Adopted 2009-09 07, OECD Guideline for the Testing of Chemicals, Crop
	Field Trial
	Cost EPACOCSPP Guidelone No. 860.1500
Guideline deviation(s):	none y y y
GLP/GEP:	
	OECD 509 Adopted 2009-09-07, OECD Guideline for the Testing of Chemicals, Crop Field Trial V V8 EPA OCSPP Guideline No. 860.1500 none
õ	



Report:	KCA 6.3.2/08; ; 2017; M-594320-02-1
Title:	Amendment no. 1 to final report - Determination of the residues of BCS-CN88460
	and prothioconazole in/on wheat and wheat, durum after spray application of
	Prothioconazole & BCS-CN88460 EC 150 in Italy, Spain, southern France and Greece S
Report No.:	16-2054
Document No.:	M-594320-02-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliamen@and of the Council of 21
	October 2009 concerning the placing of plant protection products on the market
	OECD Guideline for the Testing of Chemicals on Crop Field Trial (TG 509 published)
	in Sentember 2009)
	US EPA OCSPP Guideline No. 860.1500 on Crop@ield Trial
Guideline deviation(s):	yes, see report
GLP/GEP:	ves A Q a c C Q

I. Materials and Methods

Thirteen independent field residue trials were conducted on wheat (including durum varieties) in the southern European residue region, as follows:

In 2015, 4 supervised residue trials (southern' France Portugal and Spain) were conducted to Support the use of <u>BCS-CN88460 EC 050</u> in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460 EC 050** in on wheat and durum wheat (**BCS-CN88460** a.5) the water rate was 900 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing, except in the trial 15 2069-04 where the application was done at growth stage BBCH 65 instead of 69. This deviation is considered acceptable since the triang between application and harvest is not expected to be significantly inpacted.

4 additional supervised residue triats (southern France, Portugad and Spain) were conducted with the formulation Prothioconazole & BCS-CN88460 EC 1500n/on wheat (2017); 2017; M-580537-03-1; KCA 6.3.2). One spray application was made at a normal growth, sage of BBCH 69 and at a normal rate of 9.5 L/ha, corresponding to 75 g/ha/BCS-CN88460 a.s., the water rate was 300 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing, except in the trial 5-2106-04 where the application was done at growth stage BROH 65 instead of 60. This deviation is considered acceptable since the timing between application and harves is not expected to be significantly impacted.

Trials 15-2069-01, 15-2069-02, 15-2069-03 and 15-2069-04 were located side by side with trials 15-2116-01, 15-2116-02, 15-2116-03 and 15-2116-04. Application dates, sampling dates and varieties slightly differ between 15-2069-04 and 15-2116-04 due to the fact that 15-2116-04 had to be restarted. Nevertheless, both trials were located very close to each other (Bayer CropScience Research Farm, Brenes, Spain). The cultivation practices. Game, 91 Field, same equipment used), the weather conditions, the PHI and the types of sold are not enough different to consider these trials as independent. Thus, for the studies 15-2069 and 15-2116, only 4 trials are considered as independent trials.

Four further supervised residue trials were carried out in 2015, in southern France, Spain, Portugal and Italy with the formulation <u>Prothioconazole & Tebuconazole & BCS-CN88460 EC 250</u> in/on wheat and durum wheat (1997), M-584690-02-1; KCA 6.3.2). One spray application was made at a nominal powth rage of BBCF 69 and a nominal rate of 1.25 L/ha, corresponding to 62.5 g/ha BCS-CN88460 a.s. the water rate was 300 L/ha, reflecting local practice in the trial regions. All treatments were thade at the checkled rates and scheduled application timing except in the trial 15-2119-01 where the application was 5.9% overdosed.

Five further supervised residue trials were carried out in 2016, in southern France, Italy, Spain and Greece with the formulation <u>Prothioconazole & BCS-CN88460 EC 150</u> in/on wheat to complete the data package (**December 2017**; M-594320-02-1; KCA 6.3.2). One spray application was made



at a nominal growth stage of BBCH 69 and a nominal rate of 1.5 L/ha, corresponding to 75 g/ha BCS-CN88460 a.s.; the water rate was 300 - 400 L/ha, reflecting local practice in the trial regions. All treatments were made at the scheduled rates and scheduled application timing.

In all these trials, samples of green material (whole plants without roots) were taken immediately after the application and at several intervals thereafter (up to 28/29 days after treatment). Furthermore, samples of grain and straw were collected at the commercial harvest (BBCH 69).

In two trials (15-2069-03 and 15-2116-03) samples of grain and straw were not collected since plots had been harvested by mistake (see Appendix 8 of the respective reports).

Each field sample was placed in doubled labeled bags and stored deep-frozen within 20 hours after sampling and until dispatch to the Laboratory for Sampling, Pteparation Technique and Sample Logistics (PVTL), Bayer AG - Crop Science Division in **Sector** and Rheny, Germany. All field samples were shipped at a temperature of 18°C or below under monitored conditions during shipment and arrived at PVTL in good condition. The field samples were stored in a freezer at 18°C or below until preparation of the examination samples.

In the trials 15-2119-02 and 15-2119-03, the temperature temporarily increased above -18°C during storage but this did not affect the integrity of the samples. Similarly in trial 16-2054-01 some samples were transported temporarily above -0.8°C. These deviations were considered acceptable. For further details see Appendix 8 of the respective reports.

For the preparation of examination samples, the deep-frozen field samples were shredded and homogenized with dry ice in a cutter. Representative parts of the shredded samples were transferred into polystyrene boxes and stored at -18°C r below until analysis.

The samples were analysed for the parent compound using analytical method 01475 (1995); 2016; M-558986-01-1; referenced in MCA 4 Point 1.2) which was validated prior to the residue analysis of the samples. Additional validation recoveries were conducted for wheat (grain, straw and green material) in the study 15 2069. The samples of grain and straw were analyzed according to the procedure described in the method for dry matrices (with a soaking step with water before extraction) and the green material samples were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The LOQ was 0.01 mg/kg for parent.

In each study, concurrent recoveries were obtained from samples of green material, grain and straw. The recovery samples were spiked at levels of 0.01 mg/kg and up to 8 mg/kg, in order to adequately cover the residue levels found in the treated samples. Details of concurrent recovery data are shown in Table 6.3.2- $^\circ$. The average recoveries were within the acceptable range of 70 – 110%. The RSD values were below 20%.

JI. Findings

No residues above the LOQs were found in the control samples. The detailed results obtained for wheat treated samples are summarised below in Table 6.3.2- 6. The results were not corrected for concurrent recoveries.

The analyses were done after a maximum storage period of 398 days. In most of the cases, the time between the beginning of the sample proparation and the sample analysis did not exceed 24 hours. If not the case, the maximum storage period of extracts (30.5 hours for grain, 39 hours for green material and 76 hours for straw) was govered by stability experiments conducted in the method 01475 (

; 2016; MS 58986 01-1; referenced in MCA Section 4 under Point 4.1.2), or by additional experiment conducted in the course of the residue study 15-2069 (**1999**, G.; 2017; M-584384-02-1; KCA 6.3 2). See Table 6.1-8.

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III. Conclusions (wheat, Southern Europe)



In order to support the use in the EU of BCS-CN88460 in wheat, 12 independent trials with samplings of grain and straw were conducted in the southern European residue region in the years 2015-2016. BCS-CN88460 was applied once at an active substance rate of 62.5 or 75 g/ha per treatment All applications were at the required rates, and all trials were conducted according to GLP.

Samples were analysed for the residues of BCS-CN88460 parent compound. The results of the triâbs presented above demonstrate that:

- Residues of BCS-CN88460 dissipated rapidly in green material, from levels of 09 • on Day 0 after the treatment to 0.14-1.5 mg/kg on Day 27-29.
- •

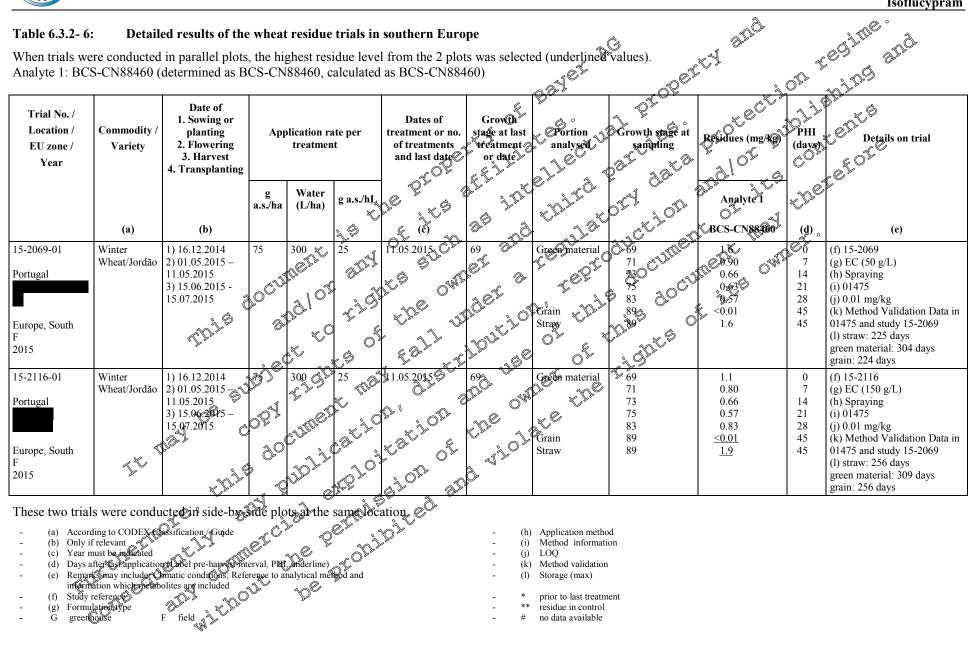
• K 01	n Day 0 aft	er the	e treatment	to 0.14-1.5 mg/kg on Day 27	ateriai, '-29. <i>"</i>	40ni i S		•0=70- <u>2</u>	yang/kg
• A	t harvest, r	esidu	les in grain	to 0.14-1.5 mg/kg on Day 27 were most of the time <0.01 in straw ranged from 0.22 to ery data for BCS-6 N88469 in	mg/kg	(only	in one tr	ial resid	ue∜was
at	t 0.042 mg/	kg ar	nd residues	in straw ranged from 0.22 to	2,4 mg	g/kg.		Ŷ,	Ô [°] 4
				Â,		ç° ,	Ŷ. Ő	۶ <u>۱</u>	
able 6.3.	2-5: 0	oncu	rrent recov	erv data før BCS-GN88464 in	wbeat	, T	í þ		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
			E			v	- Å	ry L A	~~
Study	Portion analysed	n	Fortifica tion level	Lindividual recoveries		D' Mass	[°] Mean	RSD	
	unuiyseu		(mg/kg)		Min			Кар	A A A
15-2069	green	4	0.01	8 ⁽¹⁾ ; 97 ⁽²⁾ , 104 ⁽²⁾ , 96 ⁽²⁾	89	404	Ø7	\$ 6.1	C
	material	5	0.10	$200^{(1)}; 100^{(2)}, 95^{(2)}; 96^{(3)}; 98^{(2)}$	95~	» 100 م		2.30	
		1	2.0 🔍		100	© 0 0	ð	\$	
		1	2.5 0		Q101	°_	&- '	Ky -	
		11	overall 🔬		89	104 _©	, 98 ⁽	4.1	
	grain	2 濲	Ø0.01 ©′	97(\$\$,91 ⁽¹⁾	Ň	27	2F	-	
		1	0.10		-	≪°	<u> </u>	-	
	, in the second s	Ŝ	overall		91×	* 107 [*]	≫ [°] 98	8.2	
	straw	1	<u>(</u> 0.01)		-	<u> </u>	-	-	
	õ	1	0.10		¢′-	S -	-	-	
	ð,	Ç.	200 C	10580 5 5		-	-	-	
	- Ôg - '()r 	overall		1401	105	103	2.0	
15-2116	✓ green ✓ material		0.01		<u>۲</u> -	-	-	-	
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~	$\beta$	-0.90 -0.90		-	-	-	-	
			1.0 2.0 2.0		-	-	-	-	
	Q.		overall "		95	- 104	- 99	- 4.3	
	grain	2		9906 6 7	95 96	99	99 98	4.5	
	A	2	0.100		90	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	90	-	
n an	<i>Q</i> [*]	1 O	overall		<u> </u>	99	- 98	1.8	
,¢∪`	straw 🐇	$\int_{1}^{\infty}$	\$0.01	930 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		-	-		
~~	Suu	1	0.10	928 s	-	_			
	L [°]	1 1	290 ,	100	-	-	_		
			overall		93	100	97	3.7	
15-2119	7) green	10	0.00	94; 102	94	102	98	-	
Ţ,	material	Â,	<b>AC</b> 10	103	-	-	-	-	
		1	3.0	82	-	-	-	-	
Æ,	y grees material	3	overall	1	82	103	95	10.2	
ŝ	grain	1	0.01	98				-	
		2	0.10	95; 95	95	95	95	-	
		3	overall		95	98	96	1.8	

Table 6.3.2- 5:



analysed       tion level (mg/kg)       Individual recoveries       Min       Max       Mean       R         straw       1       0.01       100       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       <	Study	Portion	n	Fortifica	Recov	ery (%	)		
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$\begin{array}{ c c c c c c c c c c c c c c c c c c c$			1	0.10	103	-	-	ð -	- @
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16-2054       green material       1       0.01       82 $\checkmark$ $\circ$ $ \circ$ $  \circ$ $  \circ$ $                                                              -$ <td></td> <td></td> <td>4</td> <td>overall</td> <td>ČĄ.</td> <td>91 .</td> <td><b>Č103</b></td> <td>97 🦼</td> <td>^مر 5.6 م</td>			4	overall	ČĄ.	91 .	<b>Č103</b>	97 🦼	^م ر 5.6 م
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	16-2054	green	1	0.01	82		-		~~
3     overall     82     96     90       grain     1     0.01     83     -     -     -       1     0.10     92; 92     -     -     -     -       2     overall     -     -     -     -     -       1     0.01     98     -     -     -     -       2     overall     -     -     -     -       1     0.01     98     -     -     -       1     0.10     98     -     -     -       1     2.0     93     -     -     -		material	1	1.0	91	10 <u>v</u>	-	×	<i>Q</i> -
1     0.10     92; 92     2     0     -     -     -       2     overall     -     -     83     92     89       straw     1     0.01     98     -     -     -     -       1     0.10     93     -     -     -     -     -       1     2.0     93     -     -     -     -			1	8.0			ъ° -	~ - ×	- ⁽
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straw $\begin{array}{ c c c c c c c c c c c c c c c c c c c$			1	0.10	92; 92	<b>\$</b> - (	6 -	Ø - 🖉	r
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	ľ	straw	1	0.01	98 2 2	Ő ⁹ -	<u>`</u> ,~	<u></u>	. چ
			1	0		\$ <u>~</u>	Õ -	¢	ĵ - <u> </u>
			1	2.0	93 8 7 8 3	Ô	Û	, D	
SD: relative standard deviation P: recovery conducted with wheat control samples P: recovery conducted with durum wheat control samples P:			1			<i>S</i> -	~~ <u>~</u>	<u>~0</u> -	· · · · ·
SD: relative standard deviation recovery conducted with wheat control samples recovery conducted with durum wheat control samples recovery control samples recovery conducted with durum wh			4	overall	× ~ ~ ~	92	98	°94 (	3.1
			J J		~~~				







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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	11	tion rate per atment	Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion an Bysed	Growth stage at sampling		PHH (days)	egil ne o gild hild hild gail
	(a)	(b)		ater /ha) g a.s./h	L (c) and				BCS-ON88460		
15-2069-02 France Europe, South F 2015	Winter Wheat/ Aubusson	1)16.10.2014 2) 02.05.2015 - 05.05.2015 3) 20.06.2015 - 02.07.2015	75 300	At ADY	AP its	er arr	Grain ULA Coreen material	0.089 0.089 0.000 0.000 0.000 0.000		0	<ul> <li>(f) 15-2069</li> <li>(g) EC (50 g/L)</li> <li>(h) Spraying</li> <li>(i) 01475</li> <li>(j) 0.01 mg/kg</li> <li>(k) Method Validation Data in 01475 and study 15-2069</li> <li>(l) straw: 225 days green material: 308 days grain: 224 days</li> </ul>
15-2116-02 France Europe, South F 2015	Winter Wheat/ Aubusson						Green material	69 77 75 77 80 89 89 89	$ \begin{array}{c}     1.6 \\     1.1 \\     0.68 \\     0.88 \\     0.84 \\     \underline{<0.01} \\     \underline{0.87} \end{array} $	0 6 14 21 28 49 49	(f) 15-2116 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 256 days green material: 321 days grain: 256 days
These two trials	weresconduc	cted in side-by E ^{DDD}	ide plots of	the same for	ation. al						
<ul> <li>(a) Accordi</li> <li>(b) Only if</li> <li>(c) Year mu</li> <li>(d) Days aff</li> <li>(e) Remark</li> <li>(f) Study re</li> <li>(g) Formula</li> <li>G greentee</li> </ul>	ng to CODEX (Na relevant ist be inducated ter as rapplication frag includer Or tion which are tabo ference the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the table of the set of the set of the set of the set of the table of the set of the set of the set of the set of the table of the set of the set of the set of the set of the table of the set of the set of the set of the set of the table of the set of th	sification / Guide sification / Guide function of the second se	rval, Pbt, mider ence to analytic	cline) COL al méteod and C		- (h) - (i) - (j) - (k) - (1) - * - ** - #	Application method Method informatic LOQ Method validation Storage (max) prior to last treatmar residue in control no data available	d on ent			



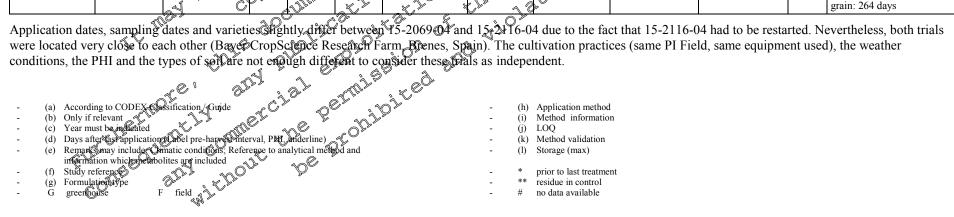
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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting		lication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage at sampling	, Kesiuues (iiig/kg)	s (	eginde Details on trial
			g a.s./ha	Water (L/ha)	g a.s./hL	e S	XH J	CE ^B CUI	S°	analyte 1		ents
	(a)	(b)				(c) 0 ²⁰		1200	an to	BCS-0188460	C'(q)	€ 0 ¹⁰ (e)
15-2069-03 France Europe, South F 2015	Winter Wheat/ Arezzo	1) 28.10.2014 2) 07.05.2015 – 15.05.2015 3) 25.06.2015 – 07.07.2015		Ň	. 4	OF JUL	en and	Concen material Concen material Child Cegulato Cegulato Cegulato	ON THEIR	0.50 1.3 0.00 0.00 0.00 0.15 mail 0.15 mail 0.15 mail	0 14 21 28 0	(f) 15-2069 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) green material: 306 days
15-2116-03 France Europe, South F 2015	Winter Wheat/ Arezzo	1) 28.10.2014 2) 07.05.2015 - 15.05.2015 - 07.07.2015 - 07.07.2015	02 ¹	301 02 c t 0 c 2 0 0 0 1	25. 0 ^f 7. 10 6 100 5 100 5		DUITION DUITION DUITION	Green material	69 20 72 123 123 177 83 10 1 2 9 10 1 9	0.48 0.39 0.38 0.20	0 7 14 21 28	(f) 15-2116 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) green material: 307 days
These two trials	were conde	ted in side-by-s	identots	s at the s	ame loca	tion. K.		<i>y</i> .				
F 2015 15-2116-03 France Europe, South F 2015 These two trials - (a) Accordi - (b) Only if - (c) Year m - (d) Days af - (e) Remark information - (f) Study r - (g) Formula - (g) Formula	ing to CODEX (Sa relevant ust be interated ter as Papplication Smay include Or tion which are the ference tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the tion which are the ti	sification/Guide sification/Guide aboel pre-harosterinte matic conditions; Refer lites are included field	CT CT	D D D D D D D D D D D D D D D D D D D	AP 101 Br Mile Bd and		- (h) - (i) - (j) - (k) - (l) - * - ** - #	Application method Method informatic LOQ Method validation Storage (max) prior to last treatme residue in control no data available	d on ent			



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage at sampling	Residues (mg/kg)	PHA (days)	egitme ° Details on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) 00		e ^{\$} .		Qualyte 1 BCS-QN88460		ED ^{TE} (e)
15-2069-04 Spain Europe, South F 2015	Durum Wheat/Vitron	1) 12.01.2015 2) 10.04.2015 – 20.04.2015 3) 01.06.2015 – 30.06.2015	75 OCUI	300 102	25 28 EV 2014	16.042043	and and	seaw 10	85,10,2 89,000,000,000,000,000,000,000,000,000,0	9.66 0.67 0.01 0.01 0.67 0.01 0.67 0.01		(f) 15-2069 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 242 days green material: 337 days grain: 241 days
15-2116-04 Spain Europe, South F 2015	Durum Wheat/ Euroduro	1) 05.02.20 (5) 2) 23.0 (2015 – 01.05 2015 3) 01.06.2015 – 30.06.2015		t tight vinen			95 44	Green moterial Green moterial Cann Straw	12 73 83 6 89 89 89 89	$2.2 \\ 1.6 \\ 0.97 \\ 0.74 \\ 0.78 \\ < 0.01 \\ 1.9 $	0 7 14 21 28 51 51	(f) 15-2116 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 264 days green material: 323 days grain: 264 days





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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage at sampling	Oinou Residues (mg/kg)	PHA (days)	egitroe and and a setails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) 000	27 02 2 2 2 2 2	e ^{\$}	arties.	Qnalyte 1 D BCS-OV88460		ED ^{LO} (c)
15-2119-01 France (Languedoc Roussillon) Europe, South F 2015	Wheat/ P22R58	1) 29.10.2014 2) 23.04.2015 – 30.04.2015 3) 03.07.2015	66	RED ^É		29.043043 0 F jt B 0 F gjj C D	29 JUL	Grain ULA Service	69 0.0 27 83 10 10 10 10 10 10 10 10 10 10	<u>14</u>	0 44 21 29 65 65	(f) 15-2119 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 340 days green material: 398 days grain: 333 days
15-2119-02 Spain (Albacete) Europe, South F 2015	Wheat/Sarina	1) 20.02.2015 2) May 2015 3) June 2015		E E E E E E E E E E E E E E E E E E E		1010	DUTT	Green material	69 0 75 77 77 77 89 89	$ \begin{array}{c} 1.1 \\ 0.28 \\ 0.17 \\ 0.16 \\ 0.19 \\ \underline{<0.01} \\ 0.33 \end{array} $	0 7 14 21 28 40 40	(f) 15-2119 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 344 days green material: 377 days grain: 337 days

These two trials were not conducted in side-by-side plots. They are independent trials. In the trials 15-2119 02, the temperature temporarily increased above -18°C during storage but this did not affect the integrity of the samples. This deviation was considered acceptable. For further details see Appendix 8 of the respective report + 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100



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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	lication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion and sed	Growth stage at sampling	QLQ Residues (mg/kg)	PHA Cays)	eginthe Jud Octails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) per				BCS-ON88460		EOF (e)
15-2119-03 Portugal (Ribatejo) Europe, South F 2015	Wheat/ Valbona	1) 12.12.2014 2) May 2015 3) June 2015	CUI	LED ^E	9202A		2.5 J.L.C.	Grain J. J. Constraints	69 001 77 77 101 89 001 89 001 101 101 101 101 101 101 10	$\begin{array}{c} & & & & & & \\ & & & & & & & \\ & & & & $	13	<ul> <li>(f) 15-2119</li> <li>(g) EC (250 g/L)</li> <li>(h) Spraying</li> <li>(i) 01475</li> <li>(j) 0.01 mg/kg</li> <li>(k) Method Validation Data in 01475 and study 15-2069</li> <li>(l) straw: 355 days green material: 389 days grain: 348 days</li> </ul>
15-2119-04 Italy Europe, South F 2015 These two trials	Durum Wheat/Duilio	2) 07.05.2015- 12.05.2015- 3) 15.06.2015- 30.06.2015			222-32-0-5- -5- -5- -5- -5- -5- -5- -5- -5- -5	EQUIS	ANC OWN	Areen material Arean material Grain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain Arain	69 04 75 77 89 89 89	$2.5  0.79  1.1  0.84  1.1  \leq 0.01 1.8$	0 7 14 20 28 38 38 38	(f) 15-2119 (g) EC (250 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 354 days green material: 385 days grain: 347 days

In the trial 15-2119-03, the temperature temporarily increased above -18°C during storage but this did not affect the integrity of the samples. This deviation was considered acceptable. For further details see Appendix 8 of the respective port.
(a) According to CODEX substitution, Guide
(b) Application method
(c) Year must be indicated
(d) Days after by piptication to be pre-have thinterval, PBL underline)
(e) Remark sharp include of matic conditions. Reference to analytical method and information which reference
(f) Study reference
(g) greenhouse
(g) greenhouse
(h) Application
(h) Application method
(h) Application method
(h) Application to be pre-have thinterval, PBL underline)
(h) Application method
(h) Application method
(h) LOQ
(h) Method information
(h) Study reference
(h) Study reference
(h) Study reference
(h) Application to be an application of the sample to analytical method and information thick reference
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Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Арр	olication ra treatmen		Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Growth stage at sampling	QIDO Residues (mg/kg)	PH <del>I</del>	egil Me Betails on trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c) 00 ⁰⁰	20 12 12 12 12 12 12 12 12 12 12 12 12 12			Qnalyte 1 BCS-ON88460		EOTC (e)
16-2054-01 Italy Europe, South F 2015		1)30.12.2015 2)10.04.2016 - 20.04.2016 3) 01.06.2016 - 30.06.2016	75	dl ^{or}	18.8 29 2027 2027	15.04 3046	692 J. D. C.	Grain VI at C Server Control of C		$\begin{array}{c} 1.2 \\ 0.48 \\ 0.46 \\ 0.70 \\ \underline{< 0.01} \\ < 0.01$	21 28 49	(f) 16-2054 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 283 days green material: 332 days grain: 278 days
16-2054-02 Spain Europe, South F 2015		1) 19.01 2018 2) 1004 2016 - 21.04 2016 3) 01.06.2016 - 30.06.2016	75 02 2 2 2 2 2 2 2 2 2	300 tO t 1911 t 1911		for star	69 JE L	Green material	71 77 85 89 89	$ \begin{array}{r} 1.7\\ 1.2\\ 0.89\\ 0.22\\ 0.21\\ \underline{< 0.01}\\ \underline{1.3}\\ \end{array} $	0 7 14 21 28 49 49	(f) 16-2054 (g) EC (150 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2069 (l) straw: 277 days green material: 326 days grain: 272 days

These two trials were not conducted in side by side plots. They are independent trials.

* samples transported temporarily above -18°C. This deviation was considered acceptable. For further details see Appendix 8 of the respective report.
(a) According to CODEX transitication / Guide
(b) Only if relevant
(c) Year must be initiated
(d) Days after gas application of bel pre-hape writterval, PB, anderline)
(e) Remarks may include Commatic conditions. Reference to analytical method and information which pretatolites are included
(f) Study reference
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(h) Application at available

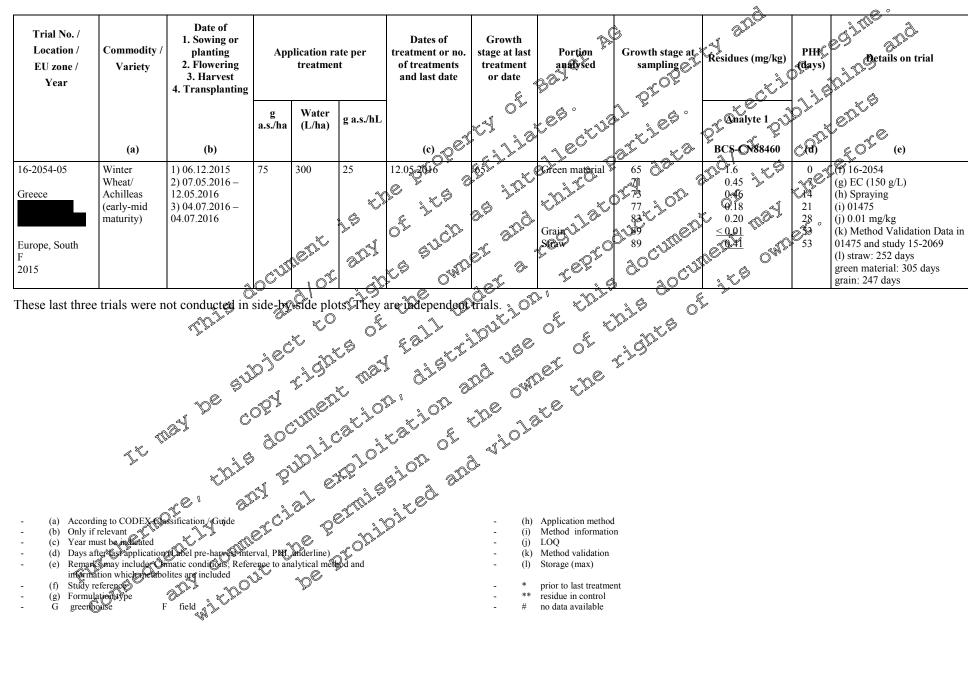
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9.101 J.L.J. Date of Trial No. / 1. Sowing or Dates of Growth Details on trial 2 Location / Commodity / Growth stage at РН₫ planting Application rate per treatment or no. stage at last Portion Residues (mg/kg) an ay sed sampling 2. Flowering (days) treatment of treatments treatment EU zone / Variety わるう 10¹ 3. Harvest and last date or date Year 4. Transplanting OF Onalyte 1 Water g g a.s./hL 'P (L/ha) a.s./ha BCS-0788460 LE Or CR) ¢0% (a) **(b)** (e) 9.9 jt^s 50°1.7 j.n.t.¢ 16-2054-03 Winter 1)16.11.2015 75 300 25 en material ALT 16-2054 65 0 N^e 1.3 (g) EC (150 g/L) Wheat/ 2) 10.05.2016 -1.5 Ø.78 France Calabro 16.05.2016 (h) Spraying £) ISA I' 3) 25.06.2015 -Grain J. J. C. 21 (i) 01475 J.L.J. 21 28 28 28 28 -25 1 gootiner Ĝ 0.91 30.06.2016 \$JJCH (j) 0.01 mg/kg 0.91 <u>< 0.01</u> he²⁴ (k) Method Validation Data in Europe, South TEBION 01475 and study 15-2069 - 90 CUM (1) straw: 259 days, 2015 Dr t ^B green material: 304 days, WELO Creen margin grain: 254 days 1255 7:05.001+ Ì 1.1 16-2054-04 1) 19.10.2015 °75 69 71 (f) 16-2054 Winter 0 S. 2) 10.05.2016-Õ Wheat/ 0.51 6 (g) EC (150 g/L) 10[£] *°' OF I (a) According to CODEX constitution (Guide Constitution)
 (b) According to CODEX constitution (Guide Constitution)
 (c) According to CoDEX constitution)
 (c) 17.05 **201**6 3) 05.07.2016 -France Orgrain 0.27 14 (h) Spraying 0.23 21 (i) 01475 28 0.14 (j) 0.01 mg/kg 52 (k) Method Validation Data in < 0.01 0.22 52 01475 and study 15-2069 (1) straw: 248 days, green material: 300 days, grain: 243 days

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### Comparison of the wheat results for the three formulations tested

Since residues in grain at harvest are often <0.01 mg/kg, the comparison of the results for the different formulations used was done using the results in straw at harvest. The data sets 1, 2 and 3 were so compared to each other's using the statistical tests: Kruskal-Wallis H-Test and Mann-Whitney U-test,  $\alpha = 0.05$ . The same approach was done for the data sets 4, 5 and 6.

				1	
Dataset 1	Dataset 2	Dataset 3	Datas 🔁 4	Dataset 5	
EC050 EUN	EC150 EUN	EC250 EUN	EC050 EUS	EC150 EUS	<b>EC250 EUS</b>
0.94	0.84	0.38	LO L	1.9 ° Č	1.4 0 0
1.7	1.2	3.6 《	0.71	Q.87 Q	0.33
0.074	0.12	3.3		×1.9 × 5	2.3
0.43	0.82	1.5	No Q	1,6	Q.8 2 ~ ~
	0.19			AV.3 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	
	0.054		\$ \$ \$		
	0.40			022 Č	
	0.071			0.41 0	<u></u>
EUN: northern H		US: southern Ei	trope 🔊 🖑		

The results of these statistical tests indicate that the populations from the data sets 1, 2 and 3 are not significantly different from each other's. The same applies for the datasets 4, 5 and 6.

The residue data for the different formulations can thus be combined in the following table to establish MRLs. When trials were conducted in and by-side plots, the nighest residue level from the 2 plots was selected. The selected data are compiled in Table 6.6.2-7.

°	S .		×	a a	for wheat trials	
Table 6.3.2- 7:	Summary	of BCS-C	N88460 re	sidue data	for wheat trials	
(C)		, ×	A %	"0"		

Crop	Northern/ Southern field or glasshouse	STMR (a)	HR (b)
Wheat	Northern $02 \times 001$ $0$ $0$ $0$	< 0.01	< 0.01
Grain	Southern 11 ~0.010 0.0420 6	< 0.01	0.042
	Northern . @054; @071; 0.92; 0.16; 0.38; 0.40; 0.82; 0.94;	0.61	3.6
Straw	× 1.5; 1.7; 3.3; × 6 × ×		
	Southern 0.22, 0.33, 0.41; 0.27; 1.57.4; 1.6; 1.8; 1.9; 1.9;	1.5	2.4

(a) Supervised Trials Median Residue of the median residue level estimated on the basis of supervised trials relating to the critical GAP (b) Highest residue

The results of the statistical rests Kruskal-Wallis H-Test and Mann-Whitney U-test,  $\alpha = 0.05$  indicate that the straw residue data from northern Europe are not significantly different from the straw residue data in southern Europe.

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#### CA 6.4 **Feeding studies**

## **European dietary burden calculations**

BCS-CN88460 is sought for use on cereals which parts of this crop might be fed to livestock (grain, straw and by-products of grain).

The dietary burdens were therefore calculated for different groups of livestock as described in the OECD Guidance Document on Residues in Livestock (ENV/JM/MONQ(2013)8 dated of 04-Sep-2013) and using the Excel spreadsheet dated of 2017 available in the EU Commission website (pesticides mrl guidelines animal model 2017.xls).

Based on the proposed plant residue definition for risk assessment (BCS-CN88460 garent compound input values were derived from the residue data as summarised under CA 6.3.1 and 6.3.2 These inp data are summarized Table 6.4-1.

Table 6.4- 1:	Input residue data fo	r livestøck dietøry	burden calculations
---------------	-----------------------	---------------------	---------------------

Feed commodity	Median di	etary burden 🗸 🖉	Maximum dietary burden 🚔 🛛 🛴 °
	(mg/kg)	Comment ~	Maximum dietary burden A
Barley straw	0.29	STMR from N£SEU	34 HR from N+SEU
Oat straw			
Rye straw	0.29 Ö	STMR from N+SEC	3.6 S KR from H+SEN
Triticale straw	Q,		
Wheat straw	·¥	STMR from %+SEU	
Barley grain	0.00 %	STMR from SFSEU	9.01 STOAR from N+SEU
Oat grain	K G		
Rye grain	0.01	STAR from SEU	0.01 STMR from SEU
Triticale grain	.1		
Wheat grain 🔬			
Brewer's grain	0.007	STMR-P (0.01 x 0.67 a)	0.067 STMR-P (0.01 x 0.67 a)
Brewer's grain Distiller's grain Wheat gluten	, 0.03 <i>3</i> 0)	STMR-P (0.01 3.3 b)	Q.033 STMR-P (0.01 x 3.3 b)
Wheat gluten	0.011	STMR (0,0) x 1.15	Ø.011 STMR-P (0.01 x 1.1 °)
Wheat milled bo products	0.014	STMR-P (0,01 x 1.4 ° d)	0.014 STMR-P (0.01 x 1.4 ^{cd} )

SEL southern Europe NEU: northern @urop No SEUmorthermand southern Europe



			r			0
A using a la	exp	y burden ressed	Above	exp	ry burden oressed	Highest
Animals	5	/kg bw/d	0.004 mg		g/kg DM	contributing
	Median	Maximum	/kg bw	Median	Maximum #	🖓 commodifies 🖉
Cattle (Beef)	0.003	0.025	Yes	0.11	1.05	Barley straw
Cattle (Dairy)	0.004	0.041	Yes	0.11	1.05	Barley Straw
Sheep (Ram/Ewe)	0.007	0.070	Yes	<u>@</u> 20	2.49	Barley straw
Sheep (Lamb)	0.009	0.089	Yes	\$0.20	2.40 2.10	Barloy Straw
Swine (Breeding)	0.000	0.000	No 2	0.01	0.01.	Millet of Millet
Swine (Finishing)	0.000	0.000	No V	0.01	×9.01	Wheat Sypdt
Poultry (Broiler)	0.001	0.001	O _{No}		0.00	Distiller's Quain & dried o
Poultry (Layer)	0.003	0.029	Ye	0.05	<b>9.42</b>	Wheat waw
Poultry (Turkey)	0.001	0.001	K No C			Distriller's G

Table 6.4- 2:	Anticipated dietary burden for BCS-CN88460 residues based on EU residue data and
	OECD guideline

Livestock feeding studies were conducted on dairy cow and poultry hers. Multi-region livestock diet calculations were conducted in order to conduct the studies in a manner appropriate to the entire scope of BCS-CN88460 use, allowing data to be generated in a fashion such that, for animal welfare considerations, a low number of animals will be used, while yielding salid data to evaluate expected residue levels in all key animal tissues and products.

The test substance used in the feeding studies hould be representative of the residue in the feedstuffs. In the case of the new fungicide BCS-CN88460 by far the major part of the residue in plants is formed by parent compound BCS-CN88460.

Based on the results of the metabolism studies several compounds were measured in the feeding studies:

- In milk, eggs and all tissues free residues of BCS-CN88460 parent compound and its metabolites BCS-DC20298, BCS-CY26497, BCS-CY24819, BCS-DC22055 and BCS-CX99799 were individually determined.
- Additionally, the sum of BCS-DC20298 and its conjugate M20, and the sum of BCS-CY24813 and its conjugate M19 were determined in cow liver and kidney.
- Moreover, the sum of SCS-DC22055 and its conjugate M37 was determined in hen liver.
- In the following sections (CA 6.4.1 and 6.4.2), the study data will be presented.

	n v	2
Genera Fremark: 🕺 🗸 🔍		
In this summary section (64 6.4) the	e following codes	s will be used for the metabolites:
Name Of C	<u>Metah.No.</u>	<u>Standard "dossier name"</u>
BCS-DC20298	≫ M02♀́	BCS-CN88460-2-propanol
	M42	BCS-CN88460-carboxylic acid
BCS-CY24813 5 0 5	M01	BCS-CN88460-propanol
BCS-DC22055	M06	BCS-CN88460-desmethyl-propanol
BCS-CY24813 5 5 BCS-DC22055 4 5 BCS-DC22055 4 5 BCS-CX99799 6 5	M11	BCS-CN88460-desmethyl-carboxylic acid
	M20	BCS-CN88460-2-propanol-Gluc-A
	M19	BCS-CN88460-propanol-GlucA
	M37	BCS-CN88460-desmethyl-propanol-N-GlucA



## CA 6.4.1 Poultry

<b>Report:</b> Title: Report No.:	KCA 6.4.1/01; <b>100</b> ; <b>100</b> ; <b>100</b> ; E.; 2017; M-605909-01-1 BCS-CN88460: Feeding study with laying hens M-605909-01-1
Document No.:	
Guideline(s):	OECD Guidelines for the Testing of Chemicals
	OECD Guidelines for the Testing of Chemicals (Test Guideline 505 Residues in Livestock, adopted 2003-01-08) US: EPA Residue Chemistry Test Guidelines
	US: EPA Residue Chemistry Test Guidelines
	OCSDD 960 1000 Dealeround
	OCSPP 860.1480 Meat, milk, poultry and Egg 🔗 . 🖉 🕉 🖉
	OCSPP 860.1000 Background OCSPP 860.1480 Meat, milk, poultry and Egg EU: EU Directive EC 91/414, Appendix G, 7031/VI/95 rev. 4 Evestock feeding studies
	studies
Guideline deviation(s):	none a a a a a a a a a a a a a a a a a a a
GLP/GEP:	none yes

## I. Materials and Methods

#### Test system, dosing

After an acclimatization phase of about 3 weeks, forty two laying bens (*Gatlus gatlus domesticus*) were dosed orally, via gelatin capsules, for 28 consecutive days with BCS CN88600 at dose rates of 0 mg/kg bw/day (control; 2 subgroups, 6 hens); 0.03 mg/kg bw/day (1X EU dose group; 3 subgroups, 9 hens), 0.12 mg/kg bw/day (4X EU dose group; 3 subgroups, 2 hens) and 0.48 mg/kg bw/day (16X EU dose group; 3 subgroups, 9 hens). An additional group 16XE (3 subgroups, 9 hens) was dosed at the rate of 0.48 mg/kg bw/day for 28 consecutive days simultaneously with the animals from dose group 16X. Thereafter, dosing was stopped and the animals were kept alive for further 4, 7 or 14 days in order to investigate the deparation of residues of BCS-CN88400 in eggs and tissues after the end of dosing.

The exact amounts of test item to be administered daily to each ten were calculated weekly based on the body weight determined on the Thursday preceding the week of dosing (starting on Monday). Based on this procedure 5 batches of capsules were prepared for each animal (one batch per calendar week). C.E.R. groupe prepared a dosing solution for each dose level by dissolving the test item in methanol. Depending on the minal weight and dose group, a soluble volume of about 50 µL of the corresponding test item solution was pipetted into gelatine capsules filled with cellulose powder to absorb the solven and prevent soaking of the capsule itself. The capsule was then left open for minimum 30 min to allow the solvent to evaporate and after that it was closed. The capsules and the dosing solutions were stored in a fridge at 2°C to +8°C at the animal unit of the in-life test site until use. The BCS-CN88460 content of the dosing solutions and capsules was verified by the residue analytical team at BAG-CS-HS RA directly after preparation and at appropriate intervals during and at the end of their storage at C.E.R.. The analyses were conducted using method 01511 (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (1990) (

The hens were fed with ton-supplemented commercial laying hen meal (Avi Pondeuse Farine, 88+/-1% dry matter) The feed was screened for residues of BCS-CN88460 with an LOQ of 0.01 mg/kg according to method 01475 (2016; M-558986-01-1; referenced in MCA 4 Point 4.1.2). The amount of feed consumed was monitored daily. The hens were allowed *ad libitum* access to tap water. The dose that employed in the study are summarized below in Table 6.4.1-1.



			Dose l	evels 🖉 🏷
Dose groups	Sub-groups	Number of hens	per animal	evels
			(mg/kg bw/day)	(mg/kg DMO)
control	A1, A2	6	0	
1X dose	B1, B2, B3	9	0.03 🔊	0.530 \$
4X dose	C1, C2, C3	9	0.12	2,119 2,5
16X dose	D1, D2, D3	9	0.48	× 698 ×
16XE dose	E1, E2, E3	9 🐐	0.48	© 8.140 ° ©
DM: dry matter	<u>.</u>	C		

#### Table 6.4.1-1: Summary of actual BCS-CN88460 dose administration.

*: Actual dose based on average feed consumption data collected from the study

The hens were dosed daily during 28 consecutive days via capsules given per os in the mornings fust prior to the feeding period. The control animal received a placebo (empty capsule) concurrently with the treated animals.

#### Sampling

For the purpose of this study, a "Study Day" period was defined from morning inspection, feeding and watering to sampling of eggs on the following morning. The changeover to the following study day Ô took place after sampling of eggs \$1 N

Eggs were collected thrice before the first dosing at least every third day during the first three weeks of dosage and twice during the last week of dosage. Egg samples for the deparation dose group E were collected once before the dosing phase and then at least twice again starting on the last week of the dosing phase again until the final slaughtering.

The eggs were collected in the evening and the following morning, if available. The eggs were shipped on the same day to the sample preparation and logistic lab (PVPL) at Bayer AG - Crop Science . Upon arrival at PVTL, all eggs of each sub-group were mixed (without Division, shell), chopped with gry-ice and stored at <u></u>≤-18°© until malysis.

The eggs samples collected on the overall study day 30 or dosing from the 0X (sub-group A2) and from the VoX group anymals were separated into yok and egg white.

On the day after the final dosing (less than thours after the final dose), the hens were weighed, anaesthetized with an electric shock followed by immediate exsanguination by decapitation.

Liver (entire organ), muscle (approximate) equalsized preces of leg and breast, trimmed of adherent connective fissue and fat and fat with adhering skip (overlaying skin with subcutaneous fat and abdominal fat) were taken for analysis. The tissue samples (refrigerated with dry ice) were shipped to PVTL within 24 h of sampling. Upon arrival at PVTL the tissue samples were chopped together with dry ice by means of a meat chopper and stored at 2-18°C until analysis.

Twelve hens (3 from the control group and 90 rom the 16XE group) entered into a 14-day depuration phase, following the administration of the final dose. Egg and tissue samples were collected on study days 35, 38, and 45 for analysis.

### Analysis

Tissues and eggs samples were analyzed for free residues of BCS-CN88460 and its metabolites BCS-DC20298, BCS-CX26497, BCS-CY24813, BCS-DC22055 and BCS-CX99799 by high performance liquid chromatography-electrospray ionization / tandem mass spectrometry (HPLC-MS/MS Of sing isotopically labeled internal standards. The analyses were conducted according to the ; 2017; M-599206-01-1; referenced in MCA method 01511( · Section 4 under Point 4.1.2).



In addition the sum of BCS-DC22055 and its conjugate M37 was determined in liver, after a hydrolysis step, according to the method 01511 ( ; 2017; M-599206-01-1; referenced in MCA Section 4 under Point 4.1.2). Ø)

The method 01511 was validated prior to sample analysis in a separate study ( : 2017; M-599206-01-1; referenced in MCA Section @ under Point 4.1.2). Concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance. The Limit of Quantitation (LOQ) for BCS-CN88460 and its metabolites BCS-DC20298, BCS-CY26497, BCS-CY24813, BCS-DC22055 and BCS-CX99799 was 0.01 mg/kg per analyte expressed as BCS-CN88460 in all the matrices. The LOQ for the support of BCS-D@22055 and its conjugate M37 in liver was 0.01 mg/kg expressed as BCS-CN88460.

## II. Endings

## Dose verification and storage stability

The dosing solutions for the preparation of the capsules of the different batches were analyzed for BCS-CN88460 in order to determine the content and homogeneity as well is the storage stability of BCS-CN88460 for the duration of use in-life phase of the study. The dose preparation was accurate and the capsules were shown to be stable over the course of the study

## Analysis of feedstuff

No residues of BCS-CN88460 were found above the LOQ (0.61 mg/kg) in the feedstuff. Concurrent recoveries were in the acceptable range of 70, \$10% with Relative Standard Deviations RSDs <20% (see Table 6.4.1-2).

## *In-life observations*

Feed consumption body weights and egg production were not adversel affected by treatment with BCS-CN88460. The appearance and the behavior of all birds were observed once daily throughout the study. Nothing special was observed Hens were healthy during the whole study.

## Analysis of eggs and tissues

The mean values of the confirment recovery rates per compound, sample material, and spiking level were in the range of 70-1 10%, with relative standard deviations <20%. In few cases the recovery means were slightly above 110%, or the RSO was slightly above 20%. Nevertheless, the obtained results were considered accessable since they meet the oriteria laid down in the OECD Guidance document on pesticide residue analytical methods ENV/M/MONO(2007)17. Details of recovery data are shown in Table 6.4.1-2 to Table 6.40-8.

The control samples of eggs and tissues were analyzed concurrently with the treated samples. The residues of BCS-CN88460 and its metabolities were below the respective LOQ of 0.01 mg/kg in all the Ŵ control samples.

In the eggs samples, no tree cosidues of BCS-CN88460, BCS-DC20298, BCS-CY26497, BCSDC22055 and BCS-CX 9799 were found above the LOQ of 0.01 mg/kg at any dose. Quantifiable residues above the POQ (001 mg/kg) were only found for BCS-CY24813 of the highest dose group 16X and JOXE. The highest residue level of BCS-CY24813 in eggs was 0.020 mg/kg. The plateau concentration in eggs was reached after approximately 9-11 days.

The exps samples collected on the overall study day 30 of dosing from the 16X group animals were separated by centrifugation into egg white and yolk. Both, the yolk and the egg white samples did not contain any residues of BCS-CN88460 or its metabolites above the LOQ (0.01 mg/kg).

The residues found in the eggs samples are summarized in Table 6.4.1-9 and the results for egg white and yolk in Table 6.4.1-10. For the calculation of the mean residues, in case one or two individual



values are >LOQ and the others < LOQ, it was deemed appropriate to consider residues <0.01 mg/kgas being equal to 0.01 mg/kg. This approach differs from what is reported in the study.

In the fat with adhering skin and muscle samples at all doses, free residues of BCS-CN88460 and its metabolites BCS-DC20298, BCS-CY26497, BCS-CY24813, BCS-DC22055 and BCS-CX9979 were found below the LOQ of 0.01 mg/kg.

In the liver samples at all doses, free residues of BCS-CN88460 and its metabolites BCS-DC20298 BCS-CY24813 and BCS-DC22055 were found below the LOQ of 0.01 mg/kg.

Free residues of BCS-CY26497 and BCS-CX99799 reached levels of up to 0.040 mg/kg and 0.04 mg/kg, respectively, in the samples from the 16X group Residues for the sum of BCS-DC22055 and its conjugate M37 reached levels of up to 0.079 mg/kg/jn the sample of the 16X group.

Overall residues of BCS-CN88460 were not quantifiable in eggs and tissues. The free residues of BCS-CY26497, BCS-CY24813 and BCS-CX9999 as well as free and conjugated BC9DC22955 ly with the dose level of BCS-CN88466 quantified in eggs and liver were found to increase li

After a depuration phase of 4, 7 and 14 days all measured residues of BCS-CN88460 and rits metabolites had declined to below the LQO of 0:00 mg/kg in eggs and tissues

Detailed results on the residue levels dound in tissues are summarized in Table 6.4 2 11. For the calculation of the mean residues, in cases one or two individual values are LOQU and the others < LOQ, it was deemed appropriate to consider residues <0.0 mg/kg/as being equal to 001 mg/kg. This approach differs from what is reported in the study.

All the analyses were conducted within less than 30 days after somple collection and the samples that were not analyzed within 24 h of sampling were stored deep frozen until analyses

Ø

Ő III. Conclusions  $\bigcirc$ 

O A feeding study was conducted with BCS-CN88466 on poultry in order to elucidate the levels of relevant residues in poulty tissues and in eggs,"

BCS-CN88460 was administered ofally (via capsule) to aying thens for 28 consecutive days at average dose rates of 0.03 mg/kg bw/d (12 EU dose), X 2 mg/kg bw/d (4X and 0.48 mg/kg bw/d (16X). Feed consumption, body weights, and egg production were not adversely affected by compound administration.

Prior to sacrifice, residues in eggs were measured at various intervals. After the final dose, the animals were sacrificed and the key edible tissues were analyzed for the free residues of BCS-CN88460 and its metabolites BGS-DC20298, BCS-CC26497, BCS-CY24873, BCS-DC22055 and BCS-CX99799 in all matrices. In addition, the sum of BCS-DC2205, and its conjugate M37 was determined in liver.

Overall, free residues of BCS-20188660 paront, BCS-DC20298 and BCS-DC22055 were below the LOQ in Sigs and tissues for all doses. Residues of BCS-CY26497, BCS-CY24813 and BCS-CX99799 as well as the sum at BCS DC22055 and its conjugate M37, increase line by with the dose level of BCS-CN88460. In the eggs, residues above the LOQ of 0.01 mg/kg were only found for BCS-CY24813 in the samples from the lightst dose group of 16X (maximum 0.02 mg/kg). The plateau concentration eggs was reached after approximately 9-11 days.

After a depuration phase of 4,7 and 14 days, all measured residues of BCS-CN88460 and its metabolities had declined to bolow the LOQ of 0.01 mg/kg in eggs and tissues.

The residue data provided in this study are suitable for regulatory purposes.

Æ,



Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]
	0.01	106, 104, 105, 95	103	4.9	
feed	0.10	105, 104, 107, 106	106	1.2	چر 0.01
		Overall recovery (n = 8)	104	3.6	
	0.01	94; 96; 97; 98; 99; 99; 100; 100; 100; 100; 100; 101; 102; 102;103; 104; 105; 106; 107; 107; 108; 108; 112; 114; 115; 117; 118	404 04		
hen / egg (complete)	0.10	91; 99; 99; 99; 100; 101; 101; 102; 102; 102; 103; 102; 103; 103; 103; 103; 104; 104; 105; 105; 105; 106; 107; 108; 10; 118; 113;			
		Overallirecove@ (n = \$4)	, 104 _C	5.D	
	0.01	99; 101; 405; 114 °	\$105°	<b>%</b> 9.4	
hen / egg whit**e	0.10	Q 92; <b>99</b> ; 100; 103		<b>4.7</b>	0.01
		Överall recovery (n = 8)	<b>0</b> 702 ~	Ċ,	0.01
	0.01	2 (05; 112; 113; 416 )	× 112	0 ^{4.2}	· ¥
hen / egg yolk**	0.10 🦿	× [*] 102;d+04; 105; 109 [*]	¹ 195	2.80	0.01
	, Ôg	Overall recovery (n = 8)	~\\$108_`*	<b>Å</b> \$\$6	
	0.01	103; 103 105; 107; 116 ·	10%	5.1	
hen / fat	~0.10 O			-	0.01
nen / Iat	§ 1.67	\$90; <u>21;</u> 93; <u>95</u>	<u>92</u>	1.6	0.01
	ð	Qyerall recovery (n = 10)	× 101	8.4	
õ	$\mathcal{S}_{0.01}$	106; 110, 114	<i>Q</i> 110	3.6	
	040		Ø-	-	0.01
hendliver	<u></u> ريم	93;9D V C	94	-	0.01
	9 4	S Overall recovery (n≠ 6)	105	8.2	
ţ,	g 01	§ 106; 110; 110; 112; 113; 18	112*	3.6	
hen / musche	0.10	101 ⁰ 104; 107; 108 ⁰	105	3.0	0.01
Å	ð,	Overall recovery (@ = 10)	109	4.4	

#### Table 6.4.1-2: Concurrent recovery data for BCS-CN88460 in feedstuff and poultry matrices

FL = Fortification level, RSD = Relative standard deviation, EQ = Practical limit of quantificationFortified with BCS-CN88460, determined as BCS-CN88460 and calculated as BCS-CN88460These recoveries were performed during the conduct of the study 17-8002.

 These average recoveries are considered acceptable according to OECD Guidance document on pesticide residue analytical methods ENV/04/MONG(20070)⁷. Besides, there were found no residues above the LOQ (0.01 mg/kg) these matrices
 Forthese recoveries external control material (Raiffeisenmarkt) has been used *

**



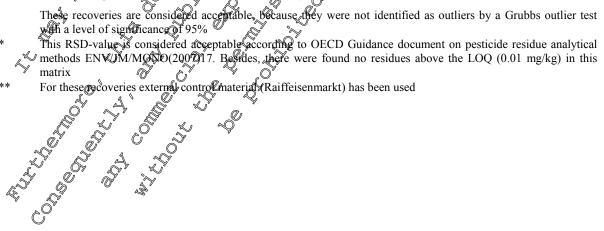
Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg
	0.01	77; 83; 85; 87; 89; 91; 92; 93; 97; 98; 100; 100; 101; 102; 106; 107; 108; 110; 111; 112; 117; 124*; 125*; 126*; 127*; 129*; 136*	105	\$ 15.0	
hen / egg (complete)	0.10	82; 84; 90; 91; 91; 92; 96; 96; 97; 101; 103; 103; 104; 105; 105; 105; 106; 106; 110; 110; 111; 114; 114; 115; 116; 117; 125*	403 4		
		Overall recovery (n = 54)	[∞] 104° 2 °~92 ∞	12.8	
	0.01	75; 96; 98; 99	^~y92 .@	<u>ملک</u> لا ،	K ² , Ş
hen / egg white***	0.10	89; 93, 99; 106	27 97 J	\$7.7	¥ ∞ .01
white		Overall recov ay (n = 8)	, 94 _@	9. <b>S</b>	
	0.01	\$4; 107; ¥08; 113 2	× 106 °	<b>7</b> .7	
hen / egg yolk***	0.10	Q98; 104; 110 ¥14		6.6	
		Overal recovery (n = 8)	<b>3706</b> 8		K ²
	0.01	Q \$9; 70; \$9; 98; \$92	Å 86 Å	018.0	Y
	0.10 🦼			- 08	
hen / fat	1.0	<b>5</b> 9; 90; <b>2</b> 4; 102	~\$ ⁹⁴	× \$23	0.01
		A Overall recovery (n = 10)	91 ^(V)	\$14.4	
	Q0.01 0	83:121*:024* V O	^م ر 109	20.9**	
hen / liver	§ 0.1 <b>6</b> /		L - O	-	
	<u>A</u> 10	× × × × × ×	× 96	-	0.01
		Overall recovery (n 6)	<b>@104</b>	15.8	
°~∕?	0.01	× 79; 105; 106, 109; 112; 1280	Ø 107	14.9	
hen muscle	<u>م</u>	102; 102; 100; 104 × ×	103	0.9	0.01
Â	9° 4'	<b>Overall recovery</b> ( $\mathbf{p} \neq 10$ )	105	11.4	

#### Table 6.4.1- 3: Concurrent recovery data for BCS-DC20298 in poultry matrices

FL = Fortification level, RSD + Relative standard deviation, LQQ = Practical limit of quantification Fortified with BCS-DC20228, determined as BCS-DC20298 and calculated as BCS-CN88460

These recoveries were performed during the conduct of the study 15-8002.

- These recoveries are considered acceptable, because they were not identified as outliers by a Grubbs outlier test with a level of significance of 95% *
- **
- ***



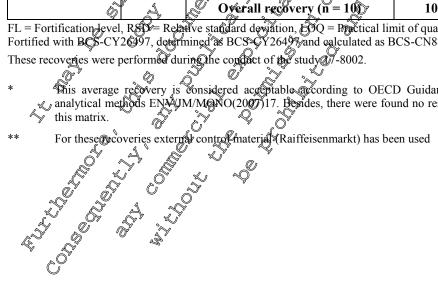


Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]
	0.01	93; 94; 94; 95; 95; 96; 97; 97; 97; 98; 98; 98; 99; 101; 102; 103; 104; 105; 106; 106; 107; 107; 108; 109; 111; 111; 116	102	6.1	
hen / egg (complete)	0.10	93; 94; 94; 96; 96; 97; 98; 99; 99; 99; 101; 101; 102; 102; 102; 103; 103; 103; 103; 103; 105; 408; 108; 109; 111; 112	9102 Q 6		
		Overall recovery (n = 53)	<b>,</b> ¥02	5,0	
	0.01	108; 118; 110; 194	111*	2.3	Y V
hen / egg white**	0.10	90 <u>;</u> 99; 104 10	0 10r	8.45	20.01 ×
		Overati recovery (n = 8)	A106 O	√7,4	
	0.01	406; k07; 108; 10 ~	0 108	© 1.6 Q	Ő
hen / egg yolk**	0.10	98,99; 100; 107	AP01 5	4.6	0.01
		^Q Overall receivery (n= 8) 5	⁰ 104 0	4.4	∼>
	0.01 *		<b>103</b>	8.4	
	0.10			Į.	
hen / fat	1.0	\$ 95; <b>9</b> 5; 98; <b>9</b> 8	^{\$\$} 97	1.8	0.01
	Z F	Overall recovery (n = 10)	× \$101	7.6	
Å	0.0 t	Q102; 112; 115 Q	110	6.2	
Ô	0,10	$\sqrt[4]{12}$		-	
hen / liver O	\$1.0 0	O & 98; 184 O 2	101	-	0.01
<u>,</u> Ø	*0* ·~	Overall recovery $(\mathbf{n} = 6)_{Q_i}$	a 107	6.3	
L.S.	<u>.</u> 0.01	102; 103; 105; 10 ³ ; 113; 113	× 107	4.5	
hen / muscle	0.10	96 ⁹ 101;193;107	101	5.8	0.01
	4	Overall recovery (n = 100	105	5.6	

#### Table 6.4.1- 4: Concurrent recovery data for BCS-CY26497 in poultry matrices

FL = Fortification level, RSP = Relative standard deviation, BOQ = Practical limit of quantification Fortified with BCS-CY26497, determined as BCS-CY26497, and calculated as BCS-CN88460

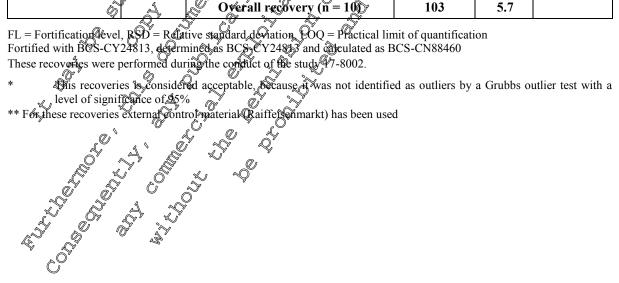
This average recovery is considered acceptable according to OECD Guidance document on pesticide residue analytical methods ENAJM/MONO(2007)17. Berides, there were found no residues above the LOQ (0.01 mg/kg) this matrix.





Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [©] () [mg/kg]
	0.01	86; 89; 95; 95; 97; 97; 98; 98; 98; 99; 99; 100; 102; 103; 103; 103; 106; 106; 107; 107; 108; 108; 111; 116; 119; 119; 127*	104	8.9	
hen / egg (complete)	0.10	89; 94; 94; 96; 96; 98; 98; 99; 100; 100; 100; 100; 101; 101; 102; 102; 102; 103; 103; 103; 103; 405; 105; 106; 107; 107; 108	€ € 101 € *		
		Overall recovery (n = 54)	<b>~</b> 402	×_7,2	
	0.01	91; 106 10; 148	106	£10.7 [°]	Y V
hen / egg white**	0.10	99; 102; 103, 109	0 103	4.6	.01 × °
		Overal recovery (n = 8)	A105 0	<i>"</i> ],7	
	0.01	402; 10 ³ , 107, 113	0 106	¢ 4.7 Ş	Ő
hen / egg yolk**	0.10	105 105; 108; 111	<u>م</u> م	2, <b>U</b>	× 0.01
		Overall receivery (n= 8)	L ^O 107 O	3.6	×
	0.01 🔌		× 103	° 5.00 €	
	0.10	~ ~ 110 ~ ~ ~	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ġ.	
hen / fat	1.0/	\$92; 9 <b>5</b> 795; 10 \$	× 96 S	3.9	0.01
	22	Overall recovery (n = 10)	× \$191 >>	6.3	
	0.0 t	S	109	7.4	
Ô	 	K NO5 N S	Ø "Ş	-	
hen / liver	\$1.0 O	0 4 98; kg2 & 2	<i>1</i> 00	-	0.01
, Q	* v	Overall recovery (n = 6)	a 105	6.4	
Ê. Î	<u>6</u> .01 ĉ	<b>\$6</b> ; 99; 99; 104; <b>\$05;</b> 11	103	7.3	
[«] ≫ hen / muscle ∝	0.10	96 ⁹ 102; 104; 106 A	103	2.9	0.01
Ő	ř "A	Overall recovery (n = 100	103	5.7	

#### Table 6.4.1- 5: Concurrent recovery data for BCS-CY24813 in poultry matrices





Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOO [mg:Ag]
	0.01	79; 83; 83; 86; 87; 93; 94; 95; 96; 98; 98; 101; 102; 104; 107; 107; 108; 109; 109; 112; 112; 113; 117; 118; 120; 123**; 123**	103	12.3	
hen / egg (complete)	0.10	89; 90; 90; 91; 94; 97; 98; 99; 99; 101; 101; 103; 103; 103; 105; 105; 105; 106; 106; 107; 409; 109; 114; 121**; 126**, 130**	2 3104		
		Overall recovery (n = 54)	<b>, 4</b> 03	14.9	
	0.01	102; 104; 105; 103°	106	Å.6	$\gamma$ $\psi$
hen / egg white***	0.10	91, 98; 98 ⁻⁴ 04	Ô ÔS	5.4%	.01 ~ °
white		Overall recovery (n=8)	Å102 Ô [°]	6.3	
	0.01	<b>6</b> ; 107, 112, 112	0 10%	© 7.1 Ç	Ŏ
hen / egg yolk***	0.10	101,702; 107; 110	1014 Š	3.0	¢ 0.01
		Overall recevery (@= 8)	⁰ 1050	3.5	*
	0.01	× × × × × × × × × × × × × × × × × × ×	104	° 9.4° ≶	
	0.10	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	2° 2°2°	Ø	
hen / fat	1.6	96; 995 V02; 104	× 100 ×	3.5	0.01
	2 K	Overall recovery (n = 19)	× 9101 ×	8.0	
	Ø 0.0}	\$ ~\$7; 105; \$25**\$ Q	109	13.2	
l 2	<u>_</u> Q 90	× × 103 × ×		-	
hen / liver	A1.0 0	O & 86; 89 D 2	88	-	0.01
5. Q	10 × 1	Overall recovery (1)=6)	a 101	13.9-	
<u>j</u>	<b>0</b> .01 ê	106 108; 109; 116 112; <b>12</b> 0	× 111*	4.4	
[«] ≫ hen / muscle ∝	0.10 ×	\$ 96, 98; 100; 100 A	101	5.4	0.01
Ĩ,	ř "A	Overall recovery (n = 100)	107	6.6	

#### Table 6.4.1- 6: Concurrent recovery data for BCS-DC22055 in poultry matrices



Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	
	0.01	74; 76; 80; 80; 89; 93; 93; 93; 94; 95; 95; 97; 98; 100; 100; 100; 103; 104; 105; 106; 107; 110; 111; 112; 116; 116; 128**	99	12.8	
hen / egg (complete)	0.10	75; 81; 82; 85; 91; 91; 94; 95; 96; 96; 97; 98; 99; 99; 101; 101; 101; 101; 102; 103; 104; 405; 108; 109; 110; 121**	\$ 98 \$ \$	29.9 29.9 29.9	
		Overall recovery (n = 54)	. <b>`</b> ØŠ	14.4	
	0.01	97; 10 <b>8</b> 113; 144	108	§7.2 [°]	y w
hen / egg	0.10	87; 92; 98; ¥12	° òr	11	<u><u></u></u>
white***		Overall recovery (n= 8)	0 ³ 103 ⁵ 0 ³	<b>310.2</b>	
	0.01	0103; 199; 11; 123*5	r 192* 5	7.0	<u>_</u> @
hen / egg yolk***	0.10	Q [*] 95; 96;99; 100, S [*]	0 98 0	Q.4	≫ 0.01
	~	• Overall recovery (n = 8)	Q 105	مي 9.0 مي	
	0.01 🔦	َ هُرِ 89:@\$; 97:497; 115 هُ	\$99 . Q	9.9	
	0.10		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		
hen / fat	<u>≪</u> ].0 4	\$, <b>0</b> 87, <b>8</b> 9; 91, <b>0</b> 7	× Q ⁹¹ ×	9 4.7	0.01
		Overall recovery (n = 10)	096 ☆	8.3	
2	Q.99	87:93;97 5	Q 92	5.5	
hen / live	Ø.10 O	0 6 1176 B	- 	-	
	0 1.0	93,96 g	\$ 95	-	0.01
		Qeverall recovery (n = 6)	y 97	10.6	
	<u>کُر0.01</u>	400; 105 103; 197; 108; 119 X	107	6.3	
hen / muscle	0,10	296; <u>9</u> 7997; 109 ~	100	6.2	0.01
 		Overall recovery (n = 49)	104	6.8	

#### Table 6.4.1-7: Concurrent recovery data for BCS-CX99799 in poultry matrices

** These recoveries are considered acceptable because they were not identified as outliers by a Grubbs outlier test with a level of significance of 95%



Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]	
	0.01	103; 111; 122*	112**	8.5		
	0.10	115	- 0	-		
hen / liver	1.0	75; 85	80	112** × 8.5 - · · · · · · · · · · · · · · · · · · ·		
		Overall recovery (n = 🚱	102	17,9		
FL = Fortification level Fortified with BCS-DC These recoveries were p * This recovery of significanc ** These averag analytical me	RSD = Relat 22055, determ performed dur is considered e of 95% e recoveries a thods ENV/JN	Overall recovery (n = 9 tive standard deviation, LOQ = Practical lin nined as free and conjugated pCS-DC2205 ing the conduct of the study 17-8002 acceptable, because it was not identified a pre considered acceptable according to OE A/MONO(2007)17.	nit of quantificati 5 and calculated a southers by a Gr of Guidence do	on on son S-CN4 wbbs outlier coment on on on on on on on on		

## Table 6.4.1- 8: Concurrent recovery data for free and conjugated BCS-DC22055 in poultry matrices



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Group	Compliandor *		BCS-DC22055	egine and			
Dose	Sampling day *	BCS-CN88460	BCS-DC20298	DCS C006407	o       BCS-CY24813 o	BCS-DC22055	BCS-CX9979
	Pre-dosing -19	< 0.01	< 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	$\frac{1}{2} \frac{1}{2} \frac{1}$		€ ² <b>≤@</b> 01
	Pre-dosing -12	< 0.01	< 0.01	¢\$0.01	0.01		<pre>0.01</pre>
	Pre-dosing -5	< 0.01	< 0.01 [°] ***0.01	2 50.01 2 < 0.01	$\frac{1}{2} = \frac{1}{2} = \frac{1}$	\$0.01	< 0.01
	1	< 0.01	¥0.01 5 °	\$ 0.01 E		0 ¹ < 0.01	< 0.01
	3	< 0.01	> < 60År		$\frac{1}{2} \frac{1}{2} \frac{1}$	O [™] < 0.01 [™] 0.01 ° [™] °	< 0.01
1X	4	< 0.0 1	0.01 SV	- 1 - 0 01 A	10 < 0.0C Ullu	2 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	< 0.01
0.03 mg/kg bw/d	8	Č0.01 . S	<u>00.01</u>	₩ ^{6,2} < 0.01 ×		م <del>ال</del> ال	< 0.01
.530 mg/kg DM	9	<u> </u>		$\sqrt{2} < 0^{0}$		× < 0.01	< 0.01
Sub-groups:	11 Think	< 0.01 💖	\$ 0.01 . 1	. A& 0.01	× × 0.01 G	< 0.01	< 0.01
B1, B2, B3	14	.< <u>0</u> 0			all all the	< 0.01	< 0.01
	16				< 0.01	< 0.01	< 0.01
	21				× 0.01	< 0.01	< 0.01
	23	COE<0.00100	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	* D < 0.01 2 -	< 0.01	< 0.01	< 0.01
	29	@0.01 \\$	\$0.01	₹ <b>0</b> .01	< 0.01	< 0.01	< 0.01
E UIL	21 23 29 Thermore 1 thermore 1 thermo	any Put es	EP & Giole Correction of the contract of the c	a Al			



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						and	
Group	Sampling day *			Residue levels of indiv Mean of 3 sub-groups	iduat analytes (mg/kg) (individual values) ***	4 <u>~</u> ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	egir and
Dose	Sumpling unj	BCS-CN88460	BCS-DC20298	BCS-CY26497		PCS DC2205	BCS-CX99799
	Pre-dosing -19	< 0.01	< 0.01	< 0.01	< 0.07	«Ö01 »	£0.01
	Pre-dosing -12	< 0.01	< 0.01	0.01 °	<u></u> 0.01 €\$ °	0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01	م آ ² < 0.01
	Pre-dosing -5	< 0.01	< 0.01	<0.01 <0.01 e ² <0.01 e ² <0.01 e ² <0.01 e ² <0.01 e ² <0.01		0.01 a0 ⁵	\$0.01
	2	< 0.01	< 0.01 ~ (0)		₹ <u>₹</u>		د 0.01 × 0.01
	3	< 0.01			\$0.01 ()	20.01 x D	< 0.01
4X	4	< 0.01		0.01 × × × ×	2 (0.00)2 2 (0.01) 2 (0.	02 (0.1)	< 0.01
0.12 mg/kg bw/d	8	< 0.01		2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	$\frac{2^{t}}{2^{t}} < 0.00^{t}$	<0.01 <0.01 <0.01 <0.01	< 0.01
2.119 mg/kg DM	9		<u> </u>	<0.01 00 ² < 0.03		< 0.01	< 0.01
Sub-groups:	11		0.01	▲ 🔊 <b>0</b> 01	2 2 < 0 0 A		< 0.01
C1, C2, C3	14	~20.00 1 - -20.01	<u> </u>		10-1-10-010 	< 0.01	< 0.01
	16	< 0.01				< 0.01	< 0.01
	21	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	\$0.01 S		√<20.01	< 0.01	< 0.01
	23	6 ⁰⁰ < 0.0 <b>1</b>			< 0.01	< 0.01	< 0.01
	30 50	0.01	× 50.01 . 5		< 0.01	< 0.01	< 0.01
	ROSI	Contraction	ALL ALL	E The Olde			
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Group	Sampling day *			<b>Residue levels of in</b> Mean of 3 sub-gro	ndividuat analytes (mg/kg) pups_(individual values) ****	A La r	.egilme .
Dose	Sumpling uny	BCS-CN88460	BCS-DC20298	BCS-CY26497	BCS CV24813	BCS DC22455	808-CX99799
	Pre-dosing -19	< 0.01	< 0.01	< 0.04		~01 » §	§0.01
	Pre-dosing -12	< 0.01	< 0.01	€ 0.01 €		C < 0.00	a 1 × 0 01
	Pre-dosing -5	< 0.01		<0.01 c \$ 0.01 c \$ 0.01		<u> </u>	<0.01 c ² < 0.01
	3	< 0.01	< 0.01	6 × 0 01 0 ×	$\sqrt{2} < 0.01$	<u>0.01 ~ 2.0</u>	ر © ¹ < 0.01
	4	< 0.01			$\frac{1}{\sqrt{2}} = \frac{1}{\sqrt{2}} = 1$	~ <0.01 × D	< 0.01
16X	8	< 0.01	<u>&lt; 0.01</u>	2 ⁵ <0.01		60.d1	< 0.01
0.48 mg/kg bw/d	9	< 0.01			(< 0.01, < 0.01, 0.15)		< 0.01
8.698 mg/kg DM	11		20.01 2001 2001 2001	1 ( ) - O	(0.014; 0.012; < @ 01)	 ↓\$\$<0.01	< 0.01
Sub-groups: D1, D2, D3	14			$\sqrt{2} = \frac{1}{2} = \frac{1}{2}$		< 0.01	< 0.01
, ,	16 The	< 0.01		10 ¹	0.01; <b>0.020; 0.013</b> )	< 0.01	< 0.01
	21	<0.01 0.01 0.01	10001 3 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5		<b>0.012</b> (<0.01; <b>0.017</b> ;< 0.01)	< 0.01	< 0.01
	23	\$0.01 5 ¹ 0.01	× <u>50.01</u>	$0.91^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{\text{M}^{M}^{M}^{\text{M}^{1}^{\text{M}^{1}^{\text{M}^{1}^{M}^{M}^{1}^{M}^{M}^{1}}}}}}}}}}$	<pre> &lt; 0.01</pre>	< 0.01	< 0.01
	31 00 1	CO + OUL			<0.01 (< 0.01; < 0.01; < 0.01)	< 0.01	< 0.01
EUII EUII	21 23 31 Dev JE Chermore ' there of the of t	ils Puble any Puble and the pe	AP 101 100 0				



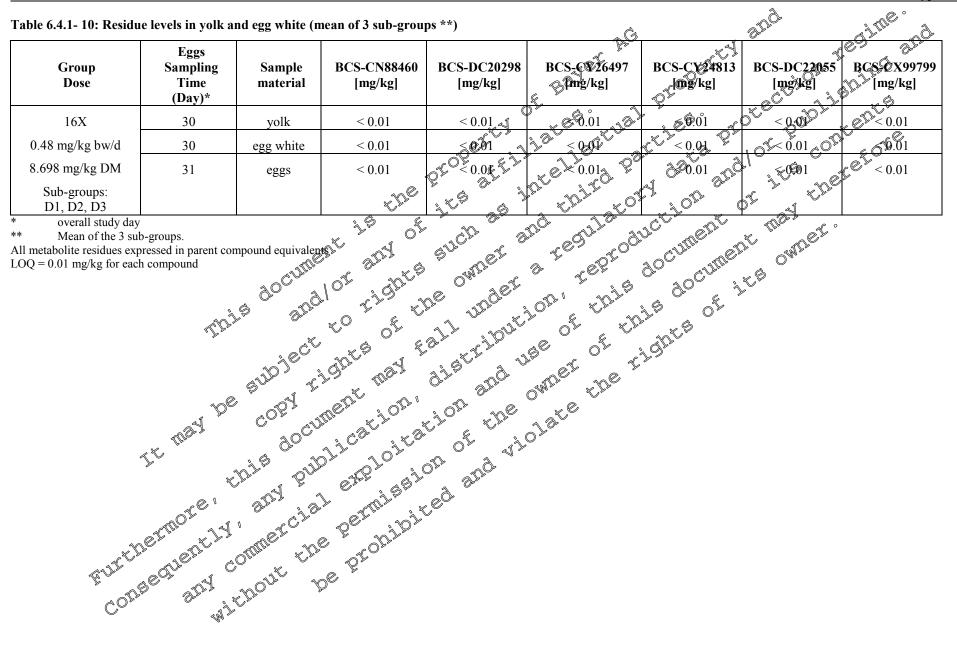
Group	Sampling day *			Residue levels of in Mean of 3 sub-gro	ndividual analytes (mg/kg) ups (individual values) ***	1 alla	egilme .
Dose	r say	BCS-CN88460	BCS-DC20298	BCS-CY26497	BCS-CY24813	BCS-DC22655	808-CX99799
	Pre-dosing -19	< 0.01	< 0.01	< 0.01	< 0.00 %	0.01	€0.01
	Pre-dosing -12	< 0.01	< 0.01	× 0.01 €	° 0.01 0°	0.00 [°] < 0.00 [°]	CL < 0.01
	Pre-dosing -5	< 0.01	< 0.01	2 - Q. Q. Q. Q.	active solution of		\$0.01
16XE	21	< 0.01	< 0.01010		<b>0.010</b> <b>0.011</b> ; <0.01	0.1 5001 C	< 0.01
depuration group 0.48 mg/kg bw/d	23	< 0.01	5 - 0.01 J	0.0 × 0.01	<b>0.011</b> <b>0.011</b> <b>0.013</b> <b>0.01</b>		< 0.01
8.140 mg/kg DM	31	0.06105 00<0.06105	ant 0.01 500		$0^{\circ} < 0.01, 10^{\circ}$	20 ² < 890	< 0.01
Sub-groups: E1, E2, E3	35 4d depuration	0.00×0.00			\$ < 0.01 0 \$ \$ < 0.01 0 \$ \$ 0.01; < 0.01 \$	<u>ن</u> المعرفة (0.01	< 0.01
	38 The state	< 0.01****	\$.01*** \$		(p.a.; < 0.00 0.01)	< 0.01***	< 0.01***
	45 14d depuration	JD 0.01****	100.01*****	0.01**** 0.01****	\$0.01**** \$0.01****	< 0.01****	< 0.01****

Mean of the 3 sub-groups calculated based of the unrounded residue sults. For the calculation of the nector residues, in case one or two individual values are >LOQ and the others < LOQ, **

** Mean of the 3 sub-groups calculated based on the unrounded residue residue is the calculation of the mean residues, in case one or two in it was deemed appropriate to consider residues <0.00 mg/kg as being equat to 0.01 mg/kg. This approach differention what is reported in the study. *** Mean value of 2 sub-groups since only one sub-group 16XE remained abive on overall study day 45 n.a. not applicable All metabolite residues expressed in parent compound equivalents LOQ = 0.01 mg/kg for each compound with the probability of the probabili



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T.L. ( 4 1	11. D			<b>4</b> •					_	pd.	jine °
<b>Fable 6.4.1-</b>	11: Kesia	ue levels i	n poultry	tissues				ŝ	Ô	6 ¹	17 and
							Res	sidue levels (mg/	kg) ** 🔬		- Orgen
	Dose	Dose	Sub-	Sampling		BCS-DC20298	a	1 [©] ^b	et	Sultavi	
Group	(mg/kg	(mg/kd	group	Time	BCS-CN88460	BCS-DC20298	BCS-CY26499	BCS-CY24813	BCS-DC22055	BCS DC22055	BCS-CX99799
	bw/d)	DM)	group	(Day)*	[mg/kg]	[mg/kg]	mg∉kg [	[mg/kg] ©	[mg/kg]	BCS DC22055	BCS-CX99799 mg/kg
Devilium Cod							KN XO				<u>KP</u>
Poultry fat			B1	29	< 0.01			@ ^C <0.01		NAO ^D	0.01
1 17	0.02	0.520	B1 B2	29		< 0.01 < 0.01		<u>~ ~ 0.01</u>	0.01 × 0.01	NA NA NA NA	<u> </u>
1X	0.03	0.530			< 0.01			< 0001	< 0.01		+ 0.01
			B3	29	< 0.01	<b>20.01</b>			< 0,0,0,0	NA C	< 0.01
				mean	< 0.01	<u>\$€01</u>	\$ < 0.01		0.04	¢ 11/1	< 0.01
	1	1		median	< 0.01					NA °	< 0.01
437	0.10		C1	30	< 0.04	0.01	5001	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	9.01	× ⊥y, 1	< 0.01
4X	0.12	2.119	C2	30	0.01	< 0.01	< 0.01		JIL = 0.01 D	NA NA	< 0.01
			C3	30	0.010 ^{11/11/1}	<u> </u>	< 0.01	e ² 0.01 20	< 0001	- 11/1	< 0.01
				meân		< <u>0.01</u>	< 0.01	€ 0.01			< 0.01
	1	1		median	<u> 1999</u> - 15	@< 0.01	D.C. < D.OI	<u> </u>	°	NA	< 0.01
			D1	30 🔊	< 0.01	5 × 0.01 Ju	<u>,</u> ≨19.01	< 0.01	-@.01	NA	< 0.01
16X	0.48	8.698	DE L	30	₩0.01 O	< 10.01	$0.01$ $0^3$	(. G(	×	NA	< 0.01
			D3	30		₹ € 0.01		0.01 0		NA	< 0.01
				mean		S. S	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	4 Ý	< 0.01	NA	< 0.01
	1	1		Swedian	$\sim < 0.01$	$\bigcirc < 0.01$	<u> </u>	<i>C</i> < 0.01	< 0.01	NA	< 0.01
16XE			Ele	35	< 6,01	0.01	< 0.01	***< 0.01	< 0.01	NA	< 0.01
depuration	0.48	8.140	EZ EZ	<u>C</u> 385	0.01	* < <u>\$0</u> ,01	~0.01 ×		< 0.01	NA	< 0.01
asparation			▶⊐ E3	45		0.01 C	< 0.01	< 0.01	< 0.01	NA	< 0.01
		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		05°		\$~ O*	J.L.				
			~	12	WO - Ju	10 ¹¹	<u>)</u>				
			K.		Clark	agil a Bibe					
			. C, 1	alle	1 al						
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	an 12.V		° c ^c) ^{6.} (
	TE .	6°Y	A	a other	NOC .	<0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0.01 <0					
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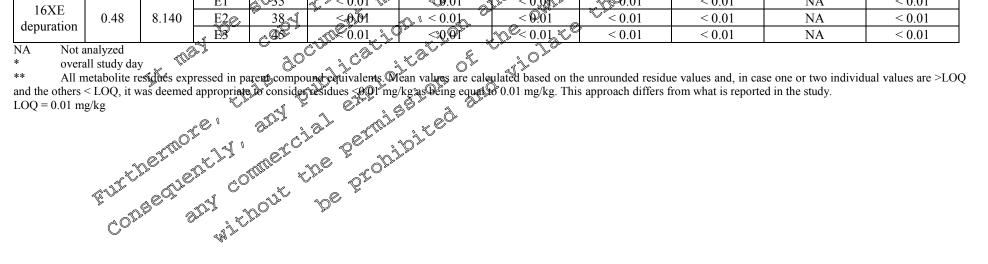
Document MCA – Section 6: Residues in or on treated products, food and feed Isoflucypram

		1								- 8-	ju ^e .
							Re	sidue levels (mg/	kg) **	Ch.	1 TON
Group	Dose (mg/kg bw/d)	Dose (mg/kd DM)	Sub- group	Sampling Time (Day)*	BCS-CN88460 [mg/kg]	BCS-DC20298 [mg/kg]	[mg/kg]	BCS-CY24813 [mg/kg]	BCS-DC22055	Sum of BCS-DC22055 and M37	BGS-CX99799
Poultry live	r		1	•					s' av	$\frac{\sqrt{mg/kg}}{\sqrt{0.01}}$	0 ^{t 9}
			B1	29	< 0.01	< 0.01	K < 0.01 K	10.9		~~~00l ~√	≥ €0.01
1X	0.03	0.530	B2	29	< 0.01	< 0.01		C<0.01	80.01	$\sim < 0.00$	0.01
			B3	29	< 0.01	< Q: Q? >>	E & & 0.01	< 0.001	0.01	& 0.01	< 0.01
	•		•	mean	< 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		<u> </u>	<i>∂</i> •0.01	\$\$0.01	< 0.01
				median	< 0.01	\$ \$ 01	» < 0.0M	69.01	<u> </u>	<i>₩</i> ₹0.01	< 0.01
			C1	30	< 0.01	< 0.01	0.015	\$ \$.0.01 ×	> < 0.01	0.012	0.045
4X	0.12	2.119	C2	30	< 0.0	0.01	0.012	J < 0.01 J. C.	9.01	0.921 °	0.023
			C3	30	0.01	< 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	[≥] ≲001°	JIC = 0.01 D	0.015	0.010
				mean	D < 0:01	< 0.00	@0.012	0.00° < 0.00°	11 0.01	0.016	0.026
				median	< 0.0 <i>1</i> ≈	0.01 <0.01	0.012		20 ^C < 9.00	0.015	0.023
			D1	030	3 < 0.01	% .01	0.040	0.01	⁰ < 0¢01 ^m	0.053	0.097
16X	0.48	8.698	D2	30 🔊	× < Q.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0,035	< 0.01	√0 .01	0.059	0.11
			TD3 ^{11.}	30	<u>₩0.01</u>	<0.0t	్ర ^{్ర} 0.019 O ²	< 0.01	×	0.079	0.061
				mean	9 .01	$0.00^{\circ} < 0.00^{\circ}$	¢*69:031	0 ⁵ < 0.05	< 0.01	0.064	0.089
	r	•	r	median	<u> </u>	₩ <u>\$</u> \$0.01	0.035	\$0.01	< 0.01	0.059	0.097
16XE			E1	JU35	[®] ≥ € 0.01 T	OP.01	0.010 < 0.010	0.01	< 0.01	< 0.01	< 0.01
depuration	0.48	8.140	E2@	<u> </u>	<u></u>	1 < 0.01	< 9.01	[™] < 0.01	< 0.01	< 0.01	< 0.01
deputation			ÊŠ	<u>C</u>	0.01	<u> </u>	0.01 5	< 0.01	< 0.01	< 0.01	< 0.01
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							Dog	idue levels (mg/	la) **	<u>.</u>	100° 2
	Dose	Dose		Sampling			N	inde levels (ing/	kg) ····	Sum of C	Aller - The
Group	(mg/kg	(mg/kd	Sub-	Time		BCS-DC20298	BCS-CV26497	R6S-CV24813	BCS-DC22055	BCS-DC22055	B68-CX99799
Group	bw/d)	DM)	group	(Day)*	[mg/kg]	[mg/kg]	[mg/kg]	[mg/kg]	[mg/kg]	and M37	1mg/kgl
		,			[8]	181		ی ا ت ہ - جا پ			
Poultry mu	scle						× ¹ < 0.01×°)° () F	r "\$°		Q ^{t 9}
			B1	29	< 0.01	< 0.01	0.01 < 0.01	\$\$\0.01 \$		VNA NA	<u>چ</u> 0.01
1X	0.03	0.530	B2	29	< 0.01	< 0.01		0.01°	<u>s</u> 0.01	NAO ^{de}	s 0 ^{\$} < 0.01
			B3	29	< 0.01	< 0:00 5	د لا الألك الألك الم	_<0@1	< 0.01 ℃		< 0 0 I
				mean	< 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		<u> </u>	Ø 0.01	NA NA	< 0.01
				median	< 0.01	© <i>≨</i> € 01	>> < 0.0to	59.01	< 0.0%		< 0.01
			C1	30	< 0.01		\$ < 0. <u>01</u>	<u>~ 8.0.01</u> ~ K	<0.01	NA NA	< 0.01
4X	0.12	2.119	C2	30	< 0.0	0.01		1	69.01	The NAC °	< 0.01
			C3	30	0.01	< 0,001	~ < 0.01 °	> ©01	JIII < 0.01 1	NA A	< 0.01
				mean	©©= <0:01	$3 \sim 0.00$		$\mathcal{O}^{\mathcal{O}} = \mathcal{O}^{\mathcal{O}}$	10.01 A	NA NA	< 0.01
	1			median		~ Ø .01	< 0.01	× م 0.01	30 < 0,00 ×		< 0.01
			D1	030	3 < 0.01 3	\$ \$.01	0.040 ¹	\$0.01	^{Os} < 0601 ^{ss}	NA	< 0.01
16X	0.48	8.698	D2	30 🔊	<u>مع جوار مع </u>	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	#.01	< 0.01	-9.01	NA	< 0.01
			دي گ	30	¥0.01 0	< 10.01	0.01 O	< 0.01	<u>کې < 0.01</u>	NA	< 0.01
					9 .01	§ 0 < 0.01	e ²⁰ .01	<u> </u>	× < 0.01	NA	< 0.01
	1			medign			~~~~ 0.0K	\$0.01	< 0.01	NA	< 0.01
16XE			E1	JU35	[™] < 0.01 m [™]	<u>09.01</u>	$0.0^{\circ} < 0.010^{\circ}$	0.01	< 0.01	NA	< 0.01
depuration	0.48	8.140	E2©	38 4	< 0.01	$0.0 \le 0.0$	< 9.01	***< 0.01	< 0.01	NA	< 0.01
1			Ē3	COS -	UTOR 0.01	<20.01	10 ⁶ <0.01 × ⁶	< 0.01	< 0.01	NA	< 0.01
NA Not a	analyzed		\$J			w Or Charles					





CA 6.4.2 Ruminants

Report:	KCA 6.4.2/01; ; 2017; M-604191-02-1
Title:	Amendment no. 1: BCS-CN88460: Feeding study with dairy sows
Report No.:	17-8001
Document No .:	M-604191-02-1 OECD Guidelines for the Testing of Chemicals
Guideline(s):	
	(Test Guideline 505 Residues in Livestock, adopted 2007-01-08)
	US: EPA Residue Chemistry Test Guidelines
	OCSPP 860 1000 Background Av and Av and Av and Av and Av and Av
	OCSPP 860.1480 Meat, milk, poultry and eggo
Guideline deviation(s):	none
GLP/GEP:	yes 4 6 5 2 2 2 2 2 2

I. Materials and Methods

Test system, dosing

After an acclimatization phase of about 3 weeks, eighteen healthy dairy oows (Polstein Frisian black) were dosed orally, via gelatine captules, for 28 consecutive days with BCS-CN88460 at dose rates of. 0 mg/kg bw/day (control, 3 cows) 0.05 mg/kg bw/day (1X dose group, 3 cows) 0.15 mg/kg bw/day (3X dose group, 3 cows), 0.5 mg/kg bw/day (0 X dose group , 3 cows) and 15 mg/kg bw/day (30X dose group, 3 cows). An additional group 50XE (3 cows) was dosed about a the rate of 19 mg/kg bw/day for 28 consecutive days simultaneously with the animals from dose group 30%. Thereafter, dosing was stopped and the animals were kept affect further 4, 7 or 14 days in order to investigate the depuration of residues of BCS CN88460 in milk and tissue after the end of dosing.

The exact amounts of test item to be administered daily to each cow were calculated based on the body weights measured at the beginning of the second week of the acelimatization period. Capsules were prepared at the test facility in the test term was weighed into capsules, which were then closed and placed in another slightly larger capsule adapted to the size of the bolus applicator. The prepared capsules were filled in bottles and handed over to Dr. Stephan Groeger (PI of in-life phase) At the in-the test site the capsules were stored at ambient temperature in the dark. A representative number of capsules, were analyzed using method 01511 (1997); 199206-01-11, referenced in MCA Section 4 under Point 4.1.2) after preparation to verify the amount of technical BCS-CN38460. Further capsules were analysed 41 days after the final administration to determine the stability of the test them during the in-life phase.

The cows were fed with a combination of cob prix and feed concentrate for dairy cattle, which were supplemented with minerals (Cobs mixture) prepared by AGRO-COBS, batch 10350000301216 (Prepared by AGROBS Gmble) Angerbreite 27, 82541 Münsing-Degerndorf, Germany). The feed was screened for residues of BCS-CN88460 with an LOQ of 0.01 mg/kg (expressed as BCS-CN88460) according to method 01475 (2016; Xt-558986-01-1; referenced in MCA 4 Point 4.1.2). The amount of feed consumed was monitored daity. The cows were allowed *ad libitum* access to tap water. The dose rates employed in the study are stramarized below in Table 6.4.2- 1.



		Dose levels					
Dose groups	Number of cows	per animal	in feed				
		(mg/kg bw/day)	(mg/kg DM) *				
Control (0X)	3	0	0 🖉				
1X dose	3	0.05	1.61				
3X dose	3	0.15	4.18				
10X dose	3	0.5	15.54				
30X dose	3	1.5 _0	48,19				
30XE dose	3	1.5	4013				
DM: dry matter			°0*				

Table 6.4.2-1: Summary of actual BCS-CN88460 dose administration.

Actual dose based on average feed consumption data geliected from the fudy

h every ever ncurrent The cows were dosed daily during 28 consecutive days via capsules asing a pill con every every after feeding and milking. The control animal received a placebo (an empty capsure) concurrently with the treated animals.

Sampling

38, 10X, 30X and 30XE were taken twice before Milk samples of the animals of the groups 0X, IX, the 1st application, at least every third ay during the first three weeks of dosage and wice during the last week of dosage. 1

The analytical samples per day consisted of about 1 of the evening much and 1 L of the morning milk. The analytical milk sample is then a mixture of both the exching and the morning milk sample, respecting the proportion of the produced milk quantity from the evening and morning. An aliquot was subjected to the residue analysis while the remainder was chopped with dry ice and stored at \leq - 18°C.

The milk samples collected on the overall straty day \$1 of the sing from the 0X (mimal H940) and from the 30X group animals were separated by centrifugation into whey (whey) and cream.

The diagnostic slaughtering of the animals took place on the day after the tonal application less than 24 hours after the final dose. The animals were terminated by stunding via a captive bolt gun followed immediately be exsanguination through severing the blood vessels of the neck. After termination, the animals were eviscerated and tissue samples were taken?

Kidneys Samples of liver (without sail bladder), perirenal fat, mesenteric fat, subcutaneous fat and muscle samples (right flank, right hind leg and right loin) were collected at necropsy. Tissue samples were cut in cubes @approximately 5 on edge length The liver was cut in cubes and a representative sample of approximately 500 & was taken thereafter. Kotneys were processed in the same way. Different muscle samples were pooled. Fai tissue samples were kept separately. All tissue samples were immediately weighed packed into plastic bags and transported to the analytical laboratory. Upon arrival at the laboratory facility the tissue samples, were chopped with dry ice. All samples were deepfrozen within 24h after sampling and stored at $\leq 18^{\circ}$ C until analysis. One portion of the fat samples was sent deep-frozen to

to determine the actual fat content.

The three dairy cows of the 30XE group were kept alive for 4 - 14 days after the last dosing in order to investigate the deputation of residues in milk and tissues. During the deputation phase milk was collected periodically. At sacrifice samples of liver, muscle, kidney and fat (perirenal, subcutaneous and mesenteric) were taken for analysis.

Tissues and milk samples were analyzed for free residues of BCS-CN88460 and its metabolites BCS-DC20298, BCS-CY26497, BCS-CY24813, BCS-DC22055 and BCS-CX99799 by high performance liquid chromatography-electrospray ionization / tandem mass spectrometry (HPLC-MS/MS) using isotopically labeled internal standards. The analyses were conducted according to the



method 01511(Section 4 under Point 4.1.2). ; 2017; M-599206-01-1; referenced in MCA

In addition the sum of BCS-DC20298 and its conjugate M20 and the sum of BCS-CY24813 and its conjugate M19 were determined in liver and kidney, after a hydrolysis step, according to the ; 2017; M-599206-04, i; referenced in MOA method 01511 (Section 4 under Point 4.1.2).

The method 01511 was validated prior to sample analysis in a separate study (

; 2017; M-599206-01-1; referenced in MCA Section 4 under Point 4.12). Concurrent recoveries were performed during sample analysis to demonstrate acceptable method performance. The Limit of Quantitation (LOQ) for BSS-CN88460 and its metabolites BQS-DC20298 BCS-CY26497, BCS-CY24813, BCS-DC22055 and BCS-CX99799 was 0.01 mg/kg per analyte expressed as BCS-CN88460 in all tissues and 0.005 mg/kg in milk, cream and whey. The LOQ for the sum of BCS-DC20298 and its conjugate M20 in liver and kinney was 0.01 mg/kg expressed as BCS-CN88460. The LOQ for the sum of BCS-Co2481 grand its conjugate 1019 in fiver and kidney was 0.01 mg/kg expressed as BCS-CN88460.

Dose verification and storage stability

Upon analysis by LC-MS/MS immediately after preparation the actual concentration of BCSCN88460 in the capsules ranged between 88% and 190% of the nominal content (average of 3 capsules per dose L^Q, m group), demonstrating an accurate preparation.

I. Findings

The stability of BCS-CN88460 in the capsules during storage for the time of the in-life phase was investigated by analyzing capsules stored at the m-life test site under the same conditions as the capsules administered to the cows. This malysis was performed 41 days after the preparation of the capsules (4 days after the final administration). The analysed set comprised 5 capsules of the 1X group and 5 capsules of the 20X group. The actual concentration of BESCN 88460 was 104% and 100% of the nominal content on the capsules of the 1X and 30 groups respectively. Therefore, the capsules were shown to be stable over the course of the study.

No residues of BCS @N88460 above the LOQ (0.01 mg/kg) were found in the feedstuff. Concurrent recoveries were in the acceptable range of 700110% with Relative Standard Deviations RSDs <20% (see Table 6.4.2-2).

L.

<u>In-life observatio</u>ns ©

° In general the feed consumption was higher during the dosing period compared to the predosing period. It is very unlikely that BCS-CN88460 did increase feed intake. It is more likely that cows were still adapting to the feeding and husbandy system when dosing started. The data given indicate that the mean calculated energy demand was not folly met by the feed consumed. But since cows were not ketotic (no findings in repeated physical examinations), milk yields were stable, and cows did not loose body weight in the coarse of the study it is concluded that energy supply was met adequately.

Analysis of milk, wilk products and tissues

The mean values of the concurrent recovery rates per compound, sample material, and spiking level were in the lange of 70. 140%, with relative standard deviations <20%. In few cases the recovery means were slightly above 110%, or the RSD was slightly above 20%. Nevertheless, the obtained results were considered acceptable according to the criteria laid down in the OECD Guidance document on pesticide residue analytical methods ENV/JM/MONO(2007)17. Details of recovery data are shown in Table 6.4.2- 2 to. Table 6.4.2- 9.



The control samples of milk and tissues were analyzed concurrently with the treated samples. The residues of BCS-CN88460 and its metabolites were below the respective LOQ of 0.005 mg/kg and 0.01 mg/kg of the control milk and tissue samples.

In the <u>milk samples</u>, quantifiable residues above the LOQ (0.005 mg/kg) were only found for BCS-CN88460 in the highest tested dose group (30X and 30XE). The highest residue level of BCS-CN88460 in milk was 0.013 mg/kg. The plateau concentration in milk was reached after approximately 9 days. No residues of metabolites above the LOQ of 0.005 mg/kg were found in any dose groups.

The milk samples collected on the overall study day 30 of dosing from the 30X group and mals were separated by centrifugation into <u>skim milk (whey) and cream</u>. The cream samples were found to contain up to 0.15 mg/kg of BCS-CN88460, 0.009 mg/kg of BCS-DC20298 and 0.005 mg/kg of BCS-CY24813 while the residues of BCS-CY26497, BCS-DC22055 and BCS-CX99799 were less than the LOQ of 0.005 mg/kg. The skim milk (whey) samples showed no residues of BCS-CN88460 or its metabolites above the LOQ of 0.005 mg/kg.

The residues found in the milk samples are summarized in Table 6.4.2-10 and the results for skim milk and cream in Table 6.4.2-11. For the calculation of the mean residues, in case one of two individual values are >LOQ and the others < LOQ it was deemed appropriate to consider residues <0.005 mg/kg as being equal to 0.005 mg/kg. This approach differs from what is reported in the study.

In <u>muscle</u>, no residues of BCS-CN28460 and its metabolites were found above the 1.00 of 0.01 mg/kg at any dose.

Free residues of BCS-DC26298, BCS-CS24813 and BCS-DC22055 at or above the LOQ of 0.01 mg/kg were not found in any of the tissue samples of any dose group S

The residues of BCS-CN88460 were found to be 0.01 mg/kg in the tissue somples of the 0X-, and 1X-groups. Residues of BCS-CN88460 above the LOQ were found in <u>perirenal fat</u> up to 0.087 mg/kg in the samples of the 3X, 10X, 303 and 30XE-group (H953; 5 days of depuration).

Residues of BCS CN88460 in <u>kidney</u> were only found in the 30X group up to 0.011 mg/kg. Residues of BCS-CN88460 in <u>lever</u> were only found in the 10X, 30X-group up to 0.02 mg/kg.

Residues of BCS-CY26497 were found to be $\sqrt[6]{0.01}$ mg/kg in the tissue samples of the 0X, 1X and 3X groups. Residues of BCS-CY26497 were found in <u>liver</u> op to 0.037 mg/kg only in the 30X group. Residues of BCS-CY26497 in <u>kidney</u> were found op to 0.074 mg/kg in the 10X and 30X group.

Residues of BCS-6X99799 were found to be 0.010 mg/kg in the tissue samples of the 0X, 1X, 3X and 10X groups. Residues of BCS-CX99799 were found in <u>liver</u> up to 0.014 mg/kg only in the 30X-group.

Residues of BCS-CX997 in kidney were found up to 0.023 mg/kg in the 30X-group.

The residues for the sum of BCS-DC20298 and N20 were found to be < 0.01 mg/kg in kidney at any dose and < 0.01 mg/kg in liver of the 0X 1X and 3X groups. The sum of BCS-DC20298 and M20 were found up to 0.091 mg/kg in liver in the 15X and 30X-groups.

The residues for the sum of BCS-CX24815 and its conjugate M19 were found to be $< 0.01 \text{ mg/kg in} \frac{\text{kidney}}{1000 \text{ kg}}$ of the 0X, 1X, 3X and 10% groups and $< 0.01 \text{ mg/kg} \frac{\text{in liver}}{1000 \text{ kg}}$ of the 0X and 1X groups. Free and conjugated residues of BCS-CY24813 were found up to 0.15 mg/kg in liver in the 3X, 10X and 30X-groups and pp to 0.016 mg/kg in kidney of the 30X-group.

Overall, residues of BCS-CN88460 above the LOQ were found only in milk, fat, kidney and liver. Residues of BCS-CY26497 and BCS-CX99799 were found only in kidney and liver and free and conjugated residues of BCS-DC20298 and BCS-CY24813 were found in liver and kidney. The free residues of BCS-CN88460, BCS-CY26497 and BCS-CX99799 as well as free and conjugated residues of BCS-DC20298 and BCS-CY24813 in fat, liver and kidney were found to increase limitation by with the dose level of BCS-CN88460.



After a depuration phase of 4 days, the measured residues of BCS-CN88460 had declined to below the LOQ of 0.005 mg/kg in milk and 0.01 mg/kg in tissues except for BCS-CN88460 in fat (0.014 mg/kg).

After a depuration phase of 7 and 14 days, all measured residues were found to be below their respective LOQ in all samples.

Detailed results on the residue levels found in tissues are summarized in Table 6.4.2- 14. For the calculation of the mean residues, in case one or two individual values are >LOQ and the others LOQ, it was deemed appropriate to consider residues <0.01 mg/kg as being equal to 0.09 mg/kg. This approach differs from what is reported in the study.

All the analyses were conducted within less than 30 days of sampling and the samples that were not a

III. Conclusions of cows in order to encidate the tovels of

A feeding study was conducted with BCS-CN88460 relevant residues in cow tissues and in milk.

ő BCS-CN88460 was administered orall Q via capsule to cover for 29 consecutive days at average dose rates of BCS-CN88460 at 0.05 mg/kg bw/day test them for the dose group 1X 0.15 mg/kg bw/day for the dose group 3X, 0.5 mg/kg bw/day for the dose group 1QX and 5.5 mg/kg bw/day for the dose groups 30X and 30XE. Feed consumption, birdy weights, and milk production were not adversely affected by compound administration L

Prior to sacrifice, residues in milk were measured at various intervals After the final dose, the animals were sacrificed and the key edible tissues were analyzed for the free residees of BOS-CN88460 and its metabolites BCS-DC20298, BCS-CY26497 CS-CY26497 BCS-DC22055 and BCS-CX99799 in all matrices. In addition the sum of BCS-DC20298 and its conjugate M2(and the sum of BCS-CY24813 and its conjugate M were determined in liver and kidney

Overall, residues of BCS-CN88460 above the LOQ were Yound only in milk, fat, kidney and liver. Residues of BOS-CY26497 and BOS-CX29799 were found only in kidney and liver and free and conjugated residues of BCS-DC20298 and BCS-CY24813 were found in liver and kidney. The free residues of BCS-CN88460, BCS-CY26797 and BCS-CX99709 as Well as free and conjugated residues of BCS DC20298 and BCS-CY2481S in fat, liver and kidney were found to increase live ly with the dose level of BCS-CN88460

Residues of BCS 2N88460 were found in mile samples only in the 30X and 30XE groups up to 0.013 mg/kg, in cream samples up to 0.15 mg/kg in the 30X-group. The plateau concentration in milk was reached after approximately 9 days

After a depuration phase of 4 days, the measured residues of BCS-CN88460 had declined to below the LOQ of 0005 mg/kg in milk and 0.01 mg/kg in tissues except for BCS-CN88460 in fat (0.014 mg/kg).

After a depuration phase of 7 and 14 days and measured residues were found to be below their respective LOQ in all samples.

The residue data provided in this study are suitable for regulatory purposes.

... Added in this s



Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOO [mg/kg]
Feedstuff / Cobs	0.01	88; 80; 97; 93	90	8.2	
mixture	0.10	97; 105; 102; 100	101	3.3	
		Overall recovery (n = 8)	95	8.5 ×	
Feedstuff / Dairy	0.01	97; 99; 96	Ø 7	1.6	
Cattle Concentrate	0.10	103; 101; 101 C	Ő 102	×J.1	
		Overall recovery (n = 6)	Q 1 <u>0</u> 0°	چ 2.7	
Feedstuff / Mineral	0.01	106; 98000	<u>401</u>	* <u>4</u> P	
feed	0.10	109;\$07; 1080	<i>≫</i> 108≪ĭ	£0.9 [°]	
		Overall recovery (n = 6)		10 100	à 4°
		91; 91; 92; 98; 95; 95, 96; 97, 98; 98;		*,	
		98; 98; 9 9; 100; 100; 100, 100; 100;			
	0.005	101, 92 ; 102 ; 102 ; 103 ; 103 ; 103 ; 103 ; 103 ; 103 ; 103 ; 103 ; 104 ; 1			, Čg
	0.005	No5; 105; 105; 105; 105; 107; 107; 107;			\approx
	~	@ 107; 107; 108; 409; 116; 141;	Q ^Y Ö		
cattle / milk	×	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$		- 0	0.005
	Z.	©2; 102; 103; 108, 106; 107; 107;		S.	
	×0.05 Å	108; 108; 108; 108; 108; 109; 109; 109; 109; 109; 110; 110; 00; 110, 10;	× 110 s.	3.2	
		400; 111; C42; 112; 112; 113;		,* <i>3.2</i>	
		· ↓ 1142 M4; 114; 115; 4Q3; 116	4		
Ű.	ð,	Overall recovers (n = 82)	× 140.5	5.7	
Č,	\$0.00\$	102; 102; 103; 406; 107, 108	<i>©</i> 105	2.5	
cattle / coopam	0,2,0	105;©10; 112 Q	© 109	3.3	0.005
E,		Overall recover (n = s)	106	3.3	
cattle / skim milk	9 [°] 0.00\$7		105	4.1	
(whey)	0405		108	4.0	0.005
		Overal recovery (n = 9)	106	4.2	
	0.0	Q03; 103 (109; 120)	109	7.4	
cattle / muscle	0 25		109	3.2	0.01
	A Ç	Overal recevery (n = 8)	109	5.3	
cattle / fat,	0,6	293; 95 ¥07; 118	103	11.2	
mesenteric	0.25	100 102 ; 103; 108	103	3.3	0.01
		Overall recovery (n = 8)	103	7.7	0.01
		ک 96; 96; 98; 101	98	2.4	
cathe/ fat, C	A.0.25	99; 101; 101; 104	101	2.0	0.01
S. O		Overall recovery (n = 8)	100	2.8	0.01

Table 6.4.2- 2: Concurrent recovery data for BCS-CN88460 in feedstuff and cattle matrices



Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]
cattle / fat,	0.01	93; 97; 101; 104	99	4.8	
subcutanenous	0.25	98; 100; 103; 106	102	3.4	20 1
		Overall recovery (n = 8)	100	4.2	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
	0.01	97; 100; 104; 105	102	3.6	
cattle / kidney	0.25	104; 105; 105; 108	106	1.6	\$97.01 A
		Overall recovery (n = 🕅	404	3.3	29.01 C
cattle / liver	0.01	96; 103; 106	⁰ 102	×5.0 (
	0.25	102; 103; 105-106	Q 1.04°	√ 1.8√	
		Overall recovery (n = 7)	× ~103	3,4	

Table 6.4.2- 3: Concurrent	recovery data	for BCS-D	20298 in	cattle	matrices

		Overall recovery (II – /)		3 14	s s
FL = Fortification level	I, RSD = Relat	ive standard deviation, LOO ⁽²⁾ Practical lin	nit of quantificati	ay a	Y N
Fortified with BCS-CN These recoveries were i	188460, determ	nined as BCS-CNSS460 and calculated as I ing the conduct of the stady 17-8601.	368-CN88460	10° 24	à 4
	periornieu uur		× A ô ^ş	, U	S N
			Ô' x Y	A X	
				S O	×.
Table 6.4.2- 3: Conc	current reco	very data for BCS-DC20298 in catt			Ĵ.
Sample material	FL	C Single Values (S)	Mean value [%]	RSD	[»] LOQ
Sample material	[mg/kg]			U	[mg/kg]
		624,63; 64; 63; 69; 73; 74; 75; 77; 79; 4		â	
		8 ⁽¹⁾ 90; 94, 94; 95; 66; 100; 100; 104;			
	0.005	105; 103; 105; 105; 106; 106; 107; 108; 10; 110; 110; 01; 115, 115;	104	21.7****	
	\$ 0	1 6 116; 1 20; 120; 121*; 128*; 129*;			
cattle / milk		33*; 136* ; 138*: 139*; Q 9*; 1 59 *	L. O		0.005
		70; 70; 73; 81; 8 3; 83; 8 3; 83; 88; 8	ý _x y		0.000
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~					
à	\$ 0.05¢	(4)01; 102; 103; 104; 104; 106; 106;	× ⁹⁷	15.6	
		107; 107; 119; 119; 119; 123*: 132*	N N		
1 de la companya de l	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Overathrecovery (n = 79)	101	19.8	
م م	0.005	\$ 107; 108; 109; 113; 145; 116	111*	3.4	
cattle / cream 🧳	0.20	S 106,107; 110	108	1.9	0.005
Ø	S YOS	• Overal recovery (n = 9)	110	3.4	
	0.005	96 Q7; 99; Q2; 104 006	101	4.0	
cattle / skiin milk (whey)	8,05	∑ © ⁷ 107 ₅ /111; 1¥6	111**	4.1	0.005
		Overal recovery (n = 9)	104	6.3	
		80;404;112	99	16.9	
cattle / muscle	0.25	81; <b>9</b> 3; 108; 108	98	13.4	0.01
Å	A' &	Overally recovery (n = 7)	98	13.6	
	0.00	65; 77; 93; 101	84	19.2	
cattle (fait, mesenteric 0	©25	91; 100; 101; 102	99	5.1	0.01
	A S	Overall recovery (n = 8)	91	14.8	
	0.01	93; 103; 110; 119	106	10.3	
cattle / fat perirenal	0.25	94; 100; 100; 106	100	4.9	0.01
Ô		Overall recovery (n = 8)	103	8.3	



Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg] _o
	0.01	79; 96; 104; 107	97	13.0	
cattle / fat, subcutaneous	0.25	96; 97; 108; 111	103	7.4	
		Overall recovery (n = 8)	100	<b>0</b> 10.2	
	0.01	114; 113; 96	108 💞	9.4	
cattle / kidney	0.25	93; 102; 98; 108	100	6.3 🔪 Ć	
		Overall recovery (n = 70)	163	8.16	
	0.01	82; 100; 112; 109	Q101	6.4	
cattle / liver	0.20	105; 102; 108; 102	L 104	2.8	
		Overall recovery (n = 8)	103°	9.0	

FL = Fortification level, RSD = Relative standard deviation, QOQ = Practical Junit of quantification Fortified with BCS-DC20298, determined as BCS-DC20298 and calculated as BCS-CN88469 0

These recoveries were performed during the conduct of the study 17-8001.

Ŷ * These recoveries are considered acceptable, because they were not identified as outliers by a stubbs officer test with a fevel Ô of significance of 95%. ð

** This average recovery is considered acceptable, because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only slightly exceeding the range and because it is only

 And a second seco *** This average recovery is considered acceptable, Decause there were found no restores of BCSDC20998 in this sample



Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	
		85; 90; 90; 92; 93; 93; 94; 94; 94; 97;			N O
		97; 97; 97; 98; 100; 101; 101; 101;		) )	
		102; 102; 102; 103; 104; 104; 105;	Ô	V.	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
	0.005	105; 105; 105; 106; 106; 106; 106;	103 🔊	7.7	
		107; 107; 107; 107; 107; 107; 107;	103	°~/	, 9' _N '
		108; 108; 111; 112; 114; 115, 116;	<u>n</u>	Ň	N N
cattle / milk		118; 125**	- A	, Ø	\$ 0.905
		96; 97; 99; 101; 102; 102; 104; 105;	<i>A</i>	õ 4	jo s
		105; 106; 106; 107; 107; 110; 110;	Q' b° é	5 4	
	0.05	110; 110; 110; 11(\$) 111; 112; 112;	\$09 ~	. 37	
		112; 112; 113; 43; 114@16; 116	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ð »	
		116; 110, 117; 124**		δ [°] .	
		Overatt recovery (n = 84)	× 4106 ~	7.9	
	0.005	104; 496; 107, 11; 116, 119	G11* 0*	\$8.4	
cattle / cream	0.20			6 5.5 Q	0005
		Overall recovery (n = 9)	102* \	5.8	ČA -
	0.005	Q.94; 105; 106; 106; 109; 110	9105 C	\$3.5	N.
cattle / skim milk	0.05		S 1090	© 6.1 /	[≫] 0.005
(whey)	~	Verallycecovery (n = 9)	e ^{ry} 1896	5.70	
	0.01	× 108, 109; 11; 1110	×10 ×	ða 4	
cattle / muscle	0:25	004; 11(\$100; 116	\$ 110°S	¥4.5	0.01
		$rac{1}{2}$ $rac{$	110	5 3.1	
	\$0.01	103; 103; 103; 108	- 104 L	2.4	
cattle / fat, mesenteric	0.25	. 5 .97; 100; 100; 108 . C	c 100 @	2.1	0.01
mesenteric		() Overall-cecovery (n = 8)	Ø 1 <b>92</b>	3.1	
	00.01	900 93; 94 98 x 5	\$ 95	2.5	
cattle / fat, perirenal	T 0.25	98; 99; 103; 107-Q	[©] 102	4.0	0.01
, Q	×.,	Querall redovery (n = 8)	Ø 98	5.1	
ja G	9.01	99; 101; 11, A11 , A	106	6.1	
cattle / fat, subcutaneous	مَنْ 0.25 مُ	× 98; 10¥; 112	102	7.7	0.01
	Q`.~	Qvorall recovery (Q= 8)	104	6.6	
Ő	6.01	§ @ 96,99;99;493 &	99	2.9	
cattle / kidne	0.25 0	259100: 419, 117	107	10.2	0.01
~Q		Overall recovery (n 8)	103	8.2	
A l	<u>0</u> 01	S 0, 99; 105; 110; 412	106	5.7	
cattle liver	×0.25	88,96; 190, 112	99	10.1	0.01
. «	N 1	Overall recovery (n = 8)	103	8.3	

#### Table 6.4.2- 4: Concurrent recovery data for BCS-CY26497 in cattle matrices

FL = Portification level, RSD Relative standard deviation, LOQ = Practical limit of quantification Fortified with BCS CY 26497, determined as BCS-CY 26497 and calculated as BCS-CN88460 These recoveries were performed during the conduct of the study 17-8001.

* These average recoveries are onside tod acceptable, because there were found no residues of BCS-CY26497 in the sample **,6** 0, 0, Ś material creat Ô

** These ecoveries are considered acceptable, because they were not identified as outliers by a Grubbs outlier test with a level of significance of 5%. 



Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg@kg]
		87; 87; 89; 95; 95; 97; 97; 97; 98; 99;		~	
		99; 99; 100; 100; 101; 101; 102; 103;		Ç,	
		103; 103; 103; 104; 104; 104; 105;		<b>P</b> *	
	0.005	106; 106; 107; 107; 107; 107; 108;	104	6.4	Õ S X
		108; 108; 108; 108; 108; 108; 108;		Ń	
		110; 110; 110; 111; 112; 112; 112;	Q,		\$ \$
cattle / milk		115; 116	L ^{O *}	Ň	Q 0.695 &
		88; 100; 101; 103; 103; 105; 105;		Å Å	
		105; 106; 106; 106; 206; 106; 106;		× [\] 0`	
	0.05	107; 107; 107; 109; 109; 109; 110; 5	×108 "	<u>Š</u> Š	°∼y 4°
		111; 111; 111; 🌒í; 112, 4Í3; 18,	à số	R' L	4 60
		114; 114; 16; 1180118; 18		, Oʻ	
		Overall recovery (n = 82)	~106 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	6,4	
cattle / skim milk	0.005	95098; 102, 105; 117, 112	× 1040	6.6	, O
(whey)	0.05			3.6	0.005
		Overall recevery (n 9)	× 104 ×	\$.6 L	**
	0.005	99;102;103;103;105;106	© [∞] _10&	2.4 0	1
cattle / cream	0.20	0 ¹ , 1020709 ¹⁰	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	496	0.005
	°∼y'	A Overall recovery (p = 9)	103	<b>3.0</b>	
	0,01	5 <u>5</u> 94; 99; 104, 09 <u>5</u> (	162	7 6.4	
cattle / muscle	0.25 L	\$ 98,101; 102; 107,5 Q	102	3.7	0.01
Ć		S Qverall recovery (n= 8) S	Ø 102 S	4.8	
	<b>39</b> .01	) O [*] 9%,97; 99, 13 O	<b>1</b> 01	8.1	
cattle / fat, mesenteric	0.25	2 A6; 98; B6; 106 V	102	5.2	0.01
	Û,	Øverall recovery (m = 8)	0 101	6.3	
aattia / fat	<b>0</b> .01	106°104; 103°; 107¢ 2°	104	2.4	
cattle / fat, perirenal	0.25	Q ⁷ ×97; 104; 905; 108 ~	104	4.5	0.01
		Overall cover (n = 8)	104	3.4	
	0.01	93; 101; <b>103</b> ; 106	101	6.0	
cattle / fat, subcutageous	0,25	J 091; 100; 100; 105	99	5.9	0.01
, Č	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Overal recovery (n = 8)	100	5.6	
Ny I	0.01	Q0; 96 Q74; 94	96	6.1	
cattle / kidney	0.25	مَنْ 94; <b>6</b> 5 ; 95; 96	95	0.9	0.01
		Overall recovery (n = 8)	96	4.1	
	0.00	ين مي المركزين (Jointon 1, 102; 111; 110	106	4.9	
cattle fiver	0.25	0 101; 108;106; 102	104	3.2	0.01
		Voverall recovery (n = 8)	105	4.0	

#### Table 6.4.2- 5: Concurrent recovery data for BCS-CY24813 in cattle matrices

FL& Fortification level, RSD Relative standard deviation, LOQ = Practical limit of quantification Fortified with BCS-CY24813, determined as BCS-CY24813 and calculated as BCS-CN88460 These recoveries were performed during the conduct of the study 17-8001.



Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	
		83; 86; 88; 90; 90; 90; 92; 92; 94; 94;		~	
		94; 95; 95; 95; 96; 96; 97; 97; 97; 98;		Ç ^a	
	0.005	98; 99; 100; 101; 102; 103; 103; 103;	101 🔏	8.9	
	0.005	103; 103; 103; 103; 104; 105; 105;		0.9	
		106; 107; 108; 108; 109; 110; 🖽;		×.	
cattle / milk		111; 113; 115; 117; 123*; 185*	Q	Ű	J 0.005 . 6
		92; 93; 95; 95; 95; 96; 96; 97; 97;	Å.	õ	
		100; 100; 100; 102; 103, 104; 104;		Ô, Â	
	0.05	104; 106; 106; 106; <b>206</b> ; 106; 106;	× 194	× 6.8	. 4 ⁹ . 59
		108; 109; 109; 100; 110; 100; 110; 111; 1129115; 124	4.8	S.	$\sim$
					à s'
		Overall/recovery (n = 82)		× 8.1	
	0.005	96; 109, 100, 172; 112, 112	0 ⁷¹⁰⁵ 27		
cattle / cream	0.20	9 <b>%</b> 9 <b>%</b> 99; 104 ~ ~ ~ ~	₩ <u>9</u> 2Û	S 5.6	0.005
		Overall recovery (n = 9)	<b>( )013</b> (C)	7,0	
	0.005	100×02; 107°107; 109; 113	J 106 D	~Q4.4 (v	<i>ÿ</i>
cattle / skim milk (whey)	0.05	95C102; 104	0 <u>1</u> 00	4.7 0	0.005
(whey)	6	Overal recovery (n = 9)	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	5.9	
	0.01	A 96; 101-103; 100	101	3.3	
cattle / muscle	@25	97,99; 106,009 v		× 5.5	0.01
		Overall recovery (n 8)	, , ,	4.4	0.01
			102 102 102 102 102 102 102 102		
cattle / fat,		~ (y 99; 99×106; 107 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	×	4.2	0.01
mesenteric 🔍	Ø.25 V	93,99; 105,106 ° °	° @01	6.0	0.01
	×.	Verall recovery (n = 8)	<b>%</b> 102	4.9	
cattle / fat,	<u>, 0</u> ,01	<u>مَنْ 92; 95; 101; 698</u> مَنْ مَنْ	O″99	7.1	
perirenal	0.25 K	90,90,96; 140, 102 % Å	98	3.9	0.01
Ő	P A	Overall recovery (n = 8)	99	5.4	
Ø	001	\$ <u>\$</u> 91.08; 100.003 °	98	5.2	
cattle / fat,	0.25	<b>Q</b> ; 95; <b>1Q</b> ; 110	100	7.7	0.01
and the second s	, Ô,	Overall revovery (n = 8)	99	6.2	
	~00.01 4	94,403; 105,110	103	6.5	
cattle / kidney	0.25	<b>190</b> ; 10 <b>5 1</b> 06; 107	105	3.0	0.01
· · ·	\$ 0y	Sverall recovery (n = 8)	104	4.7	
	A 01 A	95; 98; 101; 113	104	7.8	
cattle / Wer	0.01	94; 99; 102; 108	102	5.8	0.01
cattle / Hyer					0.01
J Z		<b>Overall recovery</b> $(n = 8)$	101	6.4	

#### Table 6.4.2- 6: Concurrent recovery data for BCS-DC22055 in cattle matrices

FL = Fortification level RSD = Relative standard deviation, LOQ = Practical limit of quantification Fortified with CS-DC 22055, the termined as BCS-DC 22055 and calculated as BCS-CN88460 These recordings were performed during the conduct of the study 17-8001

^{*} These recoveries are considered acceptable, because they were not identified as outliers by a Grubbs outlier test with a level of significance of 95%.



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#### Table 6.4.2-7: Concurrent recovery data for BCS-CX99799 in cattle matrices

FL Portification level, RSD = Relative standard deviation, LOQ = Practical limit of quantification Fortified with BCS-CX99799, determined as BCS-CX99799 and calculated as BCS-CN88460 These recoveries were performed during the conduct of the study 17-8001 * These average recoveries are considered acceptable, because there were found no residues of BCS-CX99799 in the sample material cream ** These recoveries are considered acceptable, because there were not identified as outliers by a Grubbs outlier test with a level of circuit frequency of 05% significance of 95%.



Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	
	0.01	85; 105; 111; 117	105	13.3	
cattle / kidney	0.25	106; 111; 105; 106	107	\$2.5	
		Overall recovery (n = 8)	106	<u> </u>	
	0.01	114; 81; 74; 111	95	21.5*	
cattle / liver	0.20	98; 105; 104; 102	102	3.0	
		Overall recovery (n = 8)	20	14.3	

Table 6.4.2- 8:	<b>Concurrent recovery</b>	data for free and	conjugated BCS-DC20298
-----------------	----------------------------	-------------------	------------------------

FL = Fortification level, RSD = Relative standard deviation, LOQ = Practical limit of quantificationFortified with BCS-DC20298, determined as free and conjugated BCS-DC20298 and acculated as BCS@N88469 These recoveries were performed during the conduct of the study 17-8001

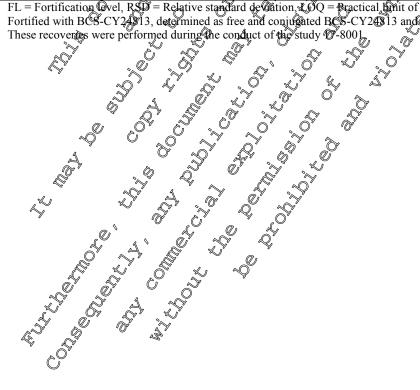
* This RSD value is considered acceptable, because it is only slightly exceeding the range and because it is considered acceptable according to OECD guideline ENV/JM/MONO(2007)17.

Table 6.4.2- 9: C	oncurrent recovery	data fo	r <i>fre</i> e	and conj	ugated	BCS-C	Y24813
1	onearrenerees		- @				

Sample material	FL [mg/kg]	Single values [%]	َکْلُوْںُ (mg/kg
	0.01	$\sim$ $\sim$ 96: 106; 83; 94 $\sim$ $\sim$ $\sim$ 95 $\sim$ 10.0 $\circ$	*
cattle / kidney	0.25	98C112; 96 103 @ 101 96	0.01
	0.25 N	Overall receivery (n # 8) S 98 J 98 9.4	
	Ø.Ø1	\$ 94; 95; 96; Q0 \$ \$ <b>99</b> \$ 7.6	
cattle / liver	Ø0.25	<b>103</b> 7.0	0.01
Ĺ		$\swarrow$ Overall recovery ( $\hat{n} \neq 8$ ) $\Im$ $0^{1}$ 101 $\Im$ 7.2	

FL = Fortification Ovel, RSD = Relative standard de Oation, LOQ = Practical Amit of quantification

Fortified with BCS-CY24913, determined as free and conjugated BCS-CY20013 and valculated as BCS-CN88460





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Group	6				al analytes (mg/kg)	E LOT	egittle on
Dose	Sampling day *	BCS-CN88460	M BCS-DC20298	ean of 3 00 ws (indiv BCS-CY26497	BCS-CY24813	BCSCDC22055	BCS- <b>E</b> X997
	Pre-dosing -19	< 0.005	< 0.005	$\bigcirc < 0.005$	< 0.0050	< 0.0030	0.005
	Pre-dosing -12	< 0.005	< 0.005	× 0005 N	× 9.005	< 6005	< 0,005
	Pre-dosing -5	< 0.005	< 0,005	~ ~ 0,005°	< 0.005	, 0.005 0 ¹	9.005
	1	< 0.005	~ © 005_ & >		D ⁰ <0005 2	< 0,005	< 0.005
1X	4	< 0.005	~Q [*] < 0.005	× 0.005 0	1 < 0.005 Ju	×9.005 _ 6	< 0.005
1	7	< 0.005	_<@,005	< 0.005	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< 0.005	< 0.005
$0.5 m \sigma/l_{\rm ex} h_{\rm ex}/d$	9	0.000		\$0.005 N	»×19.005	O < 0.€05	< 0.005
05 mg/kg bw/d	11	< 0.005	< 0,005	0.005	C<0.005C	\$ 0.005 °	< 0.005
(1 /1 D)(	14	× \$ \$ 005	9.005	<0,005			< 0.005
.61 mg/kg DM	16	C+0.005 2 2 2 2	\$ < 0.005	× 0.005 0 ×	0.005 and	<b>0</b> .005	< 0.005
	18	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< <b>93005</b>	< 0.00	0.000	S ≤ 0.005	< 0.005
	21	0 \$ 0.005 \$ Ob"	< 0.005	< 0.005	<0005 Å	< 0.005	< 0.005
	23			\$ O ^{LE} 0.005 LL	\$\$<0.005	< 0.005	< 0.005
	29	~0,005 <u></u>	× 0.005	< 0.005 ×	< 0.695	< 0.005	< 0.005
	Pre-dosing -19	× < 0.005	5 0.005 V	< 0.005	20.005	< 0.005	< 0.005
	Pre-dosing -12	> C < 0.085	< 0.005	\$ < 0.005 ⁰ *	< 0.005	< 0.005	< 0.005
	Pre-dosing -5		2 × 0.005	Ø?005	< 0.005	< 0.005	< 0.005
	2 5	≫ < 0.005	0.00 × 0.00	NA 2 0.005 D	< 0.005	< 0.005	< 0.005
3X	4 ₂₀ e	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<b>Q</b> .005	< 0.005	< 0.005	< 0.005	< 0.005
	7 1 0	0 F JE 0.005 K J	× > < 0.005	0.005	< 0.005	< 0.005	< 0.005
15 mg/kg bw/d	9 TO 05 10		> < <b>6</b> 005	⊙ ≫ < 0.005	< 0.005	< 0.005	< 0.005
<u>ي</u> بي من	KII .		Q.005 J	0.000	< 0.005	< 0.005	< 0.005
.18 mg/kg DM	14 16	0.005	0 ^{% 2} < 0.000	< 0.005	< 0.005	< 0.005	< 0.005
	16 5	× <0005 × 65	< 62005	< 0.005	< 0.005	< 0.005	< 0.005
	18	\$0.005 \$	0.005	< 0.005	< 0.005	< 0.005	< 0.005
			< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
			< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
	equeent contractions	0.005 0 ⁵	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005



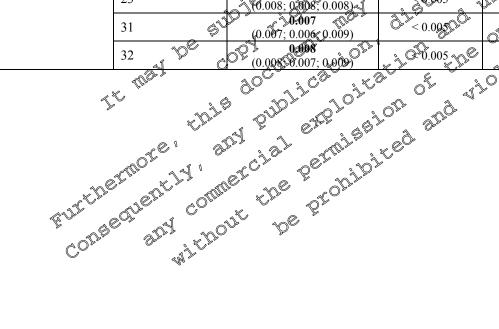
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	1					2.Dd	egille o
Group					al analytes (mg/kg)	O.D.	egine and
Dose	Sampling day *			ean of 3 cows (ind		- 	6. O. The
		BCS-CN88460	BCS-DC20298	BCS-CY26497	BCS-CY24803	DCS-DC22055 *	DUS ( A99199
	Pre-dosing -19	< 0.005	< 0.005	< 9,005	< 0.005	< 0.000	0.005
	Pre-dosing -12	< 0.005	< 0.005	\$0.005	\$0.005	£ 1005 . C	< 0.005
	Pre-dosing -5	< 0.005	< 0.005	○ < 0.005	< 0.005	× C<0.005	<b>0.005</b>
	3	< 0.005	< 0.005	C 005		0 < 0.905	€ € < 0.005
1037	4	< 0.005	< 0.000	<u>&gt;</u> @ < 0.005 ℃	0.005	< 0.005	< 0.005
10X	7	< 0.005	<b>Q</b> 005	< 0.005	<u> </u>	\0 [°] <0.005℃	§ 0.005
	9	< 0.005	€ < 0.005 € [™]	© 0.005		\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	< 0.005
0.5 mg/kg bw/d	11	< 0.005	< 0.003	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< 0.005	× 0.005 0	< 0.005
	14	< 0.005	s & 0.005	*0.905 ×	O [™] < <u>0.005</u> ″	< 0.005	< 0.005
15.54 mg/kg DM	16	< 0.005 6	< 0.005°0×	<u> </u>	0.005 V	<b>A</b> 9.005	< 0.005
	18	< 0.005	<u></u>	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>	< 0.005	< 0.005
	21	CT \$10.005	<u> </u>			- 0.005 - 0.005	< 0.005
	23	0.005 m					< 0.005
	31	& \$ 0.005 \$ 9 ^b	~ © < 0.005 () ^{© "}	SI0.005 0	< 9.005	< 0.005	< 0.005
FUCTO	The period	$ \begin{array}{c} < 0.005 \\ < 0.005 \\ < 0.005 \\ < 0.005 \\ < 0.005 \\ < 0.005 \\ < 0.005 \\ \\ < 0.005 \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $		LSE OF OF THE	rights rights		
Coller	WI TH	/ »					

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			Residu	e levels of individu	al analytes (mg/kg)	9.D.g.	i The o
Group	Sampling day *			ean of 3 cows (ind)	idual values) ^a	Orth	agir and
Dose		BCS-CN88460	BCS-DC20298	BCS-CY26497	BCS-CY2481.3	BCS-DC22055	BCS X99799
	Pre-dosing -19	< 0.005	< 0.005	< 0,005	< 0.005	< 0.000	0.005
	Pre-dosing -12	< 0.005	< 0.005	0.005	<b>\$0.005</b>	× 0.005 . 4	\$ <u>0.005</u>
	Pre-dosing -5	< 0.005	< 0.005	⊙	0.005	× C< 0.005	\$\$ <b>0</b> .005
	4	< 0.005 (< 0.005; < 0.005; < 0.005)	< 0.005	\$ 0.005 J	\$\$.005 QT		< 0.005
	7	<b>0.006</b> (0.006; 0.006; 0.007)	CP005	~ 0.905 ~	0.005 C	0 ² <0.005 ⁰	ee ⁵ < 0.005
	9	<b>0.007</b> (0.008; 0.006; 0.008)	~ 0.009 [°] ,	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< 0.005 Out	* 0.005 to	< 0.005
30X	11	<b>0.009</b> (0.008; 0.005; 0.013)	گ<0.005	~ 0.005 B		D * 1005	< 0.005
1.5 mg/kg bw/d	14	<b>0,009</b> O (0.010 0.006; 0.014	5.005 C		0-0- < 0.005 ·	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< 0.005
48.13 mg/kg DM	16	0.007 0.009		© < 0.00 €	3.0<0.005 VIII	< 0.005	< 0.005
66	18		<u> </u>	\$ OT 0.005 TO	< 0.005 F	< 0.005	< 0.005
	21 1	0.008 (0.008; 0.007; 0.008) 0.008 ©	1 \$ 0.005 N	~ <b>0</b> . <b>0</b> 05 ×	< 0.605	< 0.005	< 0.005
	23	0.008; 0 <b>30</b> 8; 0.008)		∑ [©] < 0,005 ⁰ ¹	2 2 < 0.005	< 0.005	< 0.005
	31 5	(0.007; 0.006 0.009)	0.005 D	0.005 7 LC	< 0.005	< 0.005	< 0.005
	32 ^v	0.005 0.007; 0.009)	20 ^{20.005} DC	<b>\$ 0</b> .005	< 0.005	< 0.005	< 0.005
~	TOOL S			,0 ² ,0 ²			





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Group Dose	Sampling day *			e levels of individu	al analytes (mg/kg)	D.C.D.	egilme.
Dose		BCS-CN88460	BCS-DC20298	BCS-CY26497	BCS-CY2480.3	BCS-DC22055	BCS X99799
30XE	Pre-dosing -19	< 0.005	< 0.005	< 9,005	< 0.605	< 0.000 2.4	0.005
	Pre-dosing -12	< 0.005	< 0.005	0.005	\$0.005	× 1005 %	< 0.005
Depuration group	Pre-dosing -5	< 0.005	< 0.005	o [™] < 0.005	< 0.005	× C< 0.005	S.005
	32	<b>0.008</b> (0.007; 0.009; 0.007)	< 0.005 -	\$\$0.005 to	\$ 0.005 PS	< 6005	C ^{CL+} <0.005
1.5 mg/kg bw/d	35 4d depuration	< 0.005 (<0.005; < 0.005; < 0.005)	COROOS EST	0.005	0.005 0	0 ¹ <0.005 ^C	C .005
47.13mg/kg DM	38 7d depuration	< 0.005*** (n.a.; < 0.005; <0.005)	~ 0.005 *** <u>&gt;</u>	10 < 0.00 <b>5</b> **	1< 0.005*** 0.12	< 0.005*** D	< 0.005***
	45 14d depuration	< 0.005**** (n.a.; n.a.; < 905)	₹ 20.005**®	£ 0.005*****		< 0.003****	< 0.005****

^a-mean value of three animals calculated based on unroundeefosidue results. For the edefulation of file mean residues, in one on early individual values deemed appropriate to consider residues 0.005 mg/kg as teals early do 50 mg/kg. This approach differs from what is reported if the study day **** mean value of 2 individual residue results (affinal H950 RH950 C)
**** Since only one calle of does group 30XF Temained alve on overall study day 45 (H950) no mean calles were calculated and a na. not applicable
All metabolite residues expressed in above compound equivalety.
LOQ = 0.005 mg/kg
**** brock the transformation of the mean residues in the transformation of the trans ^a – mean value of three animals calculated based on unrounded tosidue results. For the enculation of the mean explaues, in encode one or two individual values are bOQ and the others < LOQ, it was deemed appropriate to consider residues <0.005 mg/kg as long equal to 0.005 mg/kg. This approach differs from what Streported in the study of the



Table 6.4.2- 11: Re	sidue levels i	n milk and milk prod	ucts		Å	BG	ett and	Tegine .
Animal No. Sample no.	Milk sampling time (Day)**	Sample material	BCS-CN88460 [mg/kg]	BCS-DC20298 [mg/kg]	BCS-0726497	BCS-CY24813 [mg/kg] <0.005	BCS-DC22055	₽ C X99799 .BC C X99799 [mg/kg] .C X99709 .BC C X90709 .BC C X C X90709 .BC C X C X C X90709 .BC C X C X C X C X C X C X C X C X C X C
H950 0161E	31	milk	0.007	< 0.005	5 0.005 A	< 0.005	«O* ~0.005 »	
(30X) 0160E	31	cream	0.11	0,006	<u>~</u> <u>~</u> <u>0.005</u>			4 O * < 0.063
(30A) 0162E 0164E	31 31	skim milk (whey) milk	< 0.005	©0.005 © < 0.005	<0.003 <0.005	<0.005 < 0.005 < 0.005		0.005
H951 0164E			0.006 0.11 ₀₀ ©		\$ 9:005 C		<i>≈</i> 0.005 ×	< 0.005 < 0.005
(30X) = 0105E = 0105E	31	skim milk (whey)	< 0.085	\$0.005 G	< 0:005	× 0 < 0.005 0 ×	0.005 ×	< 0.005
	31	milk	\ <b>€</b> 0009 €	< 0.005 0	₹0.005 \	< 0.895	× <0.065	< 0.005
H938 0166E	31	cream	0.15 0	0,009	3. 2 × < 0.005 0 ×	200.005 C	€ 0.005 €	< 0.005
(30X) 0168E	31	skim milk (whey)	< 0.005	0.005 ×	< 0:005	~ O < 0.0 <b>0.5</b> )	0.005 NT	< 0.005
	TE Mar	cream skim milk (whey) milk cream skim milk (whey) skim m		diatrice diatrice diatrice and and tion tion	use of owner th tolate	e right		



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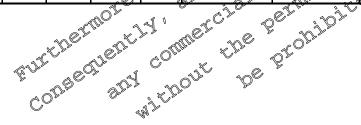
Fable 6.	4.2- 12:	Residu	e levels in Animal		nt tissues			Desidue law	(mg/kg)**	and and		and and
Group	Dose (mg/kg bw/d)	Dose (mg/k d DM)	No.	Sampl ing Time (Day) *	BCS-CN88460 [mg/kg]	BCS-DC20298 [mg/kg]	Sum of BCS-DC20298 and M20 [mg/kg]	BCSOCY 26497	BCS-CY24813 [mg%g]	Sum of BCS-CY24813 and M19	BCS-DC22055	BCS-CX99799
Muscle								1. 2 × 4 ×			ge the	. C
			H941	29	< 0.01	< 0.01		<0.00	\$0.01 ×		C 0.01 G C	) ³ / ₂ < 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	NACE Y	v < 0.01 √ < 0.01 √	0.01		© 0.01 ¢ © < 0.01 ¢	< 0.01
			H943	29	< 0.01	< 0.01	NØ	~~~<0.0↓ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	≤ 10 01	Out NA D	<b>V</b> Q <b>Q</b> 1	< 0.01
				mean	< 0.01	× \$0.01	NA NA	× 0.01	~ 0.0 ⁵	NA 4	NA NA	< 0.0.
			ħ	nedian	< 0.01	s & < 0.01		< 0:Q10				< 0.0
			H944	30	< 0.01	< 0.01 °	NA NA	2	<0.01 <0.01 <0.04	NA NA	0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01 \$ 0001	0.01 0 < 0.01	SU NAS	~§ 0.01	O < 0.0	NA S	J ^{LL} < 0.01	< 0.01
			H946	30		0.01 S	AM.	⊘ < 0.01 ⊘ €	÷09:01	NA C	< 0.01	< 0.01
				mean	$30^{\circ} < 0.00^{\circ}$	<u>, , , , , , , , , , , , , , , , , , , </u>		< 0.01 \$	G < 6200°	NA	< 0.01	< 0.0
			ň	nedian	09.01	~ 0.0X			s ≪ 0.01	NA NA	< 0.01	< 0.0
		155	H947	30	Ø.01	) < 0.01 - 0.01	NA N	< 0.001	a la car	[♥] NA	< 0.01	< 0.01
10X	0.5	15.5 4	H948	30	< 0.01	< 0.01	NAYO NAYO	< <b>0</b> .01 g	< 0.01	NA	< 0.01	< 0.01
		4	H949	30	s 60901	× \$ < 0.01 \$	NA NA NA NA NA NA	<0.01 <0.01 <0.01	× 901	NA	< 0.01	< 0.01
				mean	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.01		© [®] × 0.01	< 0.01	NA	< 0.01	< 0.0
			ħ	nedian	\$0.01	₩. [%] ⁶ < 0.01			< 0.01	NA	< 0.01	< 0.0
			H950 «	ro <b>®</b> ∕l	0.01	<0.00 1 × \$0.01 ×		< 0-01	< 0.01	NA	< 0.01	< 0.01
30X	1.5	48.13	H951	31		× \$0.01 ×	NA NA	0.01	< 0.01	NA	< 0.01	< 0.01
			-8938	31	3 (O.01 v	°°° ×0,01 °°°	KNA s	○	< 0.01	NA	< 0.01	< 0.01
		T.E	,	mean _.		a 2001	A A AA	< 0.01	< 0.01	NA	< 0.01	< 0.0.
		)J	n	nedian	30.01	0.00	NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
30XE			H953	\$5°	<0.01€	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	^N NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
depu-	1.5	47.13	H95æ	38	\$0.01 ×	KØ.01	≥ ^{Os} NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
ration			<b>11995</b> 5	45	60.01	C ¹ < 0.01	NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
	EUIT	the?	JUC DE	LI CORT		OT OTT						

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-				1								<u> </u>
		Dose	Animal	Sampl				Residue leve	els (mg/kg)**	alle		Re J
	Dose	(ma/k	No.	ing			Sum of		B	Sum of	A.CO.	O.L.C.
Group	(mg/kg	d		Time	BCS-CN88460	BCS-DC20298	BCS-DC20298	BCS-CY26497	6	<b>BCS-CY24813</b>	BCS-DC22055	<b>ØBCS-CX99799</b>
	bw/d)	DM)		(Day)	[mg/kg]	[mg/kg]	and M20	[mg(kg]	[mg/kg]	and M19	^م ر Qmg/kg	[mg/kg]
		,		*			[mg/kg]	Ę V		[mg/kg]	Ľ <u>, </u> Śř	ŝ
Kidney								) ^y _&·		<u> </u>		6°
			H941	29	< 0.01	< 0.01	< 0.01	59.01	J.O. < 0.01 C.	<b>\$0.01</b>	0.0+ C*	< 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	@.01	S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S4.01 S	₹0.01		0.01	< 0.01
			H943	29	< 0.01	< 0.01	0.01 6 3	< 0.01		≤8.01	× (0.01 ک	< 0.01
				mean	< 0.01	< 0.01	0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	* < 0.01	10.0 × 10.0		< 0.01
			п	nedian	< 0.01	\$\$.01	<u></u> © < 0.01°		0.01	≥ <u>₹</u> 0.Ď1	₩ ^L ^B < 0.01	< 0.01
			H944	30	< 0.01	< 0.01	SSS < 0.01 SSS	\$0.01	< 0.01	< 0.01	< 0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01	\$0.01 \$\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	<b>\$9</b> .01	DOS < 0.01 D	<u>39</u> 01	SSB < 0.01 SSB	0.01	< 0.01
			H946	30	< 0.01	<0.01	~0.01 ···	S @ OH		<0.01	$10.01 \ll 10.01$	< 0.01
				mean	10.01	Jul - 0.01	©©0.01	$< 0.00^{\circ}$	20 ⁶ 0.01	10 C < 0.0 D	< 0.01	< 0.01
			п	nedian	CUL < 0.014	9.01	0.04 < 0.04	\$0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	\$ \$ <b>9</b> .01	< 0.01	< 0.01
			H947	30	0.02 < 0.02	\$\$ <b>6</b> .01	< 0.0		>> < 0.01 ⁰	× 0.01	< 0.01	< 0.01
10X	0.5	15.54	H948	300	-20.01	< 0.01	<b>√0</b> .01	0.021	\$0.01	< 0.01 0.01	< 0.01	< 0.01
			H949	30	< 0.01	<6.01		0021	0.01 S	< 0.01	< 0.01	< 0.01
				mean	0.01	, G < 0.Q1	r ≈ 0.01	<u></u> 0.04,2∕	s 0, 0.01	< 0.01	< 0.01	< 0.01
			ň	nedian		≥0.01	\$ \$ Q.01	× 0.021	~ 0.01	< 0.01	< 0.01	< 0.01
			H950	31	0.04 V	\$0.01	~ < 0.01 ⁰	a 0.063 and	≥ < 0.01	0.016	< 0.01	0.020
30X	1.5	48.13	H951	31	a0.01	× <0.01 1	< 0.01		< 0.01	0.015	< 0.01	0.023
			H938	$\mathcal{O}_{31}^{21}$		<u>₹0</u> 901	< 0.01 0 < 0.01	<b>30.05</b> 0	< 0.01	0.016	< 0.01	0.014
			0.7	mean	, C 0.01		© ₹0.01	0.062	< 0.01	0.016	< 0.01	0.019
			<u> </u>	nedian	. 0.01×	\$\$ 0.01	0 × < 0.01×	0.063	< 0.01	0.016	< 0.01	0.020
30XE		J.	H953	35		0.01	~~~ <u>0</u> @L	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
depu-	1.5	47.13	H954	35 à		F < 0.06	@0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
ration			H955	45	$< 0.01^{1}$ .	× 0.01	>0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
			-0 ³			CIL SI	<i>"</i>					

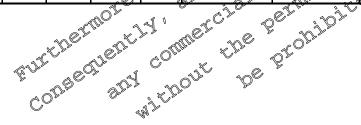


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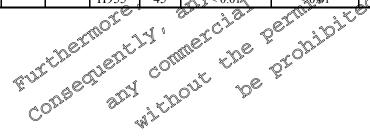
								<b>D</b> 11 1				
	_	Dose		Sampl				Residue leve	els (mg/kg)**	S. T. H		I'r.
	Dose	(ma/k	No.	ing			Sum of	ſ	Pr-	Sum of	~ ^{69°}	9.100
Group		d		Time	BCS-CN88460	BCS-DC20298	BCS-DC20298	BCS-CY26097	BCS-CY24813	/ ^ ^v	BCS-DC22055	<b>BCS-CX99799</b>
	bw/d)	DM)		(Day)	[mg/kg]	[mg/kg]	and M20	[mg(kg]	[mg/kg]	and M19	^م ر Qmg/kg	[mg/kg]
		,		*			[mg/kg]	ę. V	<u><u></u></u>	[mg/kg]	1 D D D D D D D D D D D D D D D D D D D	ŝ
Liver	-						,	) ^b é.		· · · · · · · · · · · · · · · · · · ·		Ç.
			H941	29	< 0.01	< 0.01	< 0.01	× 0.01	J. < 0.Q1 C	L	2 ⁰ < 0.04	< 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	Ø.01	< 0.01	× 0.01	€<0.01 €	<u>~</u> 0.01	<u>م</u> ركة < 0.01
			H943	29	< 0.01	< 0.01	0 0.01 5	< 0.Ø1		0.01	< 0.01 €	< 0.01
				mean	< 0.01	< 0.0 K	₿ [₩] 0.01	$\sim$ $< 0.00$		10.0 > 100	0.01	< 0.01
			n	nedian	< 0.01	10 ^{9.01}	$\sim$ $0.01$	\$\$\$ .01	< 0.040	₹ 0.Ď1	× 0.01	< 0.01
			H944	30	< 0.01	< 0.01 \$ < 0.01	\$\$\$ < 0.01	₹0.01 ©	< 0.0 ř	< 0.01	< 0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01	لاً ⊘0.01 €	0.01	20 ⁵ < 0.013	375 <b>9</b> .01	2 < 0.011 D	0.01	< 0.01
			H946	30	< 0.01	< 0101	~ 0.01 × 0	<u>-</u> @.01	5 (0.01 5 (0.01 0 (0.01)	<0.01	<u>10 &lt; 0.01</u>	< 0.01
				mean	0.01	Jul - 0.01	Q 0.01	× < 0.40	20 ^{&lt;0.01}	0.0D	< 0.01	< 0.01
			n	nedian	C ² < 0.01	9.01	0 $1$ $< 0$	\$0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	s. ¥5€0.01	< 0.01	< 0.01
			H947	30	0.0× < 0.0	\$ <b>6</b> 01	C 0.030		> < 0.01 ⁰	6.040	< 0.01	< 0.01
10X	0.5	15.54	H948	300	<b>9.913</b>	<0.01 C	<b>3</b> .031	$0^{-} < 0.01 \%^{-}$	<u></u> 0.01	0.033	< 0.01	< 0.01
			H949	30	< 0.01	<6.01		00.01	××<0.01 \$	0.036	< 0.01	< 0.01
				mean	_ A.011	, Ĝ < 0. <b>Q</b> [0	°≫0.027	LO < 9.94	s 6 0.01	0.036	< 0.01	< 0.01
			ľ	nedian		₹ 0.01	<u>, 6^{°°} (,039</u> )	~< 0.01	< 0.01	0.036	< 0.01	< 0.01
			H950	31	0.048	\$0.01	0.00	AC 0.032 AA	≥ < 0.01	0.12	< 0.01	0.014
30X	1.5	48.13	H951	31	<b>0.020</b>	<0.01	0.065	0.037	< 0.01	0.15	< 0.01	0.010
			H938	$\mathcal{O}_{31}^{21}$		\$ 9.01	0.053	<b>\$9.016</b>	< 0.01	0.064	< 0.01	< 0.01
			a de l	mean	C0.016	~?~ < <i>0.</i> ?	0.069 🖉	0.028	< 0.01	0.11	< 0.01	0.011
			, <i>n</i>	nedian	0.648	\$ 0.01	0 0.063	0.032	< 0.01	0.12	< 0.01	0.010
30XE		P	H953	35		×0.01 €	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
depu-	1.5	47.13	H954	38	_ < <b>0</b> .01	1	@ 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
ration			H955	45	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	9.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
	I		-0 ³			CIT AND	<u></u>	•	-	-	-	





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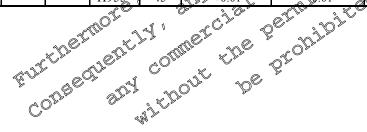
				a 1				D 1 1	1 ( /1 ) 4 4			
	D	Dose	Animal	···· I.				Residue leve	els (mg/kg)**	Qiber		her d
G	Dose	(mg/k	No.	ing			Sum of	all a	Fra-	Sum of	L.C.S.	O.D.
Group	(ing/ Kg	d		Time	BCS-CN88460	BCS-DC20298	BCS-DC20298	BCS-CY26497	BCS-CY24813	<b>BCS-CY24813</b>	BCS-DC22055	<b>BCS-CX99799</b>
	bw/d)	DM)		(Day)	[mg/kg]	[mg/kg]	and M20	[mg(kg]	[mg/kg]	and M19	Low Market	[mg/kg]
		,		*			[mg/kg]	<u>e</u>	Q ¹	[mg/kg]	1 Shr	ŝ
Fat, me	esenteric							j ⁱ ĝ		° *	D'L'	
			H941	29	< 0.01	< 0.01	NAC	< 0.01 < 0.01 0 0 01	Q. ^{Q.} < 0.01 €		200 < 0.04 0.01	< 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	ØX N	\$_0\$<0.0bC	0.01		0.01	o.01 × 0.01
			H943	29	< 0.01	< 0.01	NA & Y		~ ~ 0.01 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	A A		< 0.01
				mean	< 0.01	< 0.01	NA NA	× < 0,00	< 0.01	JI MA	NA CONA	< 0.01
				median	< 0.01	× <b>1</b>	ŝ NA	li B.	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NA	NA NA	< 0.01
			H944	30	< 0.01	< 0.01	NA S	₹0.01	< 0.01	NA	< 0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	NA	0.01 < 0.01 $3$	0.01 0.01 0.01	NA V	© 0.01	< 0.01
			H946	30	0.010	< 0.01	NA	્રજી.64		A A	0.01	< 0.01
				mean	<b>6.01</b>	0.01	er NA	< 0.00	30 ^{60.01}	NAO	NA NA	< 0.01
				median	C ^{UL6} < 0.01	0.01	NA	<b>√</b> 0.01			NA	< 0.01
			H947	30	0.03	× 901	e NAS		< 0.01 ° <	¢ NA	< 0.01	< 0.01
10X	0.5	15.54	H948	30¢	<b>A</b> .041	× < 0.01 × ×	NA P		\$ 0.01	NA NA	< 0.01	< 0.01
			H949∢	\$\$30	0.020 K	< 2.04	NA J	09.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NA	< 0.01	< 0.01
				[®] mean	<b>\$0</b> .033	<u>6</u> < 0.010		~ < 0,0%	\$ 0.01	NA	< 0.01	< 0.01
				median			NAO	≈ ~ 0.01	~ 0.01	NA	< 0.01	< 0.01
			H950	31	0.085	<b>N</b> Ø.01	NA O	0.01	< 0.01	NA	< 0.01	< 0.01
30X	1.5	48.13	H951	31 7931	<b>0.07</b> 7	≪ <0.01	1474	$\bigcirc$ < 0.01 $\oslash$	< 0.01	NA	< 0.01	< 0.01
			H938	°Q'31	<u> 0.068</u>		NA C	<b>\$ 05.0</b> 1	< 0.01	NA	< 0.01	< 0.01
			a	mean	<b>09.0</b> 77	0.0%	NA Share	<u> </u>	< 0.01	NA	< 0.01	< 0.01
	-		TUCO	median	ð ^{0°} 0.07%		NA	$0^{\circ} < 0.01$	< 0.01	NA	< 0.01	< 0.01
30XE		I.	Н953	35 🔬	\$ < 0.010 ×	<b>9</b> .01	NA NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
depu-	1.5	47.13	H954	38	~@01	2 < 0.01 2 < 0.01 2 0.01 2 0.01	<b>MA</b>	< 0.01	< 0.01	NA	< 0.01	< 0.01
ration			H955	45	<pre>&lt; 0.01</pre>	\$0 <b>.9</b> 1	NA NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
				-	S OF	Aller of		- 0.01	. 0.01	1 12 1	· 0.01	- 0.01





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			Animal	G 1				Dogiduo lov	la (ma/lia)**		<u> </u>	n ^e ,
	Dasa	Dose	Animai No.	Sampl			G <b>6</b>	Residue leve	els (mg/kg)**		Č.	ng.
Crown	Dose	(mg/k	190.	ing Time	DCG CN004(A	DCG DCAAAAA	Sum of	Des cuacíón	BCS CV24912	Sum of	BCS-DC22055	J.L.
Group	(mg/kg bw/d)	d			BCS-CN88460	BCS-DC20298	BCS-DC20298	BCS-CY26497	BCS-CY24813	<b>15</b> CS-CY24813	BCS-DC22055	<b>BCS-CX99799</b>
	Dw/u)	DM)		(Day) *	[mg/kg]	[mg/kg]	and M20 [mg/kg]		[mg/kg]	and M19 [mg/kg]	<u>`</u> Qmg/kgl	[mg/kg]
Fat, pe	rirenal							<u> </u>				<u>S</u>
			H941	29	< 0.01	< 0.01	NA		J. < 0.01 C -	NA A	0.01 0.01	< 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	A A	S < 0.0₺C	₹0.01	NA S	<b>0.0</b> 1	< 0.01
			H943	29	< 0.01	< 0.01	OP NAE >	Q.01	Q ⁰ < 0.01	A A	< 0.01	< 0.01
				mean	< 0.01	< 0.01	NA	$\sim 0.00$	<i>∎</i> < 0.01	STOP W	0.01	< 0.01
			1	nedian	< 0.01	<b>A9</b> .01	Ś NĂ	9.01	< 0.04	NA	* L < 0.01	< 0.01
			H944	30	< 0.01	< 0.01	NAS	0.01	<0.0 Å	NĂ 🧳	< 0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01	<u>نَمْ &lt; 0.01</u>	NA a	20 < 0.01 J	\$\$.01	NA NA	×(0.01	< 0.01
			H946	30	< 0.01	<b>\$0</b> .01	NA NA		0.01 JUL	-NA	0.01 0.01 0.01	< 0.01
				mean	<b>6</b> 0.01	QL < 0.01	NA NA		a 0 ^{60.01}	NAO NAO	< 0.01	< 0.01
			1	nedian	CV2 < 0.014	× 0.01	ON NA	\$0.01	< 0.04C	NA NA	< 0.01	< 0.01
			H947	30	0.039	< 0.01 C	NA NA		< 0.01 ⁰	NA NA	< 0.01	< 0.01
10X	0.5	15.54	H948	300	<b>\$.94</b> 1	× < 0,01 %		0" < 0.01 ° "	\$0.01	O [™] NA	< 0.01	< 0.01
			H949	30	0.021 🌾	- 1000		00.01	× 0.01	NA	< 0.01	< 0.01
				mean	A.034	_ G < 0£0D	NA NA	e C - C - C - C - C - C - C - C - C - C	s 6 0.01	NA	< 0.01	< 0.01
			1	nedian	0.030	o.01	NAU	~~~ 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NA	< 0.01	< 0.01
			H950	31	ر (0.0 <b>80</b> مال	TR 0.01	NA ^{OL}	0.01	< 0.01	NA	< 0.01	< 0.01
30X	1.5	48.13	H951	31		↓ 0.01 ×	NA NA	$0^{\text{We}} < 0.01^{\text{W}}$	< 0.01	NA	< 0.01	< 0.01
			H938	$\bigcirc 31$	۵.07 <u>5 م</u>	× 0.01 >	O ^{VE} NANE	\$ 0.01	< 0.01	NA	< 0.01	< 0.01
			TRONY	mean	CØ.081	< 0,04	NA	S < 0.01	< 0.01	NA	< 0.01	< 0.01
	-		/	nedian	<u> </u>	↓~0.01	O AA	< 0.01	< 0.01	NA	< 0.01	< 0.01
30XE		T	H953	35	\$ < 0.000 ×	20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20.01 20	> No	< 0.01	< 0.01	NA	< 0.01	< 0.01
depu-	1.5	47.13	H954	38	< 201	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u>S</u> NA	< 0.01	< 0.01	NA	< 0.01	< 0.01
ration			H955	45	<u></u> <0.01	10.01	U ^s INA	< 0.01	< 0.01	NA	< 0.01	< 0.01





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		D.	Animal	Sampl				Residue leve	els_(mg/kg)**	AL ^O		A M
	Dose mg/kg	Dose (mg/k	No.	ing Time	BCS-CN88460	BCS-DC20298	Sum of BCS-DC20298	BCS-CY26697	BCS-CY24813	Sum of SCS-CY24813	BCS=DC22055	BCS-CX99799
	bw/d)	d DM)		(Day)	[mg/kg]	[mg/kg]	and M20	[mg/kg]	[mg/kg]	and M19	م ُ (mg/kg	[mg/kg]
		DNI)		*			[mg/kg]	e Be		[mg/kg]	S.S.	Å
Fat, subc	cutanen	nous					(	) ^v g ·	al r	· ·	10 ¹	
			H941	29	< 0.01	< 0.01	NAC	\$\$ 0.01	0.010	NA A	Q < 0.0%	⊘, < 0.01
1X	0.05	1.61	H942	29	< 0.01	< 0.01	A A	> < 0.0bC	0.01	NA S	<b>O</b> .01	< 0.01
			H943	29	< 0.01	< 0.01	NA EX	\$0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NA	<0.01 € ⁵	< 0.01
				mean	< 0.01	< 0.01	NA			O'RE MA	60.01	< 0.0
				nedian	< 0.01	0.01	S NĂ	0.01	0.000	NA	× 0.01 × 0.01	< 0.0
			H944	30	< 0.01	<0.01 > < 0.01	≫ NA _D S	~~0.01 ~ O		NA NA	< 0.01	< 0.01
3X	0.15	4.18	H945	30	< 0.01	\$\$ ^{\$} <0.01	NA ONA	() < 0.01 () · · · · · · · · · · · · · · · · · ·	250.01		Q, 20.01	< 0.01
			H946	30	< 0.01	<0.01	NA C	<b>B</b> .91	005<0.0101	AQC 1	×10.01 ≪21.01	< 0.01
				mean	10.01	Dr. < 0.01	NA		0,01	NAP	< 0.01	< 0.0
				nedian	C < 0.05	9.01		\$0.01	<u> </u>		< 0.01	< 0.0
			H947	30	0.033	<0.01 × 20.01	e Não		< 0.01 ^{Os}	¢ ŇA O NA	< 0.01	< 0.01
10X	0.5	15.54	H948	30	<b>B</b> 028		NA E	< 0.01	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	~ 1171	< 0.01	< 0.01
			H949≪	30	0.013	<0.01	NA NA	0.01	~0.01 S	NA	< 0.01	< 0.01
				mean	<u>0.024</u>		NA NA	<u> </u>	\$ 0.01	NA	< 0.01	< 0.0
<u> </u>				nedian	0.0280	≥ <u>₹ 0.01</u>	NAP NAP	< 0.01	≪ <i>≤ 0.01</i>	NA	< 0.01	< 0.0
2037	1.5	40.12	H950	31	0.051		NAC ^O	₩ ⁰ .01	< 0.01	NA	< 0.01	< 0.01
30X	1.5	48.13	H951 H938	$\mathcal{O}_{31}^{\underline{\partial}_1}$		∑ < 0.01 1 ≈0.01	NA NA	0 < 0.01	< 0.01 < 0.01	NA NA	< 0.01	< 0.01
			H938		0 ⁰ 0.06600	~0.01 ~0.00 ~0.00	<i>v v</i>	< 0.01	< 0.01	NA NA	< 0.01 < 0.01	< 0.01
			- CL'OS #	mean nedian	0.657	\$ 0.01	NA NA	< 0.01	< 0.01	NA NA	< 0.01	< 0.0
			<i>្ក /</i>	25 %			NA NA	< 0.01	< 0.01	NA NA	< 0.01	< 0.01
OVE		~	H054	22		$\sim 0.01$		< 0.01	< 0.01	NA	< 0.01	< 0.01
30XE	15	17 12		120			UINA	< 0.01	< 0.01	INA	< 0.01	< 0.01
$\begin{array}{c c} 30XE \\ depu-ration \\ A N-verall stuce \\ C A \\ M d the other \\ OQ = 0.01 \end{array}$	1.5	47.13	H055	45		<b>≤</b> 30.101	SO≫ NΔ	< 0.01	< 0.01	NΔ	< 0.01	< 0.01



#### CA 6.4.3 Pigs

The maximum dietary burden for pigs remains <0.004 mg/kg bw/day. Besides, the metabolic pathways do not differ significantly in the rat as compared to ruminants (cf CA 6.2.4). Therefore, a feeding study in pigs is not required.

#### CA 6.4.4 Fish

No residue study in fish was conducted. Currently, no test method of Guidance documents available for conducting such study. In these cases, waiving of this particular data requirement is considered acceptable according to the "Guidance document for applicants on preparing dossiers for the approxial of a chemical new active substance and the renewal of approval of the chemical active substance 283/2013 and Regulation (EU) according to Regulation (EU) No. No. 284/2013" (SANCO/10181/2013-rev.2 of 2-May-2013

Effects of processing

CA 6.5

CA 6.5.1

Nature of the residue 2017 M-594823-01-1 **Report:** Nature of the residues of [pyrazole 4-14C]BCS-CN88460 and [phenyl-UL-14C]BCS-Title: CS8846Q n processed commodifies - High temperature bydrolysis Report No .: EnSa-16-0135 Document No. 2 594825-044 OECD Guideline for the Testing of Chemicals 50 P Guideline(s): Nature of the Pesticide Residues in Progessed Commodities - High Temperature Hydrologis, adopted 2007-10-06 Regulation (EC) No(1/107/2009 amended by Commission Regulation (EU) No 283(2013 (Europe)) US EPA OCSPP not applicable Guideline deviation(s) **GLP/GEP:** Executive Summary

The hydrolytic degradation behaviour fr [pyrazole-4-14C]BCS-CN88460 and [phenyl-UL-14C]BCS-CN88460 under conditions representative for food processing operations was investigated. The following conditions were tested:

Pasteurisation:	90 °C at pH 4 for 20 min
Baking brewing, boiling:	100 °C at pH 5 for 60 min
Sterifisation v v	120 °C at pH 6 for 20 min

BCS-C 888460 was predominantly stable under all tested conditions. The identification rates were very high and in the range of 98.0% to 99.1%. Degradation products detected under the tested



conditions representatively for food processing were very minor ( $\leq 0.5\%$  and  $\leq 0.005$  mg/L) and were not further investigated.

All material balances were in the range of 104.2 to 110.5% demonstrating that no volatile degradation products were formed.

	I. Materials and Methods
A. Materials	
Table 6.5.1- 1:	I. Materials and Methods
Chemical structure	$ \begin{array}{c} F \\ N \\ H_{3}C \end{array} \\ \begin{array}{c} 0 \\ N \\ H_{3}C \end{array} \\ \begin{array}{c} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 $
Radiolabel position	pyrazoké 4-14Cjo 5 phenye UL-14Cj
Radiochemical purity	
Chemical purity (%)	5 99% (HPLC) 5 5 5 5 99% (HPLC)
Specific activity	3.90 MBg/mg 234,000,000 dpm/mg
B. Study Design	

# Preparation of radiolabelled Stock and Dest Solutions:

The [pyrazole-4-¹⁴C] and [phenol-UL  14 C] labelled test compound was each dissolved in acetonitrile. An aliquot of each solution was filled up to 10 mL with acetonitrile. An aliquot of the diluted solution (4 mL) was again further diluted with 6 mC acetonitrile yielding the respective stock solutions.

The targeted application rate for this study was approx. 1 mg test compound/L buffer solution. Therefore both pyrazele- and phenyl-labeled test compounds were prepared as stock solution dissolved in acetonitrile and aliquots thereof containing the respective amount of test compound for the target concentration were added to a respective amount of buffer solution assuring for final test solutions with acetonitrile content < 1%.

solutions with acetonitrile content  $< \frac{100}{100}$ . After preparation of each final test solution, aliquots were taken for LS and HPLC analyses and the remaining aliquot ( $\frac{100}{100}$ ) of the test solution in the test vial was exposed to the respective processing condition.

# Experimental conditions:

Based on different processing operations, tests for each test compound were carried out with sterilised, citrate bufferent drinking water at three different pH levels and three different temperatures: pH 4 /  $90^{\circ}$ C, pH 5 /  $100^{\circ}$ C and pH 6 /  $120^{\circ}$ C. The treatment duration was 20 min, 60 min and 20 min for the three scenarios, respectively. The tests at  $90^{\circ}$ C and  $100^{\circ}$ C were carried out using a Reacti Therm heating/stirring module. The tests at  $120^{\circ}$ C were performed in an autoclave. The intended test periods listed in the table above do not include the time until reaching the test temperature or the ambient



temperature after test termination. The temperature was recorded in a separate vial filled with 7 mL buffer.

The vials of the test solutions were closed with a septum and crimp top and placed in a dry brock heater or an autoclave. The vials were weighed before and after hydrolysis to correct for by ssible losses by evaporation of water.

#### Sampling:

After termination of the test, the test samples were cooled to room temperature as rapidly as possible and the pH values of the samples were measured at room temperature. The samples were transferred to a measuring cylinder and the test vials were washed with a defined mount of actionitribe to release any possible remaining radioactivity in the test vial. The wash solution was then added to the samples and the solution was sonicated.

#### **C. Analytical Procedures**

The radioactivity content of each vessel was determined by LSC, three diquots of each test solution. before and after the test). For HPLC profiling of the test solutions at test termination a further alignot of each test solution was mixed with a defined amount ob emulgator to facilitate HPLC sample preparation and minimization of surface adhesion, The mixture Owere sonicated and concentrated using a rotary evaporator. Defined amount of water was added and the mixture was sonicated for homogenisation. The volume was determined, aliquots were again taken for the determination of the radioactivity content by LS measurement to check for possible losses during HPLC sample preparation and aliquots were taken for HPLC profiling of the test solution at test time after hydrolysis. Recoveries for FPLC sample preparations determined for all test solutions ranged from 99.0% to 103.2% confirming that no radioactivity was lost during HPCC sample preparation.

Aliquots of all samples were analysed and quantified by HPLC with radiodetection by reversed phase chromatography using an acidic water/acetonitrile/THF gradienO  $\bigcap$ 

Parent compound was identified in both pyrazole and phenyl dabelled test solution pH 5 after processing by IC-MS and LC-MS/MS analysis and by HPLC co-chomatography with the nonradiolabelled reference compound. Furthermore, the assignment and identification of parent compound was achieved by comparison of HPLC metabolite profiles of the sample extracts of the current study with each other.

# II: Results and Discussion

Material Balance concentrations determined in the test solutions before and after incubation and a material balance was established for all tests? The mount of accounting in the test solutions accounted for 0.7% for the tests with the pyrazole-label and for 0.9% for the sets with the phenyl-label.

Based on the results of the LSC measurements of the test solutions after hydrolysis, the concentration of the test compound applied was 0.976 mg/L for both the tests with the pyrazole-labelled test compound and for the pheryl-labelled test compound. All material balances were in the range of 104.2% to \$10.5% demonstrating that no radioactivity dissipated from the test systems. Detailed results for measured radioactively balances are provided below.

Et Port of the state



Test item	Processing medium	Measurement pre-processing	Measurement post-processing	Recovers [%]
		m	ng/L	
[pyrazole-4- ¹⁴ C]	pH 4	0.894	0.970	198.6
BCS-CN88460	рН 5	0.933	0.972	104.2
	pH 6	0.922	0.981	° 106 € ¢
[phenyl-UL- ¹⁴ C]	pH 4	0.930	1.027	140.5
BCS-CN88460	рН 5	0.928	0.987 0	~0106.3 ° (°
	pH 6	0.928	0.970 %	~~ 104 <b>%</b> (0 [°]

Table 6.5.1- 2:         Material Balance of Radioactivity in all
------------------------------------------------------------------

The concentration in the test solutions at test termination were calculated using the following formula

Concentration after hydrolysis  $[mg/L] \notin \frac{Total dppa^{r}_{sample after hydrolysis}}{SA \notin Totak Volume sample after hydrolysis} * 1000$ 

Aliquots of all test solutions were analysed by HPL@before and after hydrolysis HPL@ profiling of the test solutions of both labels showed that BCS-CN88460 was predominantly stable ander the tested conditions representatively for food processing.

For all tests, almost complete recovery of the parent compound was observed ( $\geq 98.0\%$ ). Degradation products detected under the tested conditions representatively for food processing were very minor ( $\leq 0.5\%$  and  $\leq 0.005$  mg/L) and were not further investigated (see tables below)

Identification rates of parent compound were very kigh and in the range of 98.0% to 99.1% of the radioactivity in the test solutions.

Table 6.5.1-3: Radiactive residues of parent compound and hydrolysis products in the [pyrazole-4-

	· · · · · · · · · · · · · · · · · · ·				
[pyrazole-4,4] C]BCS-CN88460		Processing	Conditions		
Report name	pH 4 / 90°C / 20 m	in هم المربخ من المربخ الم منابع المربخ ا	°C / 60 min	pH 6 / 120 °	C / 20 min
	Are@[%]mg/I	Acea [%]	mg/L	Area [%]	mg/L
parent compound BCS-CN88460	99.10 0.9	62 98.66	0.959	99.05	0.971
Total iden filted:	99,10 🕎 0.9	<b>6</b> 2 98.66	0.959	99.05	0.971
Total characterised:	~ 0.90 ° 60	09 1.35	0.013	0.95	0.009
Number of unknown peaks			7		4
Largest unknown peak	Ø26 C 0.0	02 0.34	0.003	0.51	0.005
Accountability	<b>300.0</b> 0.9	70 100.0	0.972	100.0	0.981



Table 6.5.1- 4:	Radioactive residues of parent compound and hydrolysis products in the [phenyl-UL-
	¹⁴ C] BCS-CN88460 test solution under the different processing conditions

Processing Conditions								
pH 4 / 90 °	C / 20 min	рН 5 / 100 °	°C / 60 min &	рн 6 / 120 °	20 min			
Area [%]	mg/L	Area [%]	mg/L	Area [%	mg/L			
98.65	1.013	<b>Č98.03</b>	<b>6</b> ⁄968	98,74	0.966 0.966			
98.65	1.013 "	98.03	_Ô [%] 0.968	<b>98</b> .74 ~	<b>\$</b> 960 0			
1.35	0.01	1.95 🖉	0.019	_O ^O 1.26 [™]	© 0.012			
	6	~		Rí vo .	B O			
0.33	©.003 €	° <b>B9</b> 2	x 0.00 <b>\$</b>	Q.42 ×	- <b>0</b> ,004			
100.0	0 1.02	Å00.0 🖉	10.987	T100,Q	A 0.972 °			
	Area [%]           98.65           98.65           1.35           0.33	98.65         1.013           98.65         1.013           1.35         0.014           6         9           0.33         0.003	pH 4 / 90 °C / 20 min     pH 5 / 100 °C       Area [%]     mg/L     Area [%]       98.65     1.013     98.03       1.35     0.014     1.95 °C       0.33     0.003 °C     92	pH 4 / 90 °C / 20 min       pH 5 / 100 °C / 60 min         Area [%]       mg/L       Area [%]       mg/L         98.65       1.013       98.03       6.968         98.65       1.013       98.03       6.968         1.35       0.014       1.95       0.019         6       11       100       100         0.33       0.003       9.92       0.003	pH 4 / 90 °C / 20 min       pH 5 / 100 °C / 60 min       pH 6 / 120 °C         Area [%]       mg/L       Area [%]       mg/L       Area [%]         98.65       1.013       98.03       98.968       98.74         98.65       1.013       98.03       90.968       98.74         1.35       0.014       1.95       0.019       1.26         6       11       90.003       9.92       0.003       90.42			

## IL, Conclusions

The hydrolytic degradation behaviour of pyrazofe 4-4C]BCS-CN88460 and [phenyl-UB⁴C]BCS-CN88460 under conditions representative for food processing operations (pasteurization, baking, brewing, boiling and sterilization) was investigated.

BCS-CN88460 was predominantly stable under all tested conditions. The identification rates were very high. Degradation products detected under the tested conditions representatively for food processing were very minor (@0.5% and  $\leq 0.005$  mg/L) and were not Birther investigated.

All material balances were in the range of 104.2 to 104.2 to 104.2 to 104.2 to 100.5% demonstrating that no volatile degradation products were formed  $\sqrt{\frac{1}{2}}$ 

# CA 6.5.2

# Distribution of the residue in inedule per and pulp

The distribution of festidues of BCS-CN88460 between peel and pulp is not relevant for crops like cereals.

# CA 6.5.3 Magnitude of residues in processed commodities

According to the data requirements of the EU Regulation (EC) No 1107/2009, studies investigating the magnitude of resources sed commodities of barley are not required because:

- The residues in cereal grains are < 0 (Ping/kg (maximum 0.042 mg/kg for wheat grain)
- The contribution of barley grain or wheat grain to the theoretical maximum daily intake (TMDI) is 10% of the ADI (actually maximum of 0.7% for wheat grain using the proposed MRL of 0.05 mg/kg) and the estimated daily intake is  $\leq 10$ % of the ARfD (actually maximum of 0.06% for wheat grain using the proposed MRL of 0.05 mg/kg) for any European consumer group diet

Nevertheless representative processing studies on barley and wheat were conducted with field samples collected from supervised residue trials conducted in Europe or Northern America and are summarized below.



#### Barley

Report:	KCA 6.5.3/01; (2017; M-579494-01-1)
-	, 2017, M-5/5494-01-1
Title:	Determination of the residues of BCS-CN88460 in/on barley and the processes
	fractions (malt sprouts; brewer's malt; brewer's grain; hops draft; brewer's yeast; beets
	pearl barley rub off and pearl barley) after spray application of BCS-CN88460 EC950
	in the field in the Netherlands and Spain
Report No.:	15-3407
Document No.:	M-579494-01-1 & A A A A
Guideline(s):	
0	Regulation (EC) No 1107/2009 of the European Panhament and of the Council of 21
	OECD Guideline for the Testing of Chemicals on Criff Field Friel (JC: 500 publick)
	the market OECD Guideline for the Testing of Chemicals on Crep Field Trial (G 509 published in September 2009)
	OECD Guideline for the Testing of Chenoreals, Magnitude of the Pesticine Residues in
	OECD Guideline for the desting of Cheapcais, Magnitude of the Pesticide Residues in
	Processed Commodities (TG 598 published in October 2008)
	OECD Guidance document on magnitude offesticide residues in processed
	commodities, ENV/IM/MONO(2008)23 ~ A O K
	US EPA OCSPP & 60.1590, Crop Field Tyral
	US EPA OCSPQ 860/ 520, Processed Good/Feed
Guideline deviation(s):	none and the start of the start
GLP/GEP:	ves Q
	commodities, ENV/M/MOXO(2008)23 US EPA OCSPP 860.1500, Crop Field Frial US EPA OCSPP 860.1520, Processed Food/Feed none yes
	Weterials and Method and the
	29 I. Materials and Methods Q Q

The study included two supervised residue trials with barley, conducted in the field in southern Europe (Spain) and northern Europe (the Netherlands) in the 2015 ceason in order to determine the magnitude of the residues of BCS CN88460 in on barley grain and their processed fractions for the processing of beer (malt sprouts, bewer's malt brewer's grain hops traff, brewer's yeast and beer) and pearl barley (pearl barley rub of and pearl barley).

#### <u>Field part</u>

In the field trials BCS-CN88460 CC 050 was sprayed once at a nominal growth stage of BBCH 61 and at a nominal rate of 7 5L /ha corresponding to 375 g as that The water rate was of 300-400 L/ha, reflecting local practice in the trial regions. The application was performed with an exaggerated dose rate (5X) to attempt to generate a commonity with quantifiable residues. All treatments were made at the scheduled rates. In the trial 15-3407-02, the application was done at growth stage BBCH 53 instead of BBCH 61. Nevertheless this deviation was considered acceptable since the timing between application and harvest is not expected to be significantly impacted.

Barley grain samples were sampled at BBCH 89, 6 Pand 58 days after the last treatment (DALT) in trials 15-3407-01 and 13-340202, respectively.

Barley grain samples for the processing of grain into beer consisted of at least 25 kg and samples intended for the processing of barley grain into pearl barley consisted of at least 5 kg sample material. The specimens for processing were sent after sampling to the processing test site at

) under ambient conditions.

Furthermore, barley grain samples of at least 1 kg were taken (sampling called "barley grain") to determine the residues at har est. They were stored deep-frozen within 24 hours after sampling, until dispatch to the Laboratory for Sampling, Preparation Technique and Sample Logistics (PVTL), Bayer AG, Crop Science Division, formerly Bayer CropScience AG, in **Germany** am Rhein, Germany

Finally, barley grain samples were taken in the field (samplings called "grain, stored" and also referenced as Raw Agricultural Commodity (RAC)) at the same time as the samples for processing,



. The processing to pearl barley took place at C

under the responsionity

stored and shipped under the same conditions (ambient temperature) as the samples for processing and deep frozen at  $\leq 18^{\circ}$ C at the very time when the processing started.

#### **Processing procedures**

The cleaning of barley grain samples took place at the processing test site at

The malting process for the production of beer was performed under the responsibility of at Versuchs- und Lehranstalt fuer

and the subsequent brewing process was conducted by

## Technische

The processing simulates industrial practice at a laboratory scale. The processing of spring barley grain into the processed fractions (malt sprouts; brewer's malt; brewer's malt; brewer's grain hops draff; brewer's yeast; beer; pearl barley rub off and pearl barley was performed simulating the common industrial processes.

#### Cleaning:

All field specimens for processing were cleaned which allows the separation of soil particles and other contaminations from the grain in a steady air flow.

Before processing start the corresponding fresh grain samples vere deep-frozen, identified as grain, stored (RAC) samples and stored deep frozen at -18° Countil analysis

#### Malting (for the processing of beer)

#### Sieving

Before malting was started, the cleaned grain samples over sieved (sieve mosh 2.5 mm). Field samples for processing into beer were then shipped by car at ambient temperature to Versuchs- und Lehranstalt fuer

#### Steeping __

The steeping process was conducted as a combined wet and dry steeping. Sieved barley grain was transferred in a special steeping vessel. During steeping water is supplied to the interior of the kernel. As a result the enzymes become active and geomination begins. Water uptake depends on the steeping time, steeping temperature, kernel size barley variety and harvest year.

## Germination

The processes during germination can be divided into growth processes, enzyme formation and metabolic changes. Towards the end of steeping the rootlets break through the base of the corn and become visible. Activation of enzymes and formation of new enzymes are essential processes during germination (starch degrading enzymes, evolvtic enzymes, protein degrading enzymes and phosphoric acid splitting enzymes). For proper performance of germination it is necessary to control the duration of germination, the mean temperature of wet air and the relative humidity of the air around the kernels. During the intensive respiration the steeped good was turned over continuously.

## Kiln-drying

After germination, the life processes are terminated by kilning. During kilning the water content of green malt is lowered down to < 10%, germination and modification are stopped; colour and flavour compounds are formed. The malt becomes stable and storable. Kiln-drying was conducted in a dry chamber. After kiln-drying the germs (= malt sprouts) were removed mechanically by a trimmer. Brewer's malt and malt sprouts were sampled immediately after end of malting and were transported



#### to

Until brewing the malt was stored at room temperature at

#### Brewing (processing of malt to beer):

The brewer's malt specimens for brewing processing were shipped by car at ambient temperature to the processing location at the p

#### Mashing

Mashing is the homogeneous mixing of ground malt and water according to a definite temperature time regime (mash program). The main purpose of mashing (the dissolution and encymatic conversion of ingredients) is to form as much extract and as good an extract as possible. Before mashing, they brewer's malt was dry milled in a special malt mill. The crushed malt was mixed with brew water. To produce "Pilsener beer", mashing was conducted in a heatable run where the mash was heated up to 76°C.

#### Lautering: Wort extraction and separation

After mashing, the wort was separated from the insoluble malt components (brewer's grain). The extract remaining in the brewer's grain was extracted by washing with hot water (first fifter runnings). The wort separation was done using a refining vat After separation, the **brewer's grain** was sampled and immediately deep-frozen.

#### *Wort boiling and conditioning Q*

After addition of hop pellets, the separated wort was boiled (about 90 min at normal pressure). This process deactivates the malt enzymes, sterilizes the wort, extracts and isometrises the essential components of the hops, precipitates high molecular proteins (called "Brich") and expels unwanted aromatic substances.

After boiling, the flows (hops draft) were separated in a whirlpool causing the sludge to deposit on the bottom in the shape of a one. For cooling and ventilating the wort on intra-plant circulation was used. By adding oxysen (intra-plant circulation), the conditions for the start of the fermentation were prepared. Hops draft was sampled and immediately deep frozen.

## Fermentation and maturation 2

The pure culture yeast fermed is sugar of the wort to alcohol and  $CO_2$ , but in the course of the yeast metabolism also unwanted by products are formed (diacetyl, higher alcohols and others). In the pilot plant the classical primary fermentation (low fermentation) was carried out in bottom fermentation containers. The fermentation temperature was 9 °C. Fermentation heat was dissipated by means of room ventilation.

The duration of main fermentation depends on temperature, on starting extract concentration of the finished wort, on the ratio of non-fermentable sugars to the extract, on the final attenuation and on the yeast cell number. As soon as the extract content of the fermented young beer was 2 % higher than the final attenuation, the storing time began Before maturation the young beer was cooled down.

During the main fermentation, the yeast deposits on the tank bottom and was sampled as brewer's yeast and immediately deeperozer.

At the beginning of maturation the young beer was stored at room temperature (warm maturation to break down the maturation) in casks. Then the young beer was stored under pressure (approx. 0.7 - 2.1 bar) at  $2^{\circ}$ C (cold maturation) for approx. 4 weeks.

In this time the remaining extract was fermented. Unwanted flavour and odorous substances were decomposed or expelled. Sludge particles and yeast settled at the bottom.

The rack beer was filtered using a special filter combination. During filtration all organisms harming the beer (bacteria and yeast) were removed and sludge particles were separated.



The final product **beer** was sampled and immediately deep-frozen.

The processed products (brewer's grain, hops draff, brewer's yeast and beer) were kept in frozen stage (at or below -18 °C within 24 h after end of sampling) and shipped under deep-frozen conditions from a fermtec GmbH to and stored deep-frozen at  $<-18^{\circ}$ C until analysis.

#### Pearl barley production:

The processing part for the preparation of pearl barley was conducted at TU

. The specimens of cleaned barley grain, for processing into pearl barley, were shipped to the processing location TU

by car at ambient temperature from

#### Conditioning

Before beginning of pearl barley production, an optimal moisture confent of barley grain of approx 14% was achieved. In order to obtain acceptable milling results a mosture content of up to 16 % was possible. Therefore the grain was not dried or damped because the optimal poisture content was already achieved.

#### Hulling

The corresponding samples were huted using a vertical pulling machine. Each sample was hulled until the stipulated abrasion for pear barles (30 - 35%) was reached. The degree of abrasion (pearling dust/bran and flour) was determined by the proportion of pear barley with respect to the total portion of cleaned grain used for hulling process. Pearly and pearl parley and pearl parley and off were sampled.

The processed products (pearly barley, pearly barley, rub off) were shipped at ambient temperature to and gored deep frozen at \$-18°C until analysis

The processes are illustrated in Diagram 6.5 1 to Piagram 6.5 2.3.

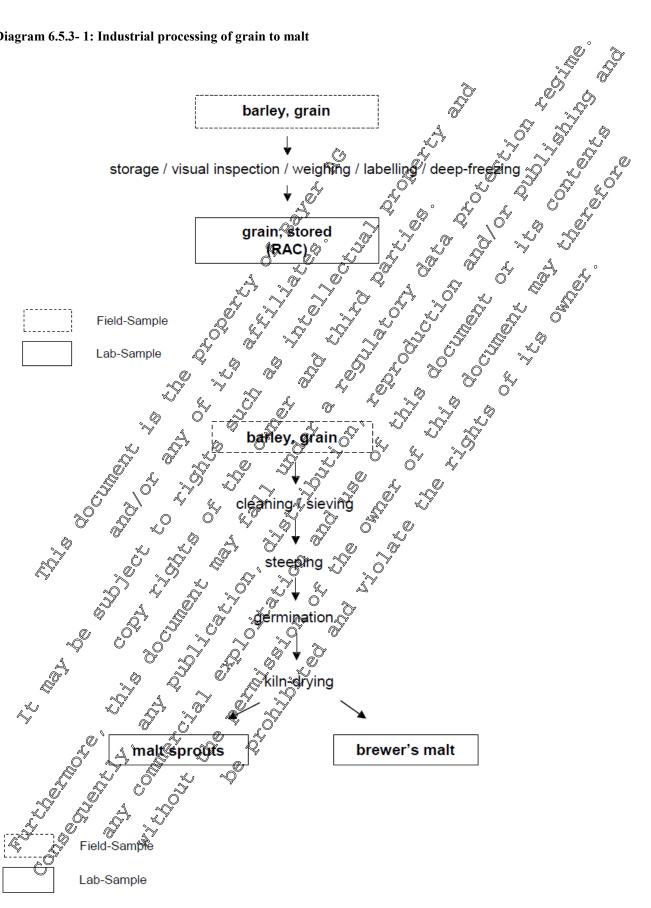
During processing barley grant laboratory samples of the various processing fractions taken at specific processing steps were immediately deep frozen and stored deep frozen at the processing test site until dispatch to RVTL. Upon reception at PVTL, samples of grain and processed commodities were stored in a freezer at 18°C or below unit preparation of the examination samples. For the preparation of examination samples, the samples of grain and processed commodities were shredded and homogenized with dry ice ip a cutor and stored at -18°C or below until analysis.

## **Residue** analysis

Ô 2 The samples were analysed for the parent compound using analytical method 01475 ( : 2016: M-558986-01-1; referenced in MCAOSection 4 under Point 4.1.2) which was validated prior to the residue analyste of the samples. Additiona Validation receveries were conducted for barley (grain) and barley (beer and brewer's yeast) in the studies 15-2066 and 15-3407, respectively. The samples of barley (grain), barley (brewer's grain), barley (brewer's malt), barley (brewer's yeast), barley (grain stored), Darley (hops draff), Darley (malt prouts), barley (pearl) and barley (pearl rub off) were analyzed according to the procedure described in the method for dry matrices (with a soaking step with water before extraction) and the barley (beer) samples were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The LOQ was 0.01 mg/kg for parent for all sample materials.

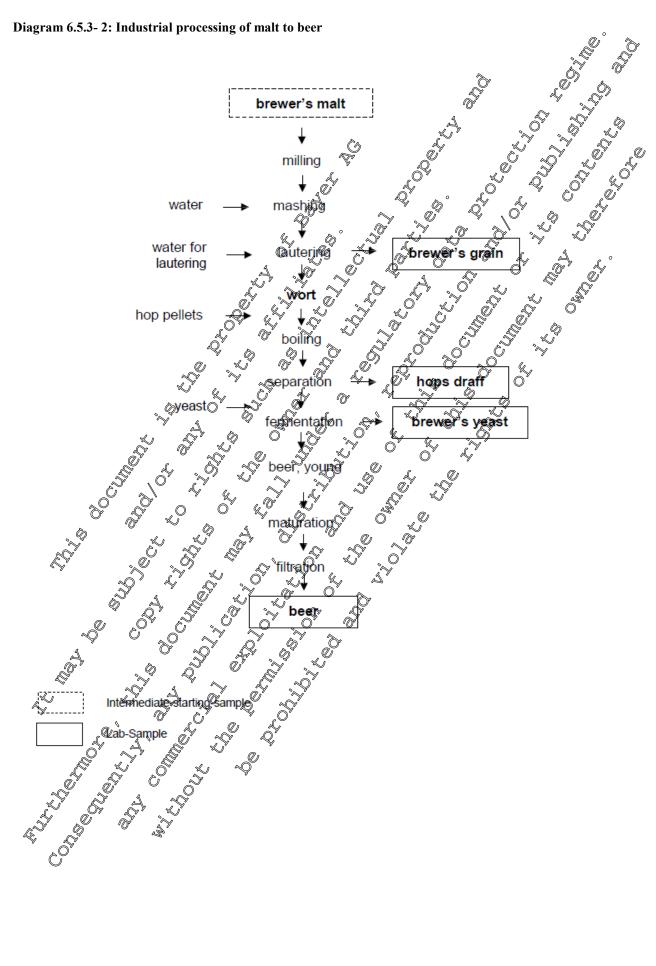


#### Diagram 6.5.3-1: Industrial processing of grain to malt

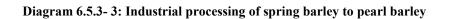


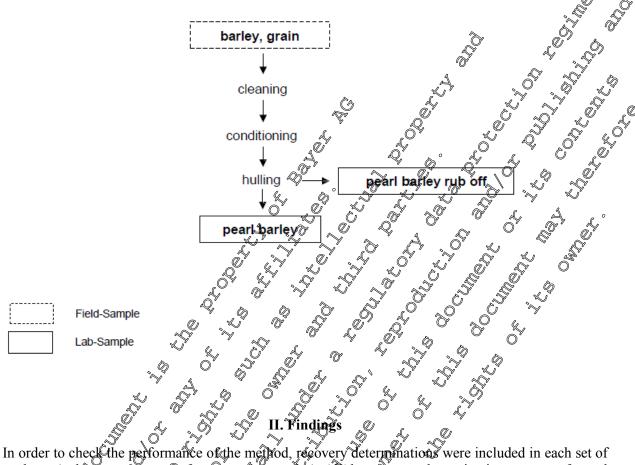


#### Diagram 6.5.3-2: Industrial processing of malt to beer









In order to check the performance of the method, recovery determinations were included in each set of analyses (at least one pecovery for the study samples). All the recovery determinations were performed concurrently to the analyses of control and treated samples from the study.

The sample materials barley brewer's grain, brewer's malt grain stored, malt sprouts, barley pearl and barley pearl rub off me considered equivalents to barley grain sample and the sample material barley hops draff is considered equivalent to sample barley brewer's yeast.

Details on concurrent performance of the result of the re

The levels of residues of BCS-CN88460 in the treated samples are summarized in Table 6.5.3-2. No residues above the LOQ were found in the control samples. The results were not corrected for concurrent recoveries  $\frac{1}{\sqrt{2}}$ 

Residues of BCS-CN88460 in barley grain a drarvest were found at 0.012 mg/kg in the first trial (the Netherlands) but  $\gtrsim 0.01$  mg/kg in the second trial (Spain).

The mean resplices tevels in the stored, barley grain (RAC for the calculation of the processing factors) were 0.015 mg/kg and 0.01 mg/kg in the first trial (the Netherlands) and second trial (Spain), respectively.

The levels of residue of BCS-CN88460 were < 0.01 mg/kg in all processed fractions except pearl barley rub of (0.032 mg/kg in the Dutch trial and 0.017 mg/kg in the Spanish trial).

The processing factors were calculated based on the residue levels in the treated processed fractions and the mean residue level of the rounded individual residues of the two RAC specimens for the corresponding processing procedure ("grain stored").When residues in the RAC and in the processed



fractions were both <0.01 mg/kg a processing factor could not be calculated. The proposed processing factors are summarised below in Table 6.5.3-3.

The analyses were done after a maximum frozen storage period of 396 days (grain) and 397 days (processed commodities). The time between the beginning of the sample preparation and the sample analysis did not exceed 24 hours.

#### **III.** Conclusions

Two residue trials were conducted in northern and southern Europe if 2015. Barlet was treated at a growth stage of BBCH 61 (53 in one trial) with an exaggerated dose rate (5X; 375, g a.s./ba) to attempt of to generate a commodity with quantifiable residues. All applications were at the equired rates

Barley grain was processed in order to obtain beer and pearl barley. The samples (RAC and processed fractions) were analysed for the residues of BCS-CN88460 patent compound.

The study was conducted according to GLP.

The results of the study clearly indicate that residues of BGS-CN88460 are diluted by the browing processing.

When barley grain are processed into pearl barley residues of BOS-CN\$8460 remain to a large extent in pearl barley rub-off and can be removed from barley grain by hulling, resulting in lower residues in the end product, pearl barley.

Q

	, ĝ		Fortiĝ-		 			
		.1	Fortig-	A A A A A A A A A A A A A A A A A A A	ery	%)		
Study	Portion	Â	cation		<i>.</i>	. O		
Study	analysed	6 m			Min	Max	Mean	RSD
			Mevel (mg/kg)		ſ	·¥		
15-3407	Beer of the second seco	A	0.01	× 81792; 9598 × 88; 100, 105 × 88; 100, 05 × 7 7 -	Ş	98	91	7.9
		3	<b>0</b> .1 &	88; 100; 105	88	105	98	9.2
•		XX.	Overall	NY N- NY	81	105	94	8.8
		<u></u>	0.301	98 ⁽²⁾ ·98 ⁽⁴⁾ ; 95 ⁽²⁾ ; 102 ⁽¹⁾ ;	90	117	102	8.4
	Brewer's grain ⁽²⁾		*	$102^{(1)}, 90^{(5)}; 110^{(7)}, 17^{(6)}$				
	Grain stored ⁽³⁾ Brewer s mal	2	\$ 0.1^~	$110^{1}; 101^{(1)}$	101	113	107	-
	Malt sprouts	Ħ	Overall	× \$ -\$	90	117	103	8.2
	Rearl ⁽⁶⁾	Ĵ,	$\sim$					
	Pearl rub off ⁽⁷⁾		Y R'					
ţ,	Brewer's yeast (8)	ð	0.01	$3^{(12^{(8)})}, 30^{(8)}; 106^{(8)}; 106^{(8)}; 106^{(8)};$	97	112	105	5.1
				97 ⁽⁹⁾				
L.	Hops drafty	3	¥ 0.1 Q		97	102	100	2.6
		28	Querall	- -	97	112	103	4.9

Table 6.5.3-1: Concurrent recovery data for BCS-CN88460 in barley and Barley matrices

RSD: Relative sondard deviation

Indexes at the values of recoveries correspond to the indexes at the commodities (given in the column – "portion analysed")

<u>Remark</u>: cample material barley brever's malt; brewer's grain; grain stored, malt sprouts, pearl barley; and pearl barley rub-Soff are considered equivalents to barley grain and sample material hops draff is considered equivalent to brewer's yeas yeas



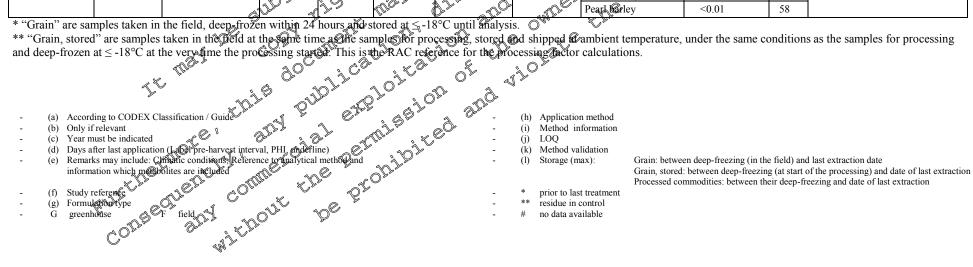
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Table 6.5.3- 2           Analyte 1: BCS-C		ed results of the h	• 1	U			A	let BG	DET TI	, (	on regime and		
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	pr			Application rate per treatment no. of			Growth stage at last treatment or Gate	Portion analyz	zed c • Residues	PHI (dagy)	Difference of the second secon
			g a.s./ha	Water (L/ha)	g a.s./hL _≪	er aft	ter.		Analyte I	L. T. B			
	(a)	(b)			, ne	Ģ(c)	JII D	<u>~~</u> ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	BES-CN88460	(d)	К ^{LL} (е)		
15-3407-01 15-3407-01-T Netherlands Europe, North F 2015	Barley Triple; summer	1) 23.04.2015 2) 29.06.2015 - 06.07.2015 3) 15.08.2015 - 01.09.2015 - 00.0015 - 00.001	375 docum anc upject coet					Grain * Buer processing Grain, stored ** Malt spronts Brewer's grant Hons draff Brewer's yeast Beer Read barley pro Grain, stored ** Pearl barley rub Pearl barley	0.012 0.012 0.018 0.018 0.018 0.015 0.015 0.01 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.013 mean: 0.015 0.012 0.012	61	<ul> <li>(f) 15-3407</li> <li>(g) EC (50 g/L)</li> <li>(h) Spraying</li> <li>(i) 01475</li> <li>(j) 0.01 mg/kg</li> <li>(k) Method Validation Data in 01475 and in study 15-3407</li> <li>(l) grain: 303 days</li> <li>grain, stored: 299 days</li> <li>malt sprouts: 161 days</li> <li>brewer's malt: 161 days</li> <li>brewer's grain: 151 days</li> <li>hops draff: 161 days</li> <li>brewer's yeast: 152 days</li> <li>beer: 115 days</li> <li>pearl barley rub off: 297 days</li> <li>pearl barley: 297 days</li> </ul>		
<ul> <li>(a) Accor</li> <li>(b) Only i</li> <li>(c) Year r</li> <li>(d) Days a</li> <li>(e) Remaninform</li> <li>(f) Study</li> <li>(g) Formu</li> <li>G green</li> </ul>	ding to CODEX Cli f relevant must be indicated ther last application ks may include: Cli ation which mean reference to the second second to the second second to the second second second to the second second second to the second second second second to the second second second second second to the second second second second second second to the second secon	assification / Guide the of (LGO) Pre-harvest interv market conditions Referen- bites are included of the the the the the of the the the the the of the the the the the the the of the the the the the the the the of the the the the the the the the the of the	al, PHI, oderli nce to that ytical	P ne) methogand C D C C C C	ni gg r Di bjit		<ul> <li>(h) Applicatio</li> <li>(i) Method ir</li> <li>(j) LOQ</li> <li>(k) Method va</li> <li>(l) Storage (rr</li> <li>* prior to las</li> <li>** residue in</li> <li># no data available</li> </ul>	n method aformation lidation tax): Grain; Grain; Proces at treatment control ailable	: between deep-freezing (in the stored: between deep-freezing ssed commodities: between the	g (at start o	l last extraction date of the processing) and date of last extraction sezing and date of last extraction		



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<b>T</b> • 1N /		Date of				Dates of		₿ [©]	J.	ð	gline .
Trial No. / Location / EU zone / Year	Commodity / Variety	1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Applicat	ion rate per	treatment	treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analyzed	Residues (mg/kg)	PHI (days)	Det Detail On trial
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	(c)~ ^{t~1}	OF FE	otual rie	ې Analyte کې BCS-C 888460		plit. ents
15-3407-02 15-3407-02-T Spain Europe, South F 2015	Barley Traveler; Malting barley	1) 18.12.2014 2) 07.04.2015 - 14.04.2015 3) 25.05.2015 - 25.06.2015 the field, deep froze	ND Ject	JORTO	125 EDE DOF DOF ED OF ED	iter as such and cowner cowner cowner cowner cowner cowner cowner cowner cowner cowner cowner	ding rec x d rec x i oin ' vise of	Grain * Beer processing Grain, stored * Brewer's math Brewer's grain Hope draff Brewer's grast Been Pearl barley processin Grain, stored ** Pearl barley processin Pearl barley processin Pearl barley processin	<pre></pre>	58 58 58 58 58 58 58 58 58 58 58 58 58 5	(r) 15-3407 (g) EC (Fog/L) (h) Spaying (i) 91475 (j) 0.01 mg/kg (k) Method Validation Data in 04475 and in study 15-3407 (g) grain: 396 days grain, stored: 321 days malt sprouts: 161 days brewer's malt: 161 days brewer's malt: 161 days brewer's grain: 149 days hops draff: 159 days brewer's yeast: 151 days beer: 114 days pearl barley rub off: 297 days pearl barley: 297 days





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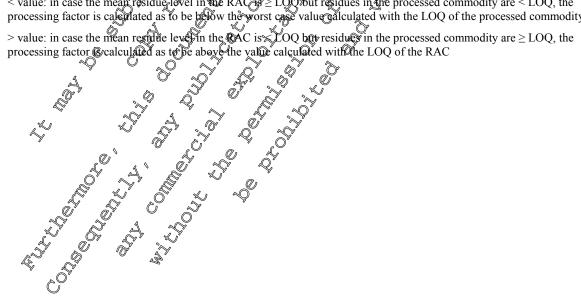
Т	L' D				
Crop, Processed commodity	Number of trials	Trial number	Residues (mg/kg)	Individual processing factors (a)	Proposed processing factor Rf
Barley, grain (RAC)	2	15-3407-01 15-3407-02	0.015 (61 days after treatment) <0.01 (58 day ofter treatment)		
Barley, malt sprouts	2	15-3407-01 15-3407-02	<0.01 <0.01	< 0.67 1. Q.	
Barley, brewer's malt	2	15-3407-01 15-3407-02		0.6₹ 0.6₹	© 0.67
Barley, brewer's grain	2	15-3407-01 15-3407-02		<0.67	جمع .67 ۲ °
Barley, hops draff	2	15-3407-0 15-3407 2		× < 9.67	\$ \$ \$
Barley, brewer's yeast	2	15-3407-02 15-3407-02	<0.04 <0.061 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	0 < 0 €7 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	مَنْ < 0.67
Barley, beer	2	¥5-3407-01		0.67 n.e.	< 0.67
Barley, pearl barley rub off		15-3407 <i>4</i> 91 275-3405-202		م م الم الم الم	2.1
Barley, pearl barley		15 ² 3407-0% 15⊻3407-092		<ul><li>&lt; 0.67</li><li>n.c.</li></ul>	< 0.67

### Table 6.5.3-3: Proposed processing factors for barley

(a): Processing factors (PE) = residues in processed commodities / residues (mean) in the RAC collected at the processing lab Š Ô ("grain stored") Ø O

No processing factor car be calculated (residues <LOQ in RAC and in processed commodity) n.c

< value: in case the mean residue level in the RAC  $2 \ge LQO$  but residues in the processed commodity are < LOQ, the processing factor is calculated as to be below the worst case value alculated with the LOQ of the processed commodity





#### Wheat

Report:	KCA 6.5.3/02; <b>Magnitude</b> , A. M.; 2017; M-600505-02-1 BCS-CN88460: Magnitude of residues in/on wheat processed fractions following treatment with BCS-CN88460 EC50
Title:	BCS-CN88460: Magnitude of residues in/on wheat processed fractions following 6
	treatment with BCS-CN88460 EC50
Report No.:	RALNN137 🔊 🔧 🖓
Document No.:	M-600505-02-1
Guideline(s):	PMRA DACO 7.4.1, Supervised Residue Trial Study,
	PMRA DACO 7 4 5 Processed Food Beed
	OECD Test Guideline 509: Crop Field Trial $\sqrt{2}$
Guideline deviation(s):	None
GLP/GEP:	yes $\int_{0}^{0^{\prime}} \int_{0}^{0^{\prime}} \int_{0}^{0} \int_{$

I. Materials and Methods

The study included two supervised residue thals with wheat, conducted in the field in Canada in the 2015 season in order to measure the potential concentration of BCS CN88460 residues in the wheat processed products of grain, aspirated grain, middlings, gern, flour, shorts, bran, wheat white bread, whole meal flour, whole meal, bread gluten, stareb, fresh pasta, cooked pasta, cooking water, dry pasta, dried and cooked pasta.

#### <u>Field part</u>

In these two trials (C1101-15RA and C1102-15PA) one untreated control plot (CTC) was used for the generation of the control samples (untreated samples).

The study design included two treated plots for each trial. The application rate in the TRTD1 plot was made at 3X the maximum seasonal label use rate. The application rate in the TRTD2 plot was made at 5X the maximum seasonal label use rate. Only the treated wheat from the TRTD2 plot was harvested, the TRTD1 plot was not used, and no further data were reported from this plot.

In each field trial, the treated plot TRTD2 was strayed once at BBGD 69 (end of flowering) with BCS-CN88460 EC50 at an application rate of 375 g a.s. Pa using a spray volume of 120-122 L/ha. The applications were made using ground-based equipment with no adjuvant. The application was performed with an exaggerated dose rate (5X) to attempt to generate a commodity with quantifiable residues.

A single composite sample of wheat grain was harvested from the TRTD2 treated plots at commercial maturity (pre-hadvest intervals (PHIS) were 69 and 67 days for C1101-15PA and C1102-15PA respectively). A single composite sample of wheat grain was harvested from the control plot on the same day the sample was harvested from the treated plot.

One control and one treated bilk wheat grain sample weighing at least 300 kg were harvested at maturity following commercial agronomic practices (threshed using a plot combine). The bulk wheat grain samples were placed into labelled (study number and sample number) containers and placed in cool (ambient) storage until shipment, via ambient transport, to the processing facility. Upon receipt at the processing facility, the samples were pransferred to frozen storage, and remained frozen until processing (maximum bulk sample ambient temperature interval was 33 days).

Triplicate samples of wheat grain, weighing a minimum of 1 kg, were collected from the UTC and TRTD2 plots at the same time the bulk wheat grain samples were harvested (samples called "grain collected at the field site"). These samples were frozen within four hours after collection, and shipped frozen, via CDS beczer truck, directly to the laboratory. Upon arrival at Bayer CropScience RTP, all samples, were immediately transferred to frozen storage (average temperature -21°C).

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#### Processing procedures

Processing took place at the processing site at GLP Technologies, 22723 State Highway 6 South Navasota, TX 77868 USA.

Samples were handled and processed in a manner that minimizes the possibility of contamination. Trials were processed independently. Control samples were processed prior to reated samples.

After removing bulk wheat grain samples for aspirated grain fraction generation and processing from freezer storage, representative unprocessed wheat (RAC) samples were collected in triplicate and placed into frozen storage (samples called "grain" or "grain collected at the processing site in Table 6.5.3-5).

Commercially representative aspirated grain and processed food feed fractions were produced follows.

#### Generation of Aspirated Grain Fraction (AGR)

Moisture content of the samples was determined with an electronic moisture analyzer of the moisture content was greater than 13.0%, a sample was dried at 110-135°F 143.3 57.2 °C) in Steelman Industries oven until the moisture content was 10.0-13.0%. Samples from trial Ct102-t5PA required drying.

To generate aspirated grain fractions, each sample was placed in a dist generation from containing a holding bin, two bucket conveyors, and a screw conveyor. As the sample was neved in the system, aspiration was used to remove light impurities (grain dust). Each sample was neved for 120 minutes. Light impurities were classified using the following sieves: 2360  $\mu$ m (8 mesh); 2000  $\mu$ m (10 mesh); 1180  $\mu$ m (16 mesh); 850  $\mu$ m (20 mesh); and 425  $\mu$ m (40 mesh). After classification of each sample, the material through the 2360  $\mu$ m sieve was recombined according to Study Director's instructions to produce one **aspirated grain fraction (ACF)**. A representative sample was removed and the ash content was determined.

#### Wheat Milling

#### Cleaning

Following AGF generation, samples were cleaned by aspiration and screening. Light impurities were removed using a Kice aspirator. After aspiration, samples were screened in an Enhanced 2 screen cleaner to separate large and small foreign particles (screenings) from the cleaned grain.

#### Germ Production

Cleaned wheat was more ture adjusted (tempered) to 16% by adding reverse osmosis (R/O) water to the wheat and mixing. After tempering for 1-5 hours, the wheat was passed through the Glen Mills disc mill. Ground material was sifted with a Swee's Dynascreen equipped with a 8-, 14-, and 30-mesh sieve. Material on top of the 30 mean sieve was aspirated to remove bran from the germ fraction. Germ (with endosperna) was passed through the reduction side of the Chopin CD-1 mill. Germ and reduced endosperna were separated using the Great Western sifter equipped with the following screens: 18, 20, 24, and 28 mesh. Germ material was aspirated again to remove additional bran and milled/sieved to remove additional endosperm. A 0.5-1.0% recovery of germ was expected. Germ fractions were collected and placed into frozen storage.

#### Flour Production

Cleaned wheat was moisture conditioned (tempered) depending on the physical property of the wheat. The physical property of the grain kernel varies depending on whether the grain has a floury or viteous kernel. In a floury kernel, a cross-section of the grain reveals a grainy soft white structure. The cross section of a vitreous grain is hard and amber colored. There are grains with an intermediate structure (a floury and vitreous part). All samples were determined to be of intermediate structure and were moisture adjusted and tempered accordingly:



- floury grain wheat: 16.5% moisture adjustment with a 24 hour +/-30 minute resting period before milling
- vitreous grain wheat: 17.5% moisture adjustment with a 48 hour +/-30 minute resting period before milling
- intermediate structure: 17.5% moisture adjustment with a 24~hour &- 30 minute resting period before milling

Tempered wheat was fed through the spout on the break side of a Chopin mill. Breaking of the wheat was accomplished by three break rolls. After passing through the break rolls, the material was ted onto the break sifter screen. The screen consists of two sizes. The screens are numbers 120 (140  $\mu$ m) and 25 (800  $\mu$ m). Material exiting the break rolls passed over the 120 tirst. Material passing through the 25 screen is "Break Flour." Material not passing through was conveyed over the 25 screen. Material passing through the 25 screen is middlings. Materiar not passing through was conveyed to the end of the sifter. Material exiting the end is Bran (Coarse). After breaking, it is necessary to determine if more than one reduction will be required. If the "Maddling" fraction is 48% of less of the starting weight, then one reduction is required. If more than 48% is obtained, two reductions are required. Samples from both trials required one reduction? Required middling fractions were collected and placed into frozen storage.

Remaining middlings were poured into the feed hopper of the reduction system Reduction is achieved through two reduction rolls. After passing through the reduction rolts, the material was fed onto a number 100 (160  $\mu$ m) reduction streer screen. Material passing through the screen is reduction flour. Material not passing through and conveyed to the end of the sifter is shorts. Representative amounts of break and reduction flours were mixed to produce standard mill run (white flour). Requested flour fractions were collected and placed into fiber storage.

Remaining standard mill run flour was used in the production of white bread Remaining break and reduction flour was used in the production of starch glutes, and pasta.

Bran exiting the break since is placed to the reduction side of the mill, but is not reduced with the rollers. The coarse bran is conveyed by beater bars over a number 146 screen (128  $\mu$ m). Material passing through the screen is "Shorts" and is added to "Shorts" from the reduction mill. Material passing over the screen and exiting the end is "Bran" Requested **bran** and **shorts** fractions were collected and placed into frozen storage.

#### Processing into White Bread

Standard mill run flour, sngar, dry milk, salt, margarine, water and dry yeast were placed in a Sunbeam bread machine. The machine was set for type bread (Basic), 2 lb (0.91 kg), loaf size and medium color. The machine automatically mixed the ingredients, let the dough rise and baked the bread. After coling requested white bread fractions were collected and placed into frozen storage.

### Processing into Whole Meal Flour and Whole Meal Bread

Cleaned wheat was ground in an Alpine on millo Ground material was whole meal flour. Requested "Whole Meal Flour" fractions were collected and placed into frozen storage. Remaining whole meal flour was used to produce "Whole Meal Bread".

Whole meal flour, brown sugar, sale margarine, water and dry yeast were placed in a Sunbeam bread machine. The machine was set for type bread (Whole Wheat), 2 lb (0.91 kg) loaf size and medium color. The machine automatically mixed the ingredients, let the dough rise and baked the bread. After cooling whole the all bread fractions were collected and placed into frozen storage.

### Wheat Gluten and Starch Production

For vital wheat gluten and starch, break flour was mixed with water at a rate of 0.4-0.8 pounds (0.18 - 0.6 kg) of water to one pound of flour (0.45 kg). The dough was allowed to rest for two hours. After resting, the dough was kneaded as water washed away the starch, leaving the gluten. Product was water washed until water ran clear, indicating all starch was removed leaving gluten. Starch was



separated from the water using centrifugation and dried in a dehydrator or Steelman Industries oven at 130-160°F (54.4 – 71.1°C) until the moisture content was less than 15%. Gluten was dried with a Blaw-Knox steam heated drum dryer. Temperature is not monitored during drying. After drying,  $\sim$  requested **starch** and **gluten** fractions were collected and placed into frozen storage.

#### Pasta (Noodle) Production

Equal parts of break and reduction flours were mixed with R/O water and salt to form a dough This dough was kneaded and allowed to rest for 20-40 minutes. Dough was fed into a Lello pasta machine, to produce a fresh Asian noodle. A portion of the **fresh noodles** were collected and placed into frozen storage. Requested fresh cooked noodles were produced by placing tresh noodles into boding water (10:1 ratio water to noodles) for 1-4 minutes. **Cooked noodles** were cooled, collected and placed into frozen storage. Requested **cooking water** fractions were also collected and placed into frozen storage.

A portion of the fresh noodles were dried for eight hours at 75.95°F ( $2^{9}.9 - 35.0^{\circ}$ ). Requested dried noodle fractions were collected and placed into frozen storage. Remaining dried poolles were placed into boiling water (10:1 ratio) for 1-4 minutes. After cooling, requested dried rooked noodles were collected and placed into frozen storage.

The processes are illustrated in Diagram 9.5.3

Wheat aspirated grain fractions, and the wheat processed commodities were stored deep-frozen  $\leq$  12°C) until shipment to Bayer CropScience,  $\square$ , NC. Upon arrival at Bayer CropScience  $\square$ , all samples, were immediately transferred to frozen storage (average temperature -21°C). The wheat grain RAC, bran, pasta (fresh, dry, cooked, and dried and cooked) white bread, and whole meal bread were homogenized with dry ice using a Robot Coupe (Model RSI2Y4 or RSI30B); wheat flour, whole meal flour, germ, middlings, shorts, Quten, starch aspirated grain fractions, and cooking water were considered homogenous. All samples were returned to frozen storage infinediately following homogenization, and the samples remained frozen of all finnes except during subsampling for analysis.

#### Residue analysis

The samples were analysed for the parent compound using analytical method LN-002-P16-01 ( 2017; M-606616-01-1; referenced in MCA Section 4 and 5 out 4, 1.2). The LOQ was 0.01 mg/kg for parent for all sample materials

BCS-CN88460 residue was chracted from wheat grain, aspirated grain fractions, and all commodity samples except cooking water by blending an aliquot of the homogenized sample in acetonitrile/water (4:1, v/v). The extract was amended with an isotopic internal standard (IS) mixture, and an aliquot was further diluted and analyzed by high performance figuid chromatography/triple stage mass spectrometry (LC/MS/MS).

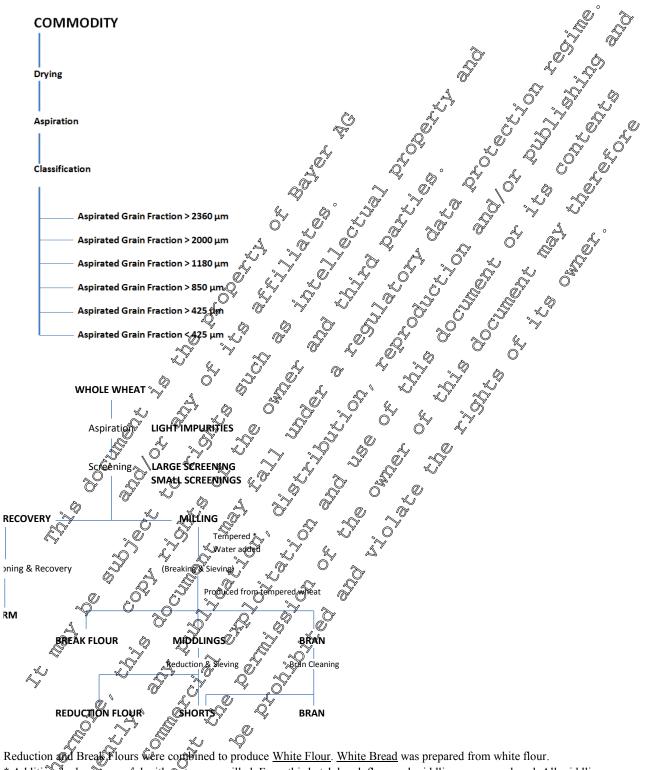
BCS-CN88460 residue was extracted from cooking water samples by diluting an aliquot with acetonitrile water (4:1, y/v) and shaking. The extract was amended with an isotopic internal standard (IS) mixture, and an aliquot was further diluted and analyzed as noted above.

Method performance was evaluated doring method validation and by use of concurrent recovery samples in the report RALNN\$7 (**1999**), A. M.; 2017; M-600505-02-1; KCA 6.5.3) by fortifying wheat grain and the wheat processed composities at 0.010 ppm and at 0.10 ppm. The method was validated in wheat apprated grain fractions at 0.010 ppm and at 2.50 ppm.

the second secon







Reduction and Break Flours were combined to produce <u>White Flour</u>. <u>White Bread</u> was prepared from white flour. * Additional wheatempered with water was milled. From this batch break flour and middlings were produced. All middlings were reduced to produce reduction flour. The additional break and reduction flours were used in the production of starch, gluten and parts (fresh, fresh cocked, dried, and dried cooked).

Cleaned wheat was ground into Whole Meal Flour. Whole Meal Bread was prepared from whole meal flour.

Break flour was used to produce Gluten. Starch was dried and collected during gluten production.

Break and reduction flour were used to produce <u>Fresh Noodles</u>; Cooked pasta (Noodles) were prepared from fresh noodles. Fresh Noodles were dried to produce <u>Dried Noodles</u>. Dried noodles were used to prepare <u>Dried Cooked Noodles</u>.



#### II. Findings

The method for determining BCS-CN88460 residue was validated in/on wheat grain, wheat grain fractions, and wheat processed commodities by measuring the recovery of BCS-CN884(d) from control matrices fortified at their LOQs of 0.010 ppm. Additional recovertes at 0.100 ppm were measured for all commodities except aspirated grain fractions. The high method validation for aspirated grain fractions was conducted at 2.5 ppm. These recoveries levels validated the method for the highest residues observed in individual matrices. Concurrent recoveries of all analytes were measured with each set of samples to verify method performance.

Details on concurrent recovery data are shown in Table 6.5.3-4. The average recoveries were within the acceptable range of 70 - 110%. The RSD values were below 20%. The method was considered valid for the analysis of BCS-CN88460 residue in all wheat matrices.

No residues above the LOQ were found in the control samples. The tevels of residues of BCS-CN88460 in the treated samples are summarized in table 65.3- 60 nly esidue values above the LOQ are reported. Any residue value that was below the LOQ is reported as tess than the EOQ. The reported residue values were not corrected for residues in controls or for concurrent recoveries.

Analysis of the triplicate wheat grain subsamples collected at the field site on the day the bulk samples were harvested confirmed that no significant degradation of BCS-CN88460 residue occurred during ambient storage and shipment of the bulk samples. Indeed, the mean residues levels of BCS-CN88460 in wheat grain (collected at the field site) were found at 0,0160 ng/kg in the first triak (C1101-15PA) but < 0.010 mg/kg in the second trial (C1402-15PA). The mean residues levels of BCS-CN88460 in wheat grain (collected at the processing site) were found at 0.0137 mg/kg in the first trial (C1101-15PA) but < 0.010 mg/kg in the second trial (C1402-15PA).

In trial C1101-15-PA, where pesidues in the RAC were above the LOO, residues of BCS-CN88460 in white flour, middlings, white bread, whole meal bread starch and pasta (fresh, fresh and cooked, dry, dry and cooked) and cooking water were below the DOQ. Besidues of BCS-CN88460 were at 2.35, 0.0189, 0.0181, 0.0134, 0.0107 and 0.0151 mg/kg if, aspirated gram fraction, bran, germ, shorts, whole meal flour and gluten respectively.

In trial C1102-15-PA, where residues in the PAC were below the LOQ, residues of BCS-CN88460 were below the LOQ in all processed commodities except spirated grain fraction (0.919 mg/kg).

The proposed processing factors calculated for each commodity for each of the two independent field trials are summarised below in vable 6.5.3- of They slightly differ from the table on page 18 of the report. In Table 6.5.3- of the processing factors were defined as the residue in the processed commodity divided by the residue in the RAC collected at the processing laboratory. When residues in the RAC and in the processed fractions were both 0.01 mg/kg of processing factor could not be calculated.

The analyses were done after a maximum frozen storage period of 402 days (grain) and 119 days (processed commodities). All sample extracts were analyzed within five days of extraction. Acceptable recoveries measured concurrently with each set of samples ensured the integrity of the sample extracts during the period of time between extraction and analysis.

Market III. Conclusions

Two residue trials were conducted in Canada. Wheat was treated once at a growth stage of BBCH 69 with an exaggerated dose rate (5X; 375-382 g a.s./ha) to attempt to generate a commodity with quantifiable residues.

Wheat grain was processed in order to obtain aspirated grain fraction, middlings, germ, white flour, shorts, bran, white bread, whole meal flour, whole meal bread, gluten, starch, fresh pasta, cooked fresh pasta, cooking water, dried pasta, dried and cooked pasta.



The samples (RAC and processed fractions) were analyzed for the residues of BCS-CN88460 parent compound.  $\hfill \circ$ 

The study was conducted according to GLP.

The results of the study indicate that residues of BCS-CN88460 are concentrated in the aspirated grain fraction, and in a lesser extent in bran and germ. Similar residue levels as in wheat grain are observed in shorts, whole meal flour and gluten, whereas a dilution of residues is observed in middlings, starch, white flour and the subsequent production of pasta (fresh, dried, fresh, and cooked, and dred and cooked), as well as in bread (prepared from white and whole meal flours).

Study	Portion analysed	n	Fortifi- cation level (mg/kg)	Individual recoveries	~	Max	Mean	A	
RALNN 137	Grain	11 6	0.01 0.1	92, 94, 96, 97, 92, 910 101, 102, 109, 95, 98 27, 97, 98, 99, 95, 102, 0	99 97 97		الم م م م		
	Aspirated Grain	3 3	000Y	93, 90, 190 0 105, 100, 106, 5	90 900	106 106	2904 v		
	Middlings	3	2 0.04 0.1	0 ² 1015101, 99         0 ² 0 ² 98, 102, 100         0 ²	990 \$	5 101 102	000 100 100	1 2	
	Germ	3 3	0.01 0.1	y @ 95, 99, 99	\$95 884	~99 \$101~\$	\$98 95	2 7	
	White Flour	3	0.91	© 191, 99, 400 ° © 395, 95, 100 °	©99 095	104 100	100 97	1 3	
	Shorts	3	0.01 0.01	9 118 114, 99 0 99, 101 102	930 88	118 102	108 101	12 2	
	Baan	U3 3 3	0.01 0.1	97, 94, 103 93, 95, 94 93, 95, 94	,©94 93	103 95	98 94	5 1	
Ĩ,	White Bread	5) 3	0.01	019,94,999 0 0 v 96,993,96 2	94 93	109 96	101 95	8 2	
	Whole meal tour	3	0.04 0.1	91,96,995 4,89 <i>6</i> 5	91 89	99 95	95 93	43	
	Whole meal	Q3 3	~0.01 0.5	97,83,97 95,91,91	92 91	97 95	95 92	3	
, 40 1	Gluten	3 3 3 3	0.01	97, 101, 95	95 97	110 101	100 99	9 2	
~	Starch	3	0.01	100, 98, 117 100, 101, 101	98 100	117 101	105 101	10 1	
	Pasta, Fresh	3 3	0.01 0.1	80, 86, 95 83, 95, 88	80 83	95 95	87 89	9 7	
L.	Paster Cooked		0.01 0.1	103, 91, 120 97, 98, 99	91 97	120 99	105 98	14 1	1
	Cooking Water	3 3	0.01 0.1	92, 95, 94 99, 96, 95	92 95	95 99	94 97	2 2	

Table 6.5.3- 4: Concurrent recovery data for	BCS-CN88460 in	wheat and v	vheat matkices
v	.01	×	0



			Fortifi-	Reco									
Study	Portion analysed	n	cation level (mg/kg)	Individual recoveries	Min	Max	Mean	RSD					
	Pasta, Drv	3	0.01	94, 89, 83	83	94) A	89	P 5					
		3	0.1	93, 92, 87	87	<i>8</i> 3°	91						
	Pasta, Dried	3	0.01	94, 96, 99	94	<u>4</u> 99	96 Ő						
RSD: Rela	and Cooked         3         0.1         101, 97, 101         97, 101         1007         37           D: Relative standard deviation         87         87         87         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         97         101         1007         37         101         1007         37         101         1007         37         101         1007         37         101         1007         37         101         1007         37         101         1007         37         101         1007												
				94, 89, 83         93, 92, 87         94, 96, 99         101, 97, 101									



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		sults of the whe	•	U				ler bc	OCT TY	and.	on regine ond
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Applicatio	on rate per	treatment	Dates of treatment or no. of treatments and last date	Growth stage At last treatment or date	Portion analyzed	Residues (mg/kg) *** ***	CPHI (days)	CONTRACTOR
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	P ^T O ^T	jntel.	in por	Analyte A	c. (d)	there t
C1101-15PA TRTD2 plot Canada Sakatchewan Region 7 America, North F 2015	Wheat Conquer	1) 21.05.2015	382	122 2017 107 70	any ight of	233072015/0 BUCID OWDER DE UDO	ale rec	Grain collected at the first site * Grain collected at the first site * Grain collected at the processing site ** Generation of Aspir Aspirated grain fractions	0 ⁰ 0.0136 0.0143 mean: <b>0.0137</b>	1000 607	<ul> <li>(h) Spraying</li> <li>(i) 2N-002-P16-01</li> <li>(j) 0.01 mg/kg</li> <li>(k) Method Validation Data in LN-002-P16-01 and in study RALNN137</li> <li>(l) grain (collected at field site): 397 days grain (collected at processing): 115 days aspirated grain fractions: 111 days germ: 98 days middlings: 97 days</li> </ul>
	J. ^E	ay De si				ai ^s ad		Germ production Germ Production Flour production Middlings Bran Shorts White flour	0.0181 <0.010 0.0189 0.0134 <0.010	69 69 69 69 69	bran: 90 days shorts: 119 days white flour: 92 days white bread: 111 days
	at the field site of	C 1 0	\$ @	Chu	M ¹ SS			Processing into white White bread	te bread <0.010	69	

* Grain collected at the field site for frozen within 4 hours and stored at organ started grain fraction generation and processing from freezer storage, representative unprocessed wheat (RAC) samples were collected and placed into frozen storage. This is the RAC reference for the processing factor adculations.
*** For wheat grain (sollected at the field site and collected at the processing factor), the results are individual analyses of three separate samples. For the processed commodities, the results are the mean of three analyses of a single sample.

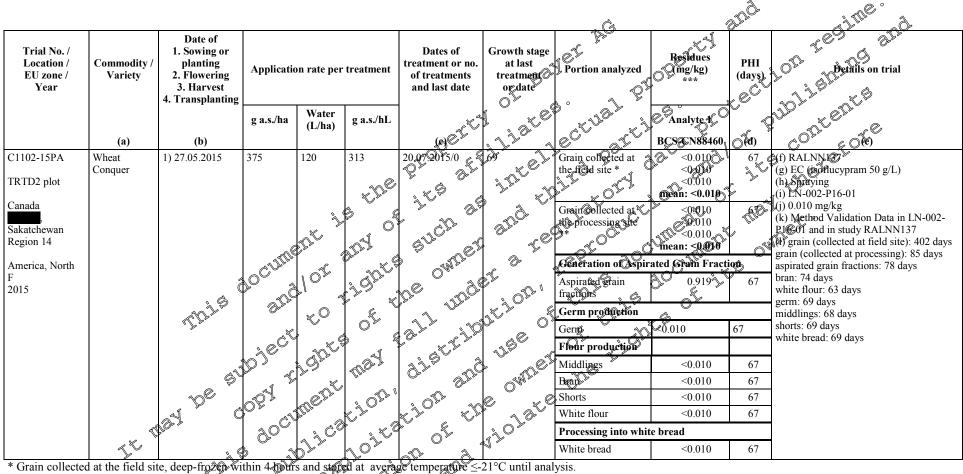


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								A.	at A Di	Ð	regine .
Trial No. / Location / EU zone / Year	Commodity / Variety	Date of 1. Sowing or planting 2. Flowering 3. Harvest 4. Transplanting	Application	n rate per	treatment	Dates of treatment or no. of treatments and last date	Growth state at last troatment or date	Portion analyze	Residues (mg/kg) e	PHA Bays)	$\frac{r^{e9}}{\rho^{1}}$
	(a)	(b)	g a.s./ha	Water (L/ha)	g a.s./hL	OT CO F			Audyte 1	ي (ما <i>بر</i> )	(e)
C1101-15PA					the		12	Processing into who	BCS-CN86460	ole	(i) LN-902-P16-01
TRTD2 plot					E Pr	JUP OF		Wholemeal flour	0.81.07	690	(j) 0.01 mg/kg (k) Method Validation Data in LN-002-
Canada				Ĵ				Whole meabbroad		<u>Gros</u>	P16-01 and in study RALNN137 (1) Whole meal flour: 90 days
Canada		This		D ^t	A	SUCH S	C C	Wheat/ghuten and st		a s	whole meal bread: 101 days
Sakatchewan Region 7			77100		JOINT .		<i></i>	CRien 30-	00151	69	gluten: 92 days starch: 110 days
•				103	, driv			Starch 🐒 🗳	0 <0.010°	69	pasta, fresh: 84 days
America, North F		× \$		1			10 ¹⁰	Pasta (Noodle) prod	// \\ V		pasta, cooked: 103 days cooking water: 112 days
2015		M.D.J.C.	Ope	×°	of		u ^{t''} of	Pasta, fresh	<0.010	69	pasta, dry: 95 days pasta, dried and cooked: 103 days
		· »	6 ⁱ U	-				Pasta cooked	<0.010	09	pasta, uned and cooked. 105 days
(continuation)			, je	all'	A		VP 7	Pasta, dry	<0.010	69 69	
		GI		<u>}</u>	TO OS -	g.r.	- salaer	Pasts dried and	<0.010	69	
		and f	J.	<u>an</u> t			0**	cooked	0.010	0,	
*** For wheat g	rain (collected	at the field site ar	Ocollected a	the pro	cessing site	e), the results are i	defividual analy	ses of three separate	e samples. For the p	rocess	ed commodities, the results are the
mean of three a		gae sample.	2000	× ĈÕ	, K	) E	10 ¹				
- (a) Acco	rding to ODEX	Classification / Gu	åe XC	22	1,0%		Application metho	hd			
- (b) Only	if relevant		a P ^{Ube}	-		- <u>5</u> (1)	Method informati	on			
- (c) Year - (d) Days	must be indicated after last applica	d tion Alabel pre-har€	en interval P	₩I underl	line		LOQ Method validation				
- (e) Rema	arks may include	Gumatic condition	s; Reference to	o analytic	il method an	a (1) s	Storage (max)	Grain: between deep	-freezing (in the field) an	d last ex	traction date
infor	nation which the	tabolites are include	d C	, P	n'i D'		Processe	d commodities: between	their deep-freezing and d	late of la	st extraction
- (f) Study	reférence	OIL TOL	the the	u A	Ope	- * r	Aspirate prior to last treatm		n the date the grain dust w	as gener	ated through the last sample extraction
- (g) Form	vation type	d tion Label pre-hart climatic condition tabolites are include chit Colum tabolites are include chit F field	, t	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		- ** I	residue in control				
- G given	nhouse	F field	y y			- # r	no data available				
(	\$0» [.]										
		Ma									



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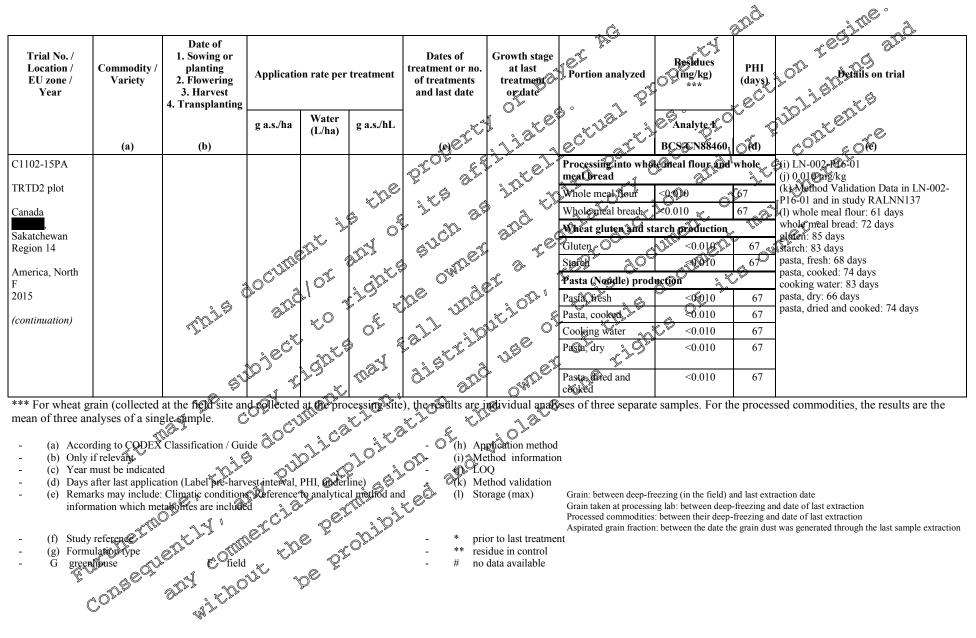
* Grain collected at the field site, deep-frozen within 4 mutrs and stated at average temperature <-21°C until analysis.

** Grain collected at processing site: after removing bulk wheat grain samples for aspirated grain fraction generation and processing from freezer storage, representative unprocessed wheat (RAC) samples were collected and placed ato frozen storage. This is the RAC reference for the processing factor calculations.

samples were collected and placed and placed at the rosenstorage. This is the RAC deference for the processing factor calculations. *** For wheat grain (collected at the field site and collected at the processing site), the results are individual analyses of three separate samples. For the processed commodities, the results are the mean of three analyses of a single sample. For the processed commodities, the results are the processing the processing site), the results are individual analyses of three separate samples. For the processed commodities, the results are the mean of three analyses of a single sample. For the processed commodities, the results are the process of a single sample in the process of the proces of the proces of



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able 6.5.3- 6:Proposed processing factors for wheat Tested GAP: 1 × 375 g a.s./ha at BBCH 69									
Crop, Processed commodity	Number of trials	Trial number	Residues (mg/kg)	Individual processing factors (a)	Proposed processing factor PF				
Wheat grain (RAC)	2	C1101-15PA C1102-15PA	0.0137 (69 days after treatment)						
Wheat, Aspirated Grain Fraction	2	C1101-15PA C1102-15PA	2.35 0.919	172@ > &2	2 2 2 2 3 172 5 4 5 7 5 7 5 7 7 7 7 7 7 7 7 7 7 7 7 7				
Wheat, Middlings	2	C1101-15PA C1102-15PA	<0.010 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	0.73 0.73 0.73	Ø 0.73 Ø				
Wheat, Germ	2	C1101-15PA C1102-15PA			1,32				
Wheat, White Flour	2	C1101-15PA C1102-15PA	×0.010 ~ ~ ~ ~ A	$0.73 \bigcirc^{\circ}$ n.c.	Ø 0.73 Ø				
Wheat, Shorts	2	C1101-15P C1102-15		∑ 0.28 	× 0.098				
Wheat, Bran	2	C1101-C5PA C1102015PA		5 [°] 1.4 n.cc	× 1.4				
Wheat, White Bread	2	C1701-15PA C1702-15PA	<00010 \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	r < 0073 ( n.c. )	√ < 0.73				
Wheat, Whole Meal Flour	2	C1101 \$15PA C110 \$15PA		0.78 n.¢	0.78				
Wheat, Whole Meal Bread	2	C1101-15PA ©102-15PA	CONTRACTOR CONTRACT	~0.73 ~n.c.	< 0.73				
Wheat, Gluten		C1104O5PA C1102015PA		✓ 1.1 ✓ n.c	1.1				
Wheat, Starch		CAU01-15PA C1102-15PA	\$0.010 \$ 5 0 5 \$0.0100 \$ 5 0 5	< 0.73 n.c.	< 0.73				
Wheat, Pasta (fresh)		C1101-15PA C1102-15PA		< 0.73 n.c.	< 0.73				
Wheat, Pasta (fresh & cooked)			$<0.010$ 57 $2^{57}$ $0^{57}$ $2^{57}$ $0^{57}$ $2^{57}$ $0^{57}$	< 0.73 n.c.	< 0.73				
Wheat, Cooking ₍ Water		C1 01-15PA SF102-150A	\$0.010 \$ \$	< 0.73 n.c.	< 0.73				
Wheat, Pasta (dry)		C110145PA ~ C1102415PAQ	0.040 <0.040	< 0.73 n.c.	< 0.73				
Wheat, Pasta (dried and cooked)		C101-15PA C1102-15PA	0.010. 0.0140	< 0.73 n.c.	< 0.73				

### Table 6.5.3- 6: Proposed processing factors for wheat

(a): Processing factors (PF) slightly differ from the table of page 18 of the report. PF = residues in processed commodifies / residues (mean) in the RAC collected at the processing lab

n.c.: No processing factor can be care and the second commodity)

< value: in case the mean residue level in the RAG is  $\geq$  LOQ but residues in the processed commodity are < LOQ, the processing factor is calculated as to be below the worst case value calculated with the LOQ of the processed commodity

> value: mean desidue 4 cel in the RAC is < LOQ but residues in the processed commodity are  $\geq$  LOQ, the processing factor is calculated as to be above the value calculated with the LOQ of the RAC



#### CA 6.6 **Residues in rotational crops**

The nature and level of residues in succeeding crops (confined rotational crops, field rotational crops) is influenced by the amount of active ingredient applied to the soil, by the degradation behaviour in a soil, and by the uptake of parent compound and soil metabolites by the roots. Additionally parent compound and soil metabolites can be metabolized by the plants.

The aerobic degradation of BCS-CN88460 in soil was investigated in laboratory studies using two different radiolabel positions - either [pyrazole-14C] or [phenyl-14C] radiolabelled active substance

(see ; 2014; M-486690-01-1. ; 2017; M-599926-01-1; K&A 7, F1.1), From 6 ; 2017; M-588260-01-1 and these studies, it can be concluded that BCS-CN88466 was slowly but steadily degraded in solunder aerobic conditions to the final degradation product CO₂. In parallel to mineralisation bound residues (NER) were formed. Three metabolites were identified in the soil extracts along with the patent compound and ¹⁴CO₂. The only major metabolite was BCS-CN88460-carboxylic acid (MJ2), which is , Nor degradable under aerobic conditions.  $\bigcirc$ , Ø

In the metabolic pathway of BCS-CN88460 in seif the following processes are involved:

- oxidation of BCS-CN88460 to result in BCS-CN88460-carboxyliv acid (M12);
- hydroxylation of BCS-CN88460-corboxylic acid (M12) to result in BCS-CN88460-jactic acid • (M10); 2 N
- CS @N884@O-desmethyldemethylation of BCS-CN884@-carboxylic acid (M12) to result L, carboxylic acid (M11); n
- mineralisation (carbon dioxide formation);
- formation of non-extractable residues (WER) ٠

Since the exposure of following crops to SCS-CN88460 soil residues cannot be excluded, the metabolism of BCS-CN88460 was investigated in pepresentative votational crops (wheat, Swiss chard and turnips) following soil application at a nominal rate of 200 g a.s a of kither [pyrazole-4-14C] or [phenyl-UL-¹⁴C] raciolabelied active substance.

The TRRs in the confined rotational crop commodities were generally low accounting for less than 0.08 mg/kg except in wheat hay and wheat straw where the values accounted for 0.114-0.220 mg/kg and 0.131-0.340 mg/kg, respectively. Parent compound was only detected in wheat forage, wheat hay, Swiss chard and turnip leaves with adjounts of equal or less than 17.0% (0.004 mg/kg) of the TRR. None of the identified metabolites accounted for more than 0.922 mg/kg and none of the unknown

with abouts of equal or k with abouts of equal or k etabolites accounted for more that r for more than 0.020 mg/kg.



#### CA 6.6.1 Metabolism in rotational crops

#### Summary of metabolism in rotational crop

The metabolism of the fungicide isoflucypram was investigated in two different metabolism styries in rotational crops following application with isoflucypram either labelled in the pyrazole of in the phenyl moiety.

Table 6.6.1- 1:	Overview over available metabolism studies in confined rop

		Ĉa .	
Rotated crops	Application	Target application	Reference
turnips, Swiss chard and wheat, plant back interval 30, 140 and 287 days	pyrazole-labelled isoflucypram	207-9 g a Sy ha	The second secon
turnips, Swiss chard and wheat, plant back interval 30, 140 and 287 days	phenyl-labelled isoflucypram	197.7 g s./ha ~	M-595695-01
	Ŷ`&`&`?		

In the two confined rotational crop studies applied with an application rate of 1987-202 g/ha of pyrazole and phenyl labelled isoflucypran, the residues of isoflucypran in rotational crops planted at all intervals were less than 0.08 tog/kg except in wheat hay and wheat straw of the pyrazole labelled confined rotational crop study where the content of isoflucypran was 0.404-0.220 mg/kg and 0.131-0.340 mg/kg, respectively. The TRRs in the different raw agricultural commodities (RACs) were generally low increased slightly from the P to the 2nd rotation and stayed stable or declined to lower values in the 3rd rotation. The TRRs in the RACs of the phenyl labelled study were lower as the TRRs found in the study with the pyrazole label.

In the confined rotational crop study with isoflacypran labelled in the pyrazole mojety, unchanged parent compound was only detected in wheat forage, Swiss chard and turnip leaves with amounts of equal or less than 7.0% (0.003 mg/kg) of the TRR. Up to thirteen pyrazole derivative metabolites were identified. As the TKR values of the confined study was generally low, none of the identified metabolites accounted for more than 0.022 mg/kg and none of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the identified of the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the unknown compounds accounted for more than 0.021 mg/kg at the transformation of the transfo

The main metabolic reactions were the cleavage of the parent compound to BCS-CN88460-N-methylcyclopropyl-pyrazole-carboxamide (named as BCS-CR60082) and following conjugation of BCS-CR60082 with alanine (with or without defluormation) or the hydroxylation and defluoronation of BCS-CR60082 followed by conjugation with systeine or glutathione. Other metabolic reactions were, demethylation, hydroxylation, dearnanties or defluoronation of BCS-CR60082, followed by conjugation with glucose factic acid, acetic ford, cysteine or glutathione. The glutathione group was afterwards degraded to mercanto alcohol with an additional conjugation with malonic acid.

In the confined rotational foo study with isoflucypram labelled in the phenyl mojety, unchanged parent compound was only detected in wheat forage, wheat hay and Swiss chard with amounts of equal or tess than 17.0% (0.094 mg/kg) of the TRR. Due to very low TRR values in the confined study, no further metabolites were identified in the conventional extracts as none of the unknown compounds was larger than 0.009 mg/kg. Acidic hydrolysis of selected extracts exhibited that the major part of residues were parent compound and conjugates of BCS-CN88460-carboxylic acid and BCS-CN88460-propanol. No label specific metabolites were detected in the CRC study with the phenyl label.



Report:	KCA 6.6.1/01; ; 2017; M-595694-02-1 。
Title:	Amendment no. 1: Metabolism of [pyrazole-4-14C]BCS-CN88460 in confined
Report No.:	EnSa-16-945
Document No.:	M-595694-02-1
Guideline(s):	OECD Guideline for the Testing of Chemicals, 502: Metabolism in Rotational Crops,
	adopted 2007-01-08 Regulation (EC) No 1107/2009 amended by Composition 🛇 👘 🖉
	adopted 2007-01-08 Regulation (EC) No 1107/2009 amended by Commission Regulation (EU) No 283/2013 (Europe) US EPA OCSPP Residue Chemistry Test
	Guideline OPPTS 860.1850: Confined Accumulation in Rotational Grops 🚿 🖉 🖉
Guideline deviation(s):	none S S S
GLP/GEP:	yes a construction of the second

#### Executive Summar

The metabolism of the fungicide isoflucypran, (BCS CN88460) was investigated in confined rotational crops after one spray application onto bare solv. The test compound was ¹⁴C-radiolabelled in the pyrazole moiety. The soil was treated with 201.9 ga.s./ha according to the envisaged use pattern. Root crops are represented by turnips, leafy crops by Swiss chard and cereals by wheat. They were sown 30 days (1st rotation), 140 days (2nd rotation) and 287 days (3rd rotation) after soft treatment.

A sample of immature Swiss chard was harvested at BBCID stage 45. Wheat for age was sampled at BBCH stage 29 and wheat hav at BBCH stage 75 to 83. At maturity turnin leaves, turnin roots, Swiss chard, wheat straw and wheat grain were harvested.

The TRRs in the different RACs were generally low (increased slightly from the 1st to the 2nd rotation and stayed stable in the 3rd rotation as shown in the bilowing table:

[pyrazole-14C	JBCS-CX88460		
Matrix &	1 st foration	2" grotation	3 rd rotation
wheat forage	£ 60.041 × 4	0.078	0.072
wheat hay wheat strage	0.kJA 0'	گ 0.220	0.187
wheat stragy		0.247	0.340
wheat grain	\$0.00 <b>4</b> *	0.011	0.016
Swiss chard (immafure)	Ø Ø Ø 31	0.062	0.056
Swiss chard (akinaturita)	0.026	0.062	0.052
turnip roots	0_006*	0.006*	0.006*
turnip roots	©0.018	0.031	0.026

Table 6.6.1- 2: TRR values in confined rotational crops after speay application onto bare soil with [pyrazole-4-14C]BCS-CN88460

* TRR values were determined by LSC measurement following combustion. Samples were not extracted ducto their amount being <0.01 mg/kg.

The majority of radioactive residues of all RACs was conventionally extracted with a mixture of acetonic le/water (8/2; v/v). The residues in the conventional extracts amounted from 52.9% to 97.2% of the TRR. Solids after extraction of wheat hay (1st, 2nd and 3rd rotation), straw (1st, 2nd and 3rd rotation) and grain (2nd and 3rd rotation) were exhaustively extracted using microwave assistance with a mixture of acetonitrile/water/formic acid (50/50/1, v/v/v). Solids after microwave extraction, apart



from the solids of wheat grain, were subsequently extracted with a mixture of dioxane/5M HCl using microwave assistance. Exhaustive extracted residues were not further characterised due to high matrix load or low TRR values ( $\leq 0.023$  mg/kg).

All RACs were sufficiently extracted. The total radioactivity in the post extraction solids PES amounted to  $\leq 9.0\%$  except for wheat grain. In wheat grain, PES amounted for up to 19.6% As this accounted for only 0.002 mg/kg of the TRR, solids were not further extracted  $\sqrt{2}$ 

Parent compound and metabolites in the conventional extracts were quantified by HPLC analysis based on reversed phase chromatography using an acidic water/acetonitrite/THF gradient.

The identification rates ranged from 21.2% to 76.6% of the TRR in wheat, from 49.9% to 81.1% the TRR in Swiss chard and from 55.4% to 92.3% of the TRR in turners.

BCS-CR60082 (M49), BCS-CN88460-cyclopropyl-pyrazole@arboxamidetAla (M66), BCS CN88460-cyclopropyl-pyrazole-carboxamide-Gly@(isomer 2, M62-i2), BCS CN88460-desfluore Nmethyl-cyclopropyl-pyrazole-carboxamide-OH-Cys (M52), BCS-CN88460-desfluore N-methylcyclopropyl-pyrazole-carboxamide-OH-GSH (M54), BCS-CN88460-desfluore N-methylcyclopropyl-pyrazole-carboxamide-OH-GSH (M54), BCS-CN88460-desfluore Corporation carboxamide-OH-lactic acid (isomer 2, M69-i2), BCS-CN88460-desfluore-cyclopropyl-pyrazolecarboxamide-Ala (M67) and BCS-CN88460-desfluore-N-methyl-cylclopropyl-pyrazole-carboxamidemercapto-Glyc-MA (M57) were identified as major compounds.

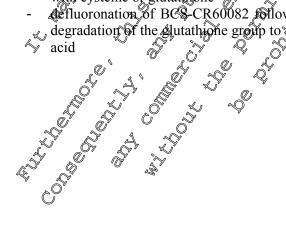
Parent compound and metabolites BGS-CN88460-Cyclopfopyl-prazole carboxamide Glyc (isomer 1, M62-i1), BCS-CN88460-cyclopropyl-pyrazole-carboxamide-OFI-lactic acid (isomer 1, M69-i1), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-oFI-lactic acid (isomer 1, M69-i1), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-desamino-Cys (M56), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide desamino-Cys (M56), and BCS-CN88460-cyclopropyl-pyrazole-carboxamide-acetic acid (M68) were quantified in low amounts only (TRR <10%) in the convergional extracts of the PACs.

All other metabolites were detected in low mounts and were characterised by their extraction and chromatographic behaviour.

On the basis of the nature and another of metabolites bound in the extracts of the crops of all rotations the metabolic pathway of [pyrazole-4-¹⁴C]BCS-CN88460 in confused rotational crops was proposed.

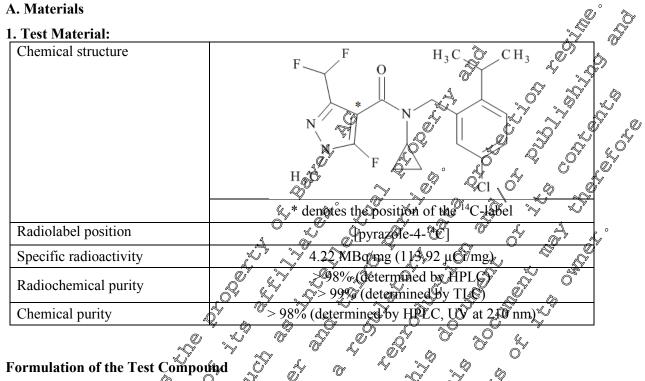
The following metabolic reactions were observed

- Every set of molecule feading to BCS-CN88460-Demethol-cyclopropyl-pyrazole-carboxamide (BCS-CR60082)
- conjugation of BCS-CR60082 with alanine lactic acid or acetic acid with or without defluorofiation of the prazoloring
- demeter latio of BCS-CR69082 followed by configuration with glucose
- hydroxylation, demnination and defluoronation of BCS-CR60082 followed by conjugation with cysteine or glutathone
- defluoronation of BCS-CR60082 followed by conjugation with glucose and glutathione and degradation of the glutathione group to mercapto alcohol, additional conjugation with malonic





#### I. Materials and Methods



356 mg of the EC 200 blank formulation was added to 22 mg of the radiolabelled test compound. After homogenisation a water acetomerile mixture 50/50  $\sqrt{\nu}$  was added to receive the ready-to-use application suspension (total volume: 100 mL). The radioactivity in the final application suspension was determined by ESC and amounted to 0.945 MBoonL. The formulated test compound was used as test item.

2. Soil: "	4", $pH$ (CaCl ₂ ) = $677$ pacify (CEC) of 75 me	, 1 🕉 clay, 20	Sesilt and 65%	sand 1.3% organ	nic carbon,
cation exchange cap	acity (CES) of 75 med	q/100 g 🖇 🤞			

N

3. Plants:		
3. Plants:		
<b>3. Plants:</b>		resentative for crop group
Spring wheat	Thasos cere	als
Spring wheat Swiss chard	Lucullus Lucul	y crops
	Rondo V Q Foot	crops
Tumps	Lucullus Ar leaf	



#### **B. Study Design**

#### **Experimental conditions:**

The application conditions simulated the maximum annual rate of 200 g a.s./ha, according to the envisaged use pattern.

The bare soil was treated on 2014-03-25. An approximately 10% higher field rate (approx. 220) a.s./ha) was used to compensate losses during the application. The application was performed with 100% mL of the application suspension (according to 94.45 MBq) using a computer controller track spraver fitted with a flat fan nozzle. The homogeneity of the sprey application was checked by determination of the radioactivity on eight filter papers (1.5 cm diameter), which were randomly placed on the soil before application. The spray application was homogeneous. After application the stock container of the application apparatus was rinsed twice with acctonitrile/water (50050; v/AP. The rinsing solution was measured for radioactivity by LSC. By subtraction of all these losses from the radioactivity of the application suspension, the actual amount applied to the soil was calculated. As a result, 201.9 g ×, a.s./ha ( $85.19 \text{ MBq/m}^2$ ) was applied.

The stability of the test compound in the application suspension was checked before and after the application by HPLC. No degradation was observed The purity of the test compound was analysed after the application by HPLC analysis and appointed to 29%.

For ageing, the soil remained undesturbed for 30 days. The soil was watered in order to maintain adequate moisture content. Before each sowing of the crops the upper soil layer was intensively mixed (approx. 10 cm depth) and soil cores (10 to 15 cm depth) were taken. Additional soil cores were sampled at the end of the 3rd rotation (harvest of wheat, 15-30 cm depth). The radioactivity in the airdried soil cores was determined bocombustion & aliquots followed by LSQ

### Sampling:

Dan Stranger Wheat Definition of BBCH-codes for cereals BBCH 29 - Center for cereals: BBCH 29 - Center for cereals: medium milk: gran content milky, grans reached final size BBCH 75 -BBCH 83 early dough fully the: gran hard, difficult to divide with thumbnail BBCH & -

#### Wheat forage

Forage was taken at approx. BBCH 29,62,  $\sqrt{335}$  and  $\sqrt{335}$  days after application). One of five rows wheat plants was cut from the posts, which remained in the soil. The forage was cut in small pieces and homogenised with Aquid autrogen using a Polytron (Kinematica). An aliquot of the homogenised sample was used for extraction. Residual sample material was stored at approx. - 18°C.

#### Wheat hay

Hay was taken at BBCH 75 83 1901, 239 and 387 days after application). One of five rows wheat plants was cut from the roots, which remained in the soil. The hay sample was dried for four days. The dried hay sample was set in strall pieces and homogenised with liquid nitrogen using a Polytron (Kinematica). In aliquot of the homogenised sample was used for extraction. Residual sample material was goved at approx. - 18°C.

### Wheat straw and grain

Straw and grain were harvested together at BBCH 89 to 92 (139, 286 and 427 days after application). The wheat plants were cut shortly above soil surface. The roots remained in the soil. The seeds were collected manually yielding the grain sample. The remaining ears and chaff were combined with the straw.



Grain and straw samples were homogenised as described for forage. The homogenised samples were stored in aliquots at approx. - 18°C. One aliquot of each sample was used for extraction.

#### Swiss chard

Definition of BBCH-codes for leaf vegetables (not forming heads): BBCH 45 - 50% of the leaf mass typical for the variety reached BBCH 49 - typical leaf mass reached

Swiss chard was harvested as an immature RAC (BBCH 45; 56, 177 and 330 days after application) and at maturity (BBCH 49; 62, 189 and 342 days after application). The samples were cut from the roots, which remained in the soil. The samples were homogenised as described for forage. The homogenised samples were stored in aliquots at approx. - 18°C. One aliquot of each sample was used for extraction.

#### Turnip leaves and roots

Definition of BBCH-codes for root and stem vegetables: BBCH 49 - expansion complete; typical form and size of roots reached

Turnip leaves and roots were harvested together at maturity (BBCH 49; 79, 212 and 356 after application). The turnips were pulled out of the soft and the leaves were separated from roots. The roots were cut into slices and the leaves into small pieces. Both were homogenised as described for forage and stored in aliquots at approx. -18°C. One aliquot of each sample was used for extraction.

#### **C. Analytical Procedures**

## Conventional Extraction and Sample Preparation of all RACs

Aliquots of the homogenised samples were extracted 2 to 5 times with acetonitrile/water (8/2, v/v). The extraction step were conducted using a Polytron homogeniser. The residues were -dried and weighed yielding the solutions. The TRR of each RAC was calculated from the specific radioactivity of the test compound, the amount of the sample used for extraction and the sum of radioactivity, measured in the extracts and the remaining solids. The purified (solid phase extraction (SPE)) and concentrated combined extracts were subjected to HPLC analysis based on reversed phase chromatography using an acidic water/acetonitrile/THF gradient. Recoveries of the concentration processes amounted from 90.9% to 111.2%

#### Exhaustive Extraction of Solids

Depending on the amount of residues in the solids of the conventional extraction, an exhaustive extraction was performed once with acetonitrile water/formic acid (50/50/1; v/v/v) using microwave assistance. All samples were purified using SPE carryidges. In case of wheat straw of the 1st rotation this was followed by a concentration process. Recoveries of the purification process amounted from 92.5% to 140.6%. Recovery of the concentration process amounted for 92.7%.

C

The remaining solids of wheat hay and strow were again subjected to an exhaustive extraction procedure using dioxane/5 M hydrochloric acid and microwave assistance. Recovery rates amounted for 97.2% to 103.6%.



#### Quantification:

Parent compound and metabolites were quantified in the conventional extracts by HPLC analysis based on reversed phase chromatography using an acidic water/acetonitrile/THF gractent. Corresponding metabolites were named with the same report name and peak ID. They were assigned to each other by comparison of the metabolite profiles and retention time, based on the HPDC profiling method.

#### Identification and characterisation:

Parent compound was identified by comparison of HPLG profiles with each other.

Metabolites BCS-CN88460-N-methyl-cyclopropyl-pyrazole-carboxamide (BCS-CR66082, M49), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-Cys, (M52) and BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-SSH (M54) were isolated in HPLC peak fractions from purified and concentrated extract of Swiss chard of the S³ rotation.

Metabolites BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ala (M66) and BCS-CN88460cyclopropyl-pyrazole-carboxamide-lactic-acid (M69, isofaer 2) were isolated in HPDC peak fractions from purified and concentrated extract from wheat hay of the to rotation.

Metabolites BCS-CN88460-cyclopropil-pyrazole-carboxanide-Glyc (M62, isomer 1 and isomer 2), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxanide-mercapto-Glyc (M36), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxanide-mercapto-Glyc (M36), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxanide-desamino-Cyc (M55), BCS-CN88460-cyclopropyl-pyrazole-carboxanide-OH-lactic acid (M69, isomer 1), BCS-CN88460desfluoro-cyclopropyl-pyrazole-carboxanide-Ala (M67) and BCS-CN88460-cyclopropyl-pyrazolecarboxanide-acetic acid (M68) were isolated in peak fractions from purified wheat hay of the 2nd and 3rd rotation.

All isolated compounds were identified by spectroscopic methods.

To support metabolite identification HPLC co-chromatography of extraors with isolated radiolabelled metabolites was performed.

All other peaks or regions additionally detected in the respective HPLC chromatograms were assigned as "unknown" and numbered accordingly. They were characterised by their extraction and chromatographic behaviour.

#### Storage stability:

All samples were stored at temperatures  $\leq 18$  °C before extraction and analysis. All RACs of the 1st rotation were extracted within maximal 12 days, of the 2^{er} rotation within 9 days and of the 3rd rotation not later than 41 days. Within maximal one month after extraction, the earliest metabolite profiles (used for quantitation of metabolites) were obtained by HPLC-analysis analysis based on reversed phase chematography using an acidic water action triperiod.

Therefore, it was concluded that the results of this study were not negatively influenced by storage effects.

#### **ÎÎ**. Results and Discussion

The TRP of each rav agricultural commodity (RAC) was calculated from the specific radioactivity of the test compound, the amount of the sample used for extraction and the sum of radioactivity, measured in the conventional extracts and the remaining solids.

The TRPs in all raw agricultural commodities (RACs) reached from low to very low values. The TRR values in the 1st rotation ranged from 0.004 mg/kg (wheat grain) to 0.131 mg/kg (wheat straw). In the 2nd rotation, the TRRs increased slightly to values between 0.006 mg/kg (turnip roots) and



0.247 mg/kg (wheat straw) and stayed constant for the  $3^{rd}$  rotation with values between 0.006 mg/kg (turnip roots) and 0.340 mg/kg (wheat straw).

RACs with an amount of > 0.01 mg/kg were conventionally extracted with a mixture of acetonitrile/water (8/2, v/v). The conventional extraction rates amounted from 52.9% to 97.2% of the TRR. Solids after conventional extraction of wheat straw (1st, 2nd and 3rd rotation), hay (1st, 2st and 3rd rotation) and grain (2nd and 3rd rotation) were further extracted with either acetonitrile/water/acetic acid (1/1/1; v/v/v) or with acetonitrile/water/formic acid (50/50/1; v/v/v) using microwave assistance. Apart from the solids of wheat grain, solids after microwave extraction were subsequently extracted with extracted with a mixture of dioxane/5 M HCl (49/1; v/v).All RACs were sufficiently extracted with extracted wi

All RACs were sufficiently extracted. The post explaction solids (PES) in the RACs ranged from 23% (= 0.001 mg/kg) of the TRR for Swiss chard (immature, 1st rotation) to 9.0% (= 0.007 mg/kg) of the TRR for wheat forage (2nd rotation). PES in wheat grain anounted for up to 19.6%. As this accounted for only 0.002 mg/kg TRR, solids were not further extracted.

Parent compound and metabolites were quantified in the conventional extracts by HPLC analysis based on reversed phase chromatography using an acidic water/actionitrile/THF gradient. They were assigned in all extracts by comparison of the metabolite profiles and retention times based on the profiling method. Corresponding metabolites were named with the same report name and peak ID.

#### Spring Wheat

The identification rates ranged from 44.9% to 60.6% in the 1st rotation, from 44.0% to 76.6% in the 2nd rotation and from 45.1% to 47.7% in the 3rd rotation. Identification rates in grain were 21.2% in the 2nd rotation and metabolites were only characterised in the 3rd rotation due to very low TRR values.

Parent compound was a minor compound in wheat, only identified in forage of the 1st and 2nd rotation with up to 7.0% (0.003 mg/kg) of the DRR. BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ala was a major metabolite with up to 25.6% (0.020 mg/kg) of the TRR in torage (all rotations) and hay (1st and 2nd rotation) but a minor metabolite in straw (all rotations), hay (3rd rotation) and grain (2nd rotation). BCS-CN88460-cyclopropyl-pyrazole-carboxamide-OH-lactic acid (isomer 2) was identified as a major compound with up to 11.9% (0.046 mg/kg) of the TRR in straw (1st rotation) and forage (2nd rotation). It was a minor compound in forage (1st and 3rd rotation), hay (all rotations) and straw (2nd and 3rd rotation), BCS-CN88460-desfluoro-cyclopropyl-pyrazole-carboxamide-Ala was identified as a major compound in wheat grain (2nd rotation) with up to 43.4% (0.002 mg/kg) of the TRR. It was a minor compound in forage (1st rotation) and straw (3rd rotation).

Minor metabolites ( 00% of the TRR) ranging from 1.1% of the TRR (0.002 mg/kg) to 9.3% of the TRR or 0.026 mg/kg were BCS-CR60082, BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 1), BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 2), BCS-CN88460-desfluoro-N-methyl cyclopropyl-pyrazole-carboxamide-OH-Cys, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-Cys, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-Lactic acid, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-lactic acid, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-lactic acid, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-lactic acid, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-lactic acid, BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-MA and BCS-CN88460-cyclopropyl-pyrazole-carboxamide-acetic acid. The respective metabolites were not detected in every part and/or rotation of wheat (see tables below).

All other metabolites were detected in low amounts and were characterised by their extraction and chromatographic behaviour.

chromatographic beraviour



#### Swiss chard

The identification rates ranged from 73.0% to 81.1% in the 1st rotation, from 44.7% to 56.4% in the  $2^{nd}$  rotation and from 43.9% to 51.3% of the TRR in the  $3^{rd}$  rotation.

Parent compound was only a minor compound in Swiss chard accounting for 60% of the TRP (0.002 mg/kg) and not identified in Swiss chard (at maturity) in the 2nd rotation. The main metabolite BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-Cys accounted for 00 to 34.2% of the TRR or 0.016 mg/kg in all three rotations. BCS-CR60082 was identified as a major compound in immature and mature Swiss chard in the 1st rotation with up to 19.4% (0.005 mg/kg) of the TRR and as a minor compound in the other rotations. BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 1) was identified as a major compound in Swiss chard (at maturity, 2nd rotation) with 12.2% (0.008 mg/kg) of the TRR and a minor metabolite in immature (2nd and 3rd rotation) and Swiss chard (at maturity, 3rd rotation). BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-GSH was identified as major compound in immature and mature Swiss chard of the 1st rotation with up to 22.9% (0.006 mg/kg) of the TRR and as a minor compound in the 2nd and 3rd rotation.

Minor metabolites (<10% of the TRR) ranging from 6.5% of the TRR (<0.001 mg/kg) to 7.3% of the TRR (0.004 mg/kg) were BCS-CN88460-cyclopropyl-carboxamide Ala, BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomed 2), BCS-CN88460-cyclopropyl-carboxamide-OH-lactic acid (isomer 1), BCS-CN88460-cyclopropyl-carboxamide-OH-lactic acid (isomer 2), BCS-CN88460-cyclopropyl-carboxamide-OH-lactic acid (isomer 2)

All other metabolites were detected in low amounts and were characterised by their extraction and chromatographic behaviour.

#### Turnips leaves

The identification rates accounted for 92,3% in the 1s rotation, for 73.3% in the 2nd rotation and for 55.4% of the TRES in the 3nd rotation.

Parent compound was only detected as a minor compound in turnip leaves of the 1st rotation. The main metabolite BCS-CN88460-destluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OH-GSH accounted for up to 25.7% of the TRR or 0.906 mg/kg inclall three rotations. BCS-CR60082 was a major compound in the 1st and 2nd rotation with up to 18.4% of the TRR or 0.004 mg/kg and a minor compound in the 3rd rotation. BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 2) was a major compound in the 1st rotation with 13.0% (0.002 mg/kg) of the TRR and a minor compound in the 1st rotation. BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 2) was a major compound in the 1st rotation. BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-mercapto-GlycMA was a major compound in the 1st rotation.

Minor metabolites (<10% of the TRR/ranging from 1.8% of the TRR (<0.001 mg/kg) to 8.1% of the TRR (0.002 mg/kg) were BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ala, BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 1), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-OU-Cys BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-Ala, and BCS-CN88460-desfluoro-Nethyl-cyclopropyl-pyrazole-carboxamide-Ala, and BCS-CN88460-desfluoro-Nethyl-cyclopropyl-pyrazole-carboxamide-Ala, BCS-CN88460-desfluoro-cyclopropyl-pyrazole-carboxamide-Ala, and BCS-CN88460-desfluoro-Nethyl-cyclopropyl-pyrazole-carboxamide-Ala, and BCS-CN88460-desfluoro-Nethyl-cyclopropyl-pyrazole-carboxamide-Ala

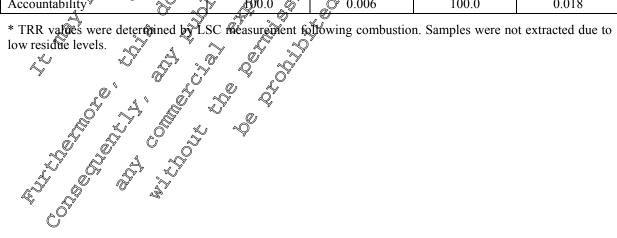
All other pretabolites were detected in low amounts and were characterised by their extraction and chromatographic behaviour.

The distribution of the radioactive residues as well as the identified and characterised compounds in confined rotational crops after spray application onto bare soil is shown in the tables below.



Table 6.6.1- 3:	Distribution of radioactivity in confined rotational crops (1 st rotation) after spray
	application onto bare soil with [pyrazole-4- ¹⁴ C]BCS-CN88460

application ont	o bare so	il with [p	yrazole-4	- ¹ ⁴ C]BC	S-CN884	60		e o
	wheat	forage	whea	it hay	wheat	t straw	whea	t grafin
	TRR =	0.041	TRR =	0.114	TRR =	0,131	TRR =	09.004*
	mg	g/kg	mg	/kg	mg	g/ko	m	kg 🔊
	%	mg/kg	%	mg/kg	%	‴mg/kg		mg/kg
Total extractable	92.9	0.038	96.1	0.110	93,6	0.123	Ra.	Øn.a.
Conventional extract (analysed)	92.9	0.0038	85. <u>7</u> Ö	0.098	749	0.102	♀n.a.∽	n.a 🖓
Losses conventional extract	n.a.	n.a.	n.a.	n.a.	Q0.6	0.001	n a	n.a.
Exhaustive extract	n.a.	n.a.	<b>0.5</b>	0.012	15.1	0.030	nsa.	Ön.a.
Post extraction solids (PES)	7.1	0.003	3.9	0.004	6A	.008	∮n.a.	n.a.
Accountability	100.0	0.041	100.0	0114	¢ <b>√</b> 00.0 _@	0.131	100.0	0004
	1	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>	ĵ j		<u> </u>	~	*
	S	wiss chare	Kimmati	re)		wissChard	fat maté	ryty) °
	ŢĮ	$\mathbf{R} = \mathbf{r}$	<b>~</b> 0.	031	LA T	\$ <b>R</b> =	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	.026
	Ň	<u> </u>	/k@ [*]	<u> </u>		Ç m	g/kg	Å'
	<u> </u>	<u>%</u>	× 40	g/kg 🦭		<u>%</u>	<u> ((()</u>	g/kg
Total extractable	9	19.2 🏾 🌱	<b>0</b> .	030	O 9	\$.0 Š	<b>\$</b>	.025
Conventional extract (analysed)	× "?	6.1	0.			6.0	¢ '¥ 0	.025
Losses conventional extract	°~y 1		"	.001 🔗	<i>b</i>	n.a	б ^х	n.a
Exhaustive extract		îa /				nîa 👸		n.a
Post extraction solids (PES)	Ŭ ĝž	2.8		001 🗹	)	4.0	0	.001
Accountability	<u>کي</u> 10	00	Ç, Ç	Ø31 🌜		00.0	0	.026
		v S	<u> </u>	0	, ô [×]	Ś.		
	d S	<u>turnip</u>	roots	<u>s</u>		1	leaves	
	K TR	R	0.0	06* _Q'	JAN STI	R =		.018
		y mg	<u>/kg 🏷</u>	<u> </u>	<i>@</i> ;		g/kg	
A		% <u>~</u> *	🔊 mg	y/kg ¥	<i>,</i>	%	m	g/kg
Total extractable	n n	.a.		xa. 🥎	9	2.3	0	.017
Conventional extract (analysed)	n, n	¢°`~	'n	.a. 🏹	9	2.3	0	.017
Losses conventional extract		.a. 🔊	<i>(</i> )) .	.a.	r	1.a.	1	n.a.
Exhaustive extract		.ą. 🗸		a.	r	1.a.	1	n.a.
Post extraction while (PDS)	s O n	മ് 🔿	° Ôn	.a.	ĺ ĺ	7.7	0	.001
Accountability		0.0	0.0 گ	)06	10	0.00	0	.018





# Table 6.6.1- 4:Distribution of radioactivity in confined rotational crops (2nd rotation) after spray<br/>application onto bare soil with [pyrazole-4-14C]BCS-CN88460

	wheat	forage	whea	t hay	wheat	straw	whea	it grain 4	F
	TRR =	0.078	TRR =	0.220	TRR =	Q247	TRR 🗲	0.010	
		/kg	mg	/kg	mg	αkg		g/kg	
	%	mg/kg	%	mg/kg	%	mg/kg	, Ô	jng/kg	¢)
Total extractable	91.0	0.071	95.7	0.211	95,5	0.236 🔉	80.4	0.000	2
Conventional extract (analysed)	91.0	0.071	83.0	0.184	_080.7	0.198 ^C	'52\$ <b>9</b> ″	04006	2
Losses conventional extract	n.a.	n.a.	jn.a.	n.a. 🛒	[©] [*] 0.6	0.001	Qa.	n.a.	s C
Exhaustive extract	n.a.	n.a.	12.0	0.02%	1253	\$035	Sy 27.6	0.003	1
Post extraction solids (PES)	9.0	0.00	4.3	0,010	4.5	0.011	19.6	0.002	
Accountability	100.0	0.078	1900.0	, <b>@</b> .220 (*	J 100.0	0.247	ľ00.0	Ø.011	
		· • • •	U Ù		~~~~	Ŵ.		Å d°	_
	Şx	viss chare	(immatu	re) 🔗	<u>s</u> Sw	uss chard			
	TR.	R =	0.0	)\$ <u>7</u> 6	۶ T.K	$R = \mathcal{O}$	ي 10	.062	
	Ŗ	🌾 🖓 mg		Ý	Ö	mg	¢ ĝ	0	
	× 9	T T	‴ ™ng	/kg	S 2	Þ Ş	* "M	g/kg	
Total extractable	🏁 _ Ø5	5.3 🖉	0.0	6	0 ~04	i.2 🖉	້ 🔊 0	.058	
Conventional extract (analysed)	°≫ ⁹⁵	5.3	T Q	60 <i>"</i> Ç'	94	1.20	S 0	.058	
Losses conventional extract	K n	a L	n.	e 🔍	s în	à ¢	1	1.a.	
Exhaustive extract	ં ્રેને.	.a.	0	.a.		a. 🔊	1	1.a.	
Post extraction solids (PES)	4	.7	Ø 06	03 🌾	^س 5	.85	0	.004	
Accountability	L 10	Q.0 S	ר.(	)62 O″	10	0.0	0	.062	
	<u>5</u> , 2		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~			v			_
		turnip	roots ू	<u>\$</u>	, S	1	leaves		
		RØ≐ ,≺	× 20.0	06*	TR	R =	0	.031	
	ð 4	<u>`</u> `, me	/kg 🛇	0 *		mg	g/kg		
	6 ⁷ 9	/0 O*	, mg	Akg 🔊	9	0	m	g/kg	
Total extractable	n n	a, C	° ≪n.	a. 🔊	93	8.1	0	.029	
Conventional extended (analysed)		a. 🔊	🖉 n.	a.	93	8.1	0	.029	
Losses conventional extract	_ ≪ n.	.a. 🖉	n	à.	n.	a.	1	n.a.	
Exhaustive extract	ζ. Č ^{''} η,	ð, ć	🖗 🖓 🕅 .	a.	n.	a.	1	n.a.	
Post extraction solids (PES)	A.	a. N	🏷 n.	a.	6	.9	0	.002	
Accountability	i .CX	<u> </u>	0.0			0.0	1	.031	-

* TRR values were determined by LSC measurement following combustion. Samples were not extracted due to low residue levels.



Table 6.6.1- 5:	Distribution of radioactivity in confined rotational crops (3 rd rotation) after spray
	application onto bare soil with [pyrazole-4- ¹⁴ C]BCS-CN88460

application onto	bare sol	with [py	razole-4-	···C]BCS	-CN8846	U	
	wheat	forage	whea	ıt hay	wheat	straw	wheat grain
	TRR =	0.072	TRR =	0.187	TRR =	00340	TRR # 0.016
	mg	g/kg	mg	/kg	mg	Жg	mg/kg
	%	mg/kg	%	mg/kg	×	mg/kg	Ming/kg
Total extractable	91.9	0.066	97	0.183	Ø5.8	0.326	85 2 0.00 4
Conventional extract (analysed)	91.9	0.066	\$5.4	0.160 C	83.4	0.283	5.7 Q.009 Q
Losses conventional extract	n.a.	n.a. 🔺	n.a.	n.a.	<b>A</b> .3	<b>%</b> 001	, n.a. n.ac
Exhaustive extract	n.a.	n.a.9	12.5	0.023	¥12.1	0.04	31.5 0,005
Post extraction solids (PES)	8.1	8006	0 ² .1 ×	0.004	42	0.014	14.8 0.002
Accountability	100.0	0.072	10090	0:¶\$7	100.0 d	≫0.340 Ĉ	100 0 0.656
	, A			ð á			
	S S	in s char	(immaru	re)	گر Sw	ies chard	Qat maturity)
	Ş (	TRR =			o s	TRE	0.052
<u></u>	. L	[©] т	wing "«		b ⁰	$\cap$	2kg
	Ĵ	× 1	∭ ∭mg	g/kg		<b>%</b> (	mg/kg
Total extractable	\$ 6,9	4.4		2,58 🖏	\$92	2.4 2	0.048
Conventional extract (analysed)	ې چې 9،	4.9		053 🖉	^ی 92	Þ	00.48
Losses convention extract	× _,	.a. S	j n	.æ,	o n	a.	n.a.
Exhaustive extract v	_ ≪ [™] n	a. S		Ža. 🖉	~~ n.	a.	n.a.
Post extraction pids (RES)	o~ &	Ç 🖉	0.0	003	7. 7	.6	0.004
Accountability	10	0.0		)56 ×	10	0.0	0.052
			7 49				

	<u></u>		turnip	leaves
	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	0.006	TRR =	0.026
		/kg 🔗	mg	/kg
	\$ % B	mg/kg	%	mg/kg
Total extractable	Par of	n.a.	92.3	0.024
Total extractable Conventional extract (analysed)	Q ^{n.a.}	n.a.	92.3	0.024
Losses conventional extract	n.ac	n.a.	n.a.	n.a.
Exhaustive 🛠 tract	n.a.	n.a.	n.a.	n.a.
Exhaustive Atract	~ n.a.	n.a.	7.7	0.002
Accounterility	100.0	0.006	100.0	0.026

* TRE value were determined by LSC measurement following combustion. Samples were not extracted due to loweresidue devels.



Table 6.6.1- 6:	Distribution of radioactivity in wheat (1 st rotation) after spray application onto b	are
	soil with [pyrazole-4- ¹⁴ C]BCS-CN88460	°

wheat foragewheat haywheat strateReport name $TRR = 0.041$ $TRR = 0.114$ $TRR = 0.114$ $mg/kg$ $mg/kg$ $mg/kg$ $mg/kg$ % $mg/kg$ % $mg/kg$ % $mg/kg$ % $mg/kg$ 0.03885.70.09878.50.03885.70.09878.5	
Report namemg/kgmg/kgmg/kg%mg/kg%mg/kg	
% mg/kg % mg/kg % ∦ mg/kg	0
	3
	,7
72.7  0.030  0.1  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070  0.070	
Conventional extract – analysed by HPLC 92.9 0.038 $85.7 \pm 0.098$ $779$ $6102$	4 Q
Conventional extract - losses $n.a.$ $(a. n.a.)$ $n.a.$ $(a. n.a.)$ $(a. n.a.)$	Č,
Identified Compounds	
BCS-CN88460 7.0 & 0.003 Q &	
BCS-CR60082 (M49) $9.2% 0.004 - 2.000% 7.0% - 20009$	
BCS-CN88460-cyclopropyl-pyrazole- carboxamide-Ala (M66)         2.2         0.004         2.2         0.012         0.007	,
BCS-CN88460-cyclopropyl-pyrazole- carboxamide-Ala (M66)	•
	_
$\begin{bmatrix} BCS-CN88460-cyclopropyl-pyrazole-\\ carboxamide-Glyc (isomer 1) (M62, isomer 1) \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\ 0 & \\$	
	1
	, 
DCS CN080460 dosfuoro N mathul	
cyclopropyl-pyrazole-carboxamide-OH cys	
cyclopropyl-pyrazole-carboxamide-OHECys + +	
DCS CN99460 dasfluara N mathed	
cyclopropyl-pyrazole-carboxamico-OH- $GSH$ $J$ 9.3 $J$ 0.004 $J$ 5.2 $J$ 0.000 6.6 0.009 (M54)	
carboxamide-OH-lactic acie (isomer 1)	
(M69, isomer 1) BCS-CN88460-desfluoro-N-methyl-	
BCS-CN88460-desfluoro-N-methyl- cyclopropyl-pyrazolo carboxamide mercapte 34.0 0.002 2.9 0.003 3.7 0.005	
cyclopropyl-pyrazole carboxamide mercapte 34.0 0.002 2.9 0.003 3.7 0.005	
BCS-CN88460-cyclopropyl-pyrazole- carboxamide-QI-lactic acid (isomer 2) (1.9 0.016 (M69, isomer 2) (1.9 0.016)	
carboxamide- $OI$ -lactic acid (somer 2) $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$ $(1.9)$	
$\square BCS-CNSS460-destructor cyclopyopyi- \square \square$	
pyrazowa-karooxamide-Ada (Miga)	
BCS-CM88460-desfhoro-N-methyl- cyclopropyl-pyrazoto-carboxamide-desamino- Cys (M55)	
cyclopropyl-pyrazolo-čarboxamide desamino-	
Cys (M55)	
BCS-CN88460-desfluero-N-methyl- cyclopropyl-pyrazole carboxamide-mercapto	
Cyclopropy1-py1a2010 carbozaniuc-mercapio-	
Glyc-MA (MŠ7)	
BCS-CN\$8460-cyclopropyl-pyrorole-	
carboxanide-acetic acid (M68)	_
Characterised in the conventional extract 32.4 0.013 40.7 0.046 32.1 0.042	
Number of unknown peaks 4 12 9	
Largest unknown peak $2^{\circ}$	_
Exhaustive stract / / / / / / / / / / / / / / / / / / /	
ACN Microwave extract 0 2 10 n.a. n.a. 7.0 0.008 12.2 0.016*	
Dioxan Microware extract         n.a.         n.a.         3.4         0.004         2.9         0.004	
Total extractable         92.9         0.038         96.1         0.110         93.6         0.123           Total identified         60.6         0.025         44.9         0.051         45.7         0.060	
Total characterised (by HPLC)         32.4         0.013         40.7         0.046         32.1         0.042	
Total not analysed         n.a.         n.a.         10.5         0.012         15.7         0.021	
Post extraction solids (PES)         7.1         0.003         3.9         0.004         6.4         0.008	
Accountability 100.0 0.041 100.0 0.114 100.0 0.131	

* Microwave extract was analysed by HPLC but not quantified due to high matrix load.



## Table 6.6.1- 7: Distribution of radioactivity in Swiss chard (1st rotation) after spray application onto bare soil with [pyrazole-4-¹⁴C]BCS-CN88460

bare son with [pyrazole-4- C]BCS-CN88400	1			
		chard		s chard
		ature)	· ·	aturity
	TRR =	0.03	TRR =	Ø.026
Report name	mg	/kg 🔊		g/Kg
	%	mg/kg	%	mg kg 🖉
Conventional extract	97.2	¢ 0.030	96,0	<b>0</b> .025
Conventional extract – analysed by HPLC	96.1	0.030	96.0 [°]	0.025
Conventional extract - losses	l p	< 0.001	v n.a. 0	pár ko
Identified Compounds	Q,	° 4	<del>پ</del> ل	Ϋ́
BCS-CN88460	⊳ 6.Q Ø	0.002	\ <u>9</u> .6	\$ 0.00L
BCS-CR60082 (M49)	18%9	.0,006	©19.4~	
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Aka (M66)	<i>P</i> 7	Ø Ø	-	A 0
BCS-CN88460-cyclopropyl-pyrazole-carboxamide Glyc	Q A	- C	0″	
(isomer 1) (M62, isomer 1)		, Oʻ	s ,	
BCS-CN88460-cyclopropyl-pyrazole-carboxanaide-Glyc	×	× Ø		0
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 1) (M62, isomer 1) BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 2) (M62, isomer 2) BCS-CN88460-desfluoro-N-methyl syclopropyl-pyrazole-	Ô "Ś			<u>ĝ</u>
carboxamide-OH-Cys (M52)	26	0.908	€ ³ 4.2°~	0.009
BCS-CN88460-desfluoro-N-metryl-cyclopropyl-pyrazyle-	A.2 6	<b>D</b>		0.000
carboxamide-OH-GSH (M54)		0.007	28	0.006
BCS-CN88460-cyclopropyl-pyrazele-carboxamide/OH-lactic			<i>Q</i>	
acid (isomer 1) (M69, isomer 1)			2	
BCS-CN88460-desfluoro-N-methyl-cyclopropol-pyracele- carboxamide-mercapto-Glyc (M156)	Å &	9		
BCS-CN88460-cyc@propyl-pyrazole-carboxamide-OH-lactic	<u> </u>	- Ay İ		
acid (isomer 2) ( $1669$ , isomer 2) $\sqrt{2}$		<i>w</i>		
BCS-CN88460 desfluero-cyclopropyk pyrazolo carboxamide-Ala	\$~ *	J		
BCS-CN88460-desfluoro-N-methol-cyclopropyl pyrazolo carboxapude-desamino-Cys (M\$5)				
BCS-CN88460-desfluoro-N-rosthyl-cyclopropyl-pyrafole-	0			
carboxamide-mercapto-Glyc MA (\$457)	×			
BCS-CN88460-cyclopropyl-pyrazole-carooxamide-aceticacid				
	22.1	0.007	14.0	0.004
Characterised in the conventional extract (HBCC) 0 "0"	23.1	0.007	14.9	0.004
Number of unknown peaks		3		2
Largest unknown peak	11.1	0.003	8.8	0.002
Exhaustive extract	n.a.	n.a.	n.a.	n.a.
Total extractable of the total of to	97.2	0.030	96.0	0.025
Total identified	73.0	0.023	81.1	0.021
Total characterised (by HPLQ) ~ ~ ~ ~	23.1	0.007	14.9	0.004
Total not analysed y	1.1	< 0.001	n.a.	n.a.
Post extraction solids (PES)	2.8	0.001	4.0	0.001
(M68) Characterised in the conventional extract (HPLC) Number of unknown peaks Largest unknown peaks Exhaustive extract Total vextractable Total identified Total characterised (by HPLC) Post extraction solids (PFS) Accontrability	100.0	0.031	100.0	0.026
$\mathcal{L}$ $\mathcal{O}^{\mathbf{y}}$ $\mathcal{L}^{\mathbf{y}}$ $\mathcal{L}^{\mathbf{y}}$				
$\lor$				



## Table 6.6.1- 8:Distribution of radioactivity in turnips (1st rotation) after spray application onto bare<br/>soil with [pyrazole-4-14C]BCS-CN88460

hip leaves 0 0 8 mg/kg 0.0017 0.0017 0.0017 0.0017 0.0017 0.001 0.001 0.001 0.001 0.001 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005
mg/kg 0.017 0.017 0.001 0.001 0.001 0.001 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.
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Table 6.6.1- 9:	Distribution of radioactivity in confined wheat (2 nd rotation) after spray application	n
	onto bare soil with [pyrazole-4- ¹⁴ C]BCS-CN88460	0

onto bare son v	·····		-		1		1	^^^^^ ^^
	wheat	forage	whea	t hay	wheat	straw	wheat	grain O
	TRR = 0.078		TRR = 0.220		TRR = 0.247		TRR +0.011	
Report name	mg	/kg	mg	/kg	mg	Akge	,mg	/kg 💭
	%	mg/kg	%	mg/kg	%	⁰ ″mg/kg	×	mg/kg
Conventional extract	91.0	0.071	83.6	0.184	812	0.201	° <b>3</b> 2.9 (	20.006
Conventional extract – analysed by	91.0	0.071	83.	0.184	80.7	0.199	52.2	0.00%
HPLC	91.0	0.071	8	0.104	Q,	a,		
Conventional extract - losses	n.a.	n.a.	́n≱.a.	n.a.	0.6	0.001	.a.	ðvn.a. 🐒
Identified Compounds			4	- Q'	<u> </u>		ç C	
BCS-CN88460	1.4	0.00			<u></u>	~~~O	02	<u> </u>
BCS-CR60082 (M49)	7.3	0.006	¢.1	£0.002,≪	/ 2.&	0.097	°~	≪ ^v
BCS-CN88460-cyclopropyl-	25.6	10.020 °	\$ 13.9°		Ô.	0.022	\$ 772	, 0.001°
pyrazole-carboxamide-Ala (M66)	25.0			0.031		₹0.022 C	7.7	
BCS-CN88460-cyclopropyl-	, A				$\overline{\gamma}$		×,	S. S
pyrazole-carboxamide-Glyc (isomer 1) (M62, isomer 1)	0 0			°≯0.007©	S.O.	0,609	Ş. (	>~
BCS-CN88460-cyclopropyl-		$\sim$	× N	$\sim$			L.	
pyrazole-carboxamide-Glyc	Q 4.2	0.003	<b>3</b> 8	Q.013	D 3.40	0.008	°~-	
(isomer 2) (M62, isomer 2)	. K. [®]	- Or -	S.		0 3.4 °		K,	
BCS-CN88460-desfluoro-N-	·~~	S		<u></u>	. Q		Þ″	
memyi-cyclopiopyi-pyiazole-	\$ 3.9	¥0.003	5 <i>@</i> r	0.012	×5.0 ~	0.012		
carboxamide-OH-Cys (M52)	<u></u>	<u> </u>						
BCS-CN88460-desfluoro-N- methyl-cyclopropyl-pyracele-	× \$7	0.007	6.5~	0.014	\$\$.5	0.014		
carboxamide-OH-GSH (M54)		5		eng :	0 4	1		
BCS-CN88460-cyclopropy		$\sim$	\$ \$		Ø			
pyrazole-carboxamide-OH lactic 🎸	<u> </u>	<u></u>	(~ ~					
acid (isomer 1) (M69, isomer 1) BCS-CN88460-desflugro-N-	O' 4				Ø1			
methyl-cyclopropyl-pyrazole-	84	0007	Q.3	7, 0.005	3.7	0.009		
carboxamide-mercapto-GOc (M26)		0.007			5.7	0.007		
BCS-CN88460-cyclopropyl-			r <u> </u>	۵ کې				
pyrazole-carboxamic OH-lastic	€ 10.2 [©]	0.068	32	<b>0.007</b>	5.9	0.015		
acid (isomer 2) (Mg9, isomer 2)				7				
BCS-CN88460-desfluoro	, Č	ő ő		0.011			12.4	0.002
Ala (M67)			4.8	0.011			13.4	0.002
BCS-CN88460-desfluoro-N-			$\overline{\Omega_{n}}$					
methyl-coclopropyl-pyrazole-	6.9	Ø.005	2.5	0.005	1.1	0.003		
carboxamide-desamine Cys (M55)		\$0.005 \$0.005						
BCS-CN88460-desfluoro-NS	r Q							
methyl-cyclopropyl		Ś~	3.2	0.007	3.8	0.009		
methyl-cyclopropyl+pyrazole- carboxamide-mercapto-Głyc-Mo (M57)	j,	<b>™</b>						
BCS-CN88460-cvcfooronvla 🔍								
pyrazole-carboxamide-acetic acid	"		2.0	0.004				
(M68) 🖉 🖉 🖂 🖓								
Characterised in the conventional	14.4	0.011	29.6	0.065	36.7	0.091	31.7	0.004
extract (HPEC)	1 I.T						51.7	0.001
Number Ounknown peaks	4	1 	1			4		5
Largest unknown peak	4.9	0.004	5.8	0.013	4.7	0.012	16.2	0.002

Table is continued on the next page



#### Table 6.6.1-9continued

							×	
	wheat	forage	wheat hay		wheat	straw	wheat grain	Y
	TRR =	0.078	TRR =	0.220	TRR = 0.247		TRR = 09.011	
Report name	mg	/kg	mg	/kg	mg	/kg	ing/kg	
	%	mg/kg	%	mg/kg	%	[©] mg/kg	% my/kg	
Exhaustive extract	n.a.	n.a.	12.0	0.027	143	0.035		
Microwave extract	n.a.	n.a.	6.7 [©]	0.015	\$1	0.020	27.6 0.003	Ø
Microwave extract - SPE	n.a.	n.a.	6.7	0.015	<b>%</b> 8.1	0.02 <b>@</b>	27.8 0.903	1
Microwave extract - SPE Losses	n.a.	n.a.	<b>6</b> 0.1	<0.00	0.1	<0001		
Dioxan Microwave extrakt	n.a.	n.a.	5.4	0.012	¢02°	Ø.015	n.a. n.a.	
Total extractable	91.0	0.071	95 _° 7	6211	~95.5 _@	, 0.236	88.4 60009	
Total identified	76.6	0.039	\$4.0	ÇÕ.119Ç	44.0	0.099	21.2 0.002	
Total characterised (by HPLC)	14.4	ر 0.011 ک	ن 29.6 ⁽⁾	0.069	36.7	0.091	√31.7 → 0.0 <b>04</b> °	
Total not analysed	n.a. 🕺	n.a.y	12.0	¢0,027	A14.9 o	0.037	27.6 0.903	
Post extraction solids (PES)	9.0	0:007	<b>@4</b> .3 、	§0.010	4.5%	0.001	<b>19.6 0.002</b>	
Accountability	160.0	¢0.078 4	×100.9Ç	0.220	100.0	<b>Q</b> :247	0.011	
Exhaustive extract Microwave extract - SPE Microwave extract - SPE Losses Dioxan Microwave extrakt Total extractable Total identified Total characterised (by HPLC) Total not analysed Post extraction solids (PES) Accountability								



## Table 6.6.1-10: Distribution of radioactivity in Swiss chard (2nd rotation) after spray application onto bare soil with [pyrazole-4-¹⁴C]BCS-CN88460

bare soil with [pyrazole-4-"C]BCS-CN88460				<i>~</i> °
	Swiss	chard	Swiss	chand
	(imm	ature)		uturiity) 🔗
	TRR =	0.0	TRR = 0	20.062
Report name	mg	/kgð	mg	/kg
	%		8	ang/kg Ø
Conventional extract	95.3 C	0.060	ý¥.2 )	× 0.058
Conventional extract – analysed by HPLC	955	0.060	$\bigcirc 94 \times 0$	0.058
Conventional extract - losses	n.a.	n.a. 🖉	n @	ñ.a. «
		11.a.	n au	
Identified Compounds	0.S	<0.001		
BCS-CN88460	0.9			
BCS-CR60082 (M49)	×9.0 ×	ý0.006	3.18	*0.002
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ala (5166)	o ² 1.80	0.000	J.8	≤ 0.001 ∘
BCS-CN88460-cyclopropyl-pyrazole-carboxartide-Glye (isomer 1)	6-8	.004 d	12.2	0.008
(M62, isomer 1)				
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isomer 2)	KJ Ö	'- <u>&amp;</u> '		O
BCS-CN88460-desfluoro-N-methyl-cxploprop4-pyrazole-				
carboxamide-OH-Cys (M52)	25.7	Ø.016	⁵ 164	0.010
BCS-CN88460-desfluoro-N-meth Cyclopropyl-pyrazolo	Q.C.	0.094	<b>6</b> .2	0.004
carboxamide-OH-GSH (M54) 🖉 🖉 👘	6.3	0.064	06.2	0.004
BCS-CN88460-cyclopropyl-pyrazole arboxapride-QP-lacticacid	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.003	2.5	0.002
(isomer 1) (M69, isomer 1)	LJ ~		2.0	0.002
BCS-CN88460-desfluoro-N-methyl-cyclopropyl@yraze	×&	$\sim 0$		
carboxamide-mercapto Ayc (M36) 🗸 🖉 📿 🛇 🛇 BCS-CN88460-cyclopeopyl-pyrazologarboxamide-OH-lactic acid 🖉		- fy		
(isomer 2) (M69, isomer 2) $\sim$	£ (	v		
BCS-CN88460-destluoro oyclopropyl-pyrazole-carboxabaide-Ala	¥ 1.2 [×]	,	1.0	0.001
(M67) & & O O & & O	1.2°	0.001	1.9	0.001
BCS-CN88460-desfluero-N-methyl gyclopropyl-pytyzole-	Ň			
carboxamide desamino-Cys (M55)	<i>~</i>			
BCS-CN88460-desfluoro N-memyl-cyclopropyl-pyrazoe-	P			
carboxamide-mercapto Glyc-MA (MSZ)				
BCS-CN88460-cyclopropyl-pyrazofe carboxamidesecetic foid (M68)				
Characterised in the conventional extract (PHPLC)	38.9	0.024	49.5	0.031
Number of unknown peaks	Ģ	1		22
Largest unknown peak $\mathcal{O} = \mathcal{O}^{\mathcal{V}}$	15.2	0.009	11.3	0.007
BCS-CN88460-cyclopropyl-pyrazofe carboxamideacetic coid (M68) Characterised in the conventional extract (HPLC) Number of unknown peaks Largest unknown peak Exhaustive extract Total extractable Total characterised (by HPLC) Total not analysed Post extraction solids (PES)	n.a.	n.a.	n.a.	n.a.
Total extractable	95.3	0.060	94.2	0.058
Totakidentified	56.4	0.035	44.7	0.028
Total characterised (by HPLC)	38.9	0.024	49.5	0.031
Total not analysed	n.a.	n.a.	n.a.	n.a.
Post extraction solida (PES)	4.7	0.003	5.8	0.004
A countability	100.0	0.003	100.0	0.062
	100.0	0.062	100.0	0.062

s cos



## Table 6.6.1-11:Distribution of radioactivity in turnips (2nd rotation) after spray application onto bare<br/>soil with [pyrazole-4-14C]BCS-CN88460

son with [pyrazole-+- C]DCS-C100400	4	
		leaves
	TRR =	
Report name	mg	kg L
	%	mg/kg y
Conventional extract	92 T	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Conventional extract – analysed by HPLC	<b>9</b> 3.1	× 0.929 ×
Conventional extract - losses	Q n.a.	🗸 🔊 n.a. 🛫 🎜
Identified Compounds	Å Ö	
BCS-CN88460	\$ \$ O	Å Å
BCS-CR60082 (M49)	<u>مَحْمَ 12.7 محمد المحمد ال</u>	. <0.004
BCS-CN88460-cyclopropyl-pyrazole-carboxamide Ala (M66)	L 87 Q	0.002
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Gly (isome 1)		
(M62, isomer 1) $\langle \sqrt{2}, \sqrt{2} \rangle$	6.1	
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Olyc (isomer 2)		× 0.00
(M62, isomer 2)		\$ 0.00
BCS-CN88460-desfluoro-N-methyl-cyclopropy pyrazove-	4.4 S	\$ ⁹ ,09001
BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole		« <u>0.006</u>
carboxamide-OH-GSH (M54)		0.000
BCS-CN88460-cyclopropyl-pyrazole-carboxapide-OH-lactic acid		- ħ
(isomer 1) (M69, isomer 1) $\sqrt[5]{9}$ $\sqrt[5]{9}$ $\sqrt[5]{9}$ $\sqrt[5]{9}$		
BCS-CN88460-desfluoro N-methyl-cyclopropyl@yrazow		0.001
carboxamide-mercapto Qiyc (M26)	×2.9 ×	0.001
BCS-CN88460-cyclopropyl-gyrazol arboxamide-OH-lactic acid @	. <i>Q</i> ,	
$(\text{isomer 2}) \qquad	O S	
(M69, isomer 2)		
BCS-CN88460 desfluged-cyclopropyl-pyrazofe-carboxamide Ala (M67)	7.2	0.002
BCS-CN88460-desfluoro-Wenethyl-cyclopropyl-pyrazole- carboxaroide-desamino-Gys (MD)	~ () 	
carboxaronde-desamino-Qys (MDS)	0 [¥]	
BCS-CN88460-desfluero-N-methyl-cyclopropyl-pyrazole- &	7.4	0.002
		0.002
BCS-CN88460-cyclopropyl pyrazole-carboxamide-acetic acid		
$\frac{(M68)}{(Mex)} = \frac{1}{2} $	10.7	0.000
Landacterised in the conventional extract (HBSC) G	19.7	0.006
Carboxamide-mercapio-Glyc-MA (AST)	9.5	0.003
Exhapstive extract	n.a.	n.a.
Total extractable	93.1	0.029
Total identified	73.3	0.029
Total abarrate and (St. HDL CS	10.7	
Total and a Constant of Consta	19.7	0.006
I otal not arraysed a s "	n.a.	n.a.
Post extraction solids (PES)	6.9	0.002
Accountability of the	100.0	0.031
$\lor$		



		forage	whea		wheat		wheat	<b>N N</b>		
		= 0.072		0.187		= 0.340	TRR =	0.016	ď	
Report name		/kg	mg	/kg		/kgÔ	mg	kg 🍌		
	%	mg/kg	%	mg/kg	%	@pig/kg	% 😽	mg∕&g		
Conventional extract	91.9	0.066	85.4	0.160	83.7 🔬	0.284	5205	<b>\$</b> 009	â	
Conventional extract – analysed	91.9	0.066	85.4 🚕	0.160	82 %	0.283		\$ 000×		
by HPLC	91.9	0.000	C.	0.100	03,40	0.285	$\swarrow$ $33.7$	y 0.009	1	
Conventional extract - losses	n.a.	n.a.	n.a.🕅	n.a.	Ø.3	0.001	n.a.Q″	nx.a.	Å	
Identified Compounds			L		,0¥	Ś	2°	2	0	
BCS-CN88460			40 <u>°</u> -		× 。	JO I	<u> </u>	°, 0	¥	
BCS-CR60082 (M49)	4.3	0.003	2.3	0.004	5.8	020	st ,		1	
BCS-CN88460-cyclopropyl-		Q	þ						l	
pyrazole-carboxamide-Ala	15.4	0.0\$(1)	7¢9°	.0015	© 2.8 ≪ )	0.010	° A	L.	l	
(M66)		O	Ű,	20015 (0005)	~ 2.8 4.) ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	a start			l	
BCS-CN88460-cyclopropyl-		1		, Q.	O,	<b>~</b>	6 ^y í		l	
pyrazole-carboxamide-Glyc	3	Ś~`^	2,9%	0⊳Q0Č	A3.2 (	€0.01J		, et al.	l	
(isomer 1) (M62, isomer 1)				L'	sy ny		\$	and	l	
BCS-CN88460-cyclopropyl-	Q.		× í	🔊 🗸		Ľ	S	0	l	
pyrazole-carboxamide-Glyc	.39×	@:002 >	\$ 3.8 Å	0.009	~3Q3	× 0.011 4			l	
(isomer 2) (M62, isomer 2)	õ ^v .	<i>1</i> 0	<b>A</b> .	S	Or of				]	
BCS-CN88460-desfluoro-N-	2.0y	0.001 0.001 0.005	07.0 A		$\zeta \sim$	0.926	, ">		]	
methyl-cyclopropyl-pyrazole-	2.0	0.001	07.0 4	0.015	7,6	0.926	×		l	
carboxamide-OH-Cys (M52)			,	y o.o.	, Q	0.0 <u>-</u> 0	0		l	
BCS-CN88460-desfluoro-Ng		0.005	r O			0:909 , 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,			l	
1 1 1 1	6.3 Q	0.003	1/8	Q9.003	^{2.6}	0.4000			l	
carboxamide-OH-GSH (M54)	7 B	O	», (	p* &		Š			l	
BCS-CN88460-cycloppiopyl-		a			×	j V			l	
pyrazole-carboxamide-OH-factic	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	Ş _	3	<b>,020</b> 06	2.2	0.008			l	
acid (isomer 1) (M99, isomer 1)	/					0.000			l	
BCS-CN88460 gesfluog-N-	×,	Ň			J.				l	
methyl-cyclopropyl-pyrazole-			1.95 1.95	0.903	a.				l	
carboxamide-mercapto-Glyc		0.001	1.9	0.903	2.0	0.007			l	
(M56)		0.001	10		5				l	
BCS-CA88460-cycloppopyl-	~~								l	
pyrazole-carboxamide-OH-lactic		Ĵ0.005	8/4	× 0 04016	8.6	0.029			l	
acid (isomer 2) (M69, isomer 2)			8¢4 0	0.910	0.0	0.027			l	
BCS-CN88460-desfluor	li su'	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0	ð					l	
	Ê	N N	ສົາງຂຶ	0.004	1.1	0.004			l	
cyclopropyl-pyrazole-0 ⁵ carboxamide Ala (M67)	°~~~~~			0.004	1.1	0.004			l	
BCS-CN88460-desfluoro-N-			Ö						l	
methyl-colopropyl-pyragole-		~~	×,						l	
carboxamide-desamino-Cys	2.1	<b>\$</b> 002	≫ 1.1	0.002	1.6	0.005			l	
			P						l	
(M55) BCS-CN88460-desfluoro	N Q	6002 24							l	
	ř 🔊								ł	
methyl-cyclopropyl-pyrazole-		Q.003	3.6	0.007	2.9	0.010			ł	
carboxamide-mercapto-Glyc-	К ^у	₽, [₩]							l	
MA (M57)									l	
BCS-CN88460-cxeloprop9-	r v		1.6	0.002	1 4	0.005			l	
pyrazole carboxamide-acetic			1.6	0.003	1.4	0.005			l	
acid (14468)									l	
Characterised in the	45.8	0.033	37.7	0.071	38.3	0.130	53.7	0.009	l	
conventional extract (HPEC)		l	2			_	20.1	0.007	l	
Number of unknown peaks		2	1		1		4	2	ł	
Largest unknown peak	6.1	0.004	3.7	0.007	6.2	0.021	22.4	0.004	l	

 Table 6.6.1-12:
 Distribution of radioactivity in wheat (3rd rotation) after spray application onto bare soil with [pyrazole-4-¹⁴C]BCS-CN88460

Table is continued on the next page.



#### Table 6.6.1- 12continued

								aî	<b>~</b>
	wheat	forage	whea	it hay	wheat	straw		t grain	Ê.
	TRR = 0.072		TRR = 0.187		TRR = 0.040		TRR 0.016		
Report name	mg	/kg	mg	/kg	mg	/kg	, Cine		<i>R</i> a
	%	mg/kg	%	mg/kg	%	mg/kg	°~~~~	¶ng/kg≪	S.
Exhaustive extract	n.a.	n.a.	12.5	0.023	12,1	0.041	31.5	0.005	, O
Microwave extract	n.a.	n.a.	7,9	0.015	<b>66</b> .7	0.023®	31.5	0,005	Ô
Microwave extract - SPE	n.a.	n.a.	<u>"@.</u> 7	0.014	6.2	0.001	24!4	0.004	
Microwave extract - SPE Losses	n.a.	n.a.	0.2	<0,001	. 8°€°		o [™] 7.1		1
Dioxan Microwave extrakt	n.a.	n.a.	4.6.	0,009	مُ 5.5	0.019	0 ^{97.1} n.a	ĵŊ.	
Total extractable	91.9	0.066	Ø ⁹ .9	<b>XØ</b> .183 🖌	95.8	0.326	85.2	0.014	
Total identified	46.2	0.033	47.7 C	0.089	459	0.153	⊖ ^y n.a.	n.a.	
Total characterised (by HPLC)	45.8	0.033	37.7%	03071	A38.3	Ô0.13Q	53.7	0,009	
Total not analysed	n.a. 🖉	n ar∕	JØ.5	0.023	¢\$12.4	0.042	ž1.5	ð.005	
Post extraction solids (PES)	80 ⁵ V	0,006	\$2.1 ×	0.004	45	0014	Å4.8	0.002	
Accountability	500.0	0.072	100.0	0487	0.0	¢0.340	100.0	0.016	
Microwave extract - SPE Losses Dioxan Microwave extrakt Total extractable Total identified Total characterised (by HPLC) Total not analysed Post extraction solids (PES) Accountability Accountability Accountability Accountability Accountability		Ø.	÷	Ű,	y O'	ð	0 O		
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# Table 6.6.1-13: Distribution of radioactivity in Swiss chard (3rd rotation) after spray application onto bare soil with [pyrazole-4-¹⁴C]BCS-CN88460

bare soil with [pyrazole-4-"C]BCS-CN884					
		chard ature)	swiss chard (at maturity)		
	TRR =	0.050	TRR =	0.052	
Report name		/kg 🔗	mg		
	%	mg/kg	%	ang/kg Ø	
Conventional extract	94.4	£ 0.053	.92.4	00.48	
Conventional extract – analysed by HPLC	94.4	0.053	©92.4~Q	0.0#8	
Conventional extract - losses	n.a	n.a. 🎽	n.a	n.a. K	
Identified Compounds	Q	<u> </u>	, L		
BCS-CN88460	>0.8 .	<0.001	\ ⁰ 1.1 ¢	0.001	
BCS-CR60082 (M49)	S~ 7.3∜	Q004	Q 4.05	×0.002	
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ala (966)	203	~0.001°	£,8	\$, 0.001 ∘	
BCS-CN88460-cyclopropyl-pyrazole-carboxamde-GL		0.603	9.5	0,005	
(isomer 1) (M62, isomer 1) $(1200 \text{ somer } 1)$	ð ^{3.4} Å	°~	€ ^{9.3} ∛	0.005	
BCS-CN88460-cyclopropyl-pyrazole-carboxamide Glyc	× KG	č 0.001	Ş.	0	
(isomer 2) (M62, isomer 2)					
carboxamide-OH-Cys (M52)	23.0	0.013	^م 21.۹ م	0.011	
BCS-CN88460-desfluoro-N-methy cyclopropyl-pyrazolo	Q.	0.005	ð.7	0.002	
carboxamide-OH-GSH (M54)		0.003	Ø: /	0.002	
BCS-CN88460-cyclopropyl-pyrazole carboxapride-QH-lactic	· \$		ĝ		
acid (isomer 1) (M69, isomer 1) BCS-CN88460-desfluoro-N-methyb-cyclopropyloyrazed		J. S			
carboxamide-mercapto Giyc (M56)	<u>_</u>	2			
BCS-CN88460-cyclopeopyl-pyrazole carboxamide-OPI-lactic	0.50	<b>@</b> .001			
acid (isomer 2) (M69; isom@2)	0.5	Ø.001			
BCS-CN88460-destluoro-cyclopropyl-parazole-carboxataide-	JY.3	0.001	1.6	0.001	
BCS-CN88460-desfluero-N-methyl&yclopropyl-pytszole-	O W				
carboxamide desamino-Cys (M55)	0.6	< 0.001			
BCS-CNSS460-desfluoro N-methyl-cyclopropyl-pyrazoe-					
carboxamide-mercapto-Glyc-MA (M50)	19				
BCS-CN88460-cyclopropyl-pyrazolo carbóxamide acetic foid (M68)					
(M68) Characterised in the conventional extract (HPLG)	43.3	0.023	48.4	0.025	
Number of unknown peaks $\sim$	1	9	1		
Largest unknown peak	7.5	0.004	5.8	0.003	
Exhaustive extract	n.a.	n.a.	n.a.	n.a.	
Total Sytractable	94.4	0.053	92.4	0.048	
Total identified	51.3	0.029	43.9	0.023	
Total characterised (by HPLC)	43.1	0.024	48.5	0.025	
Total not analysed	n.a.	n.a.	n.a.	n.a.	
Post extraction solids (PESP	5.6	0.003	7.6	0.004	
Accountability	100.0	0.056	100.0	0.052	
Characterised in the concention extract (HPLG) Number of unknown peaks Largest unknown peak Exhaustive extract Total extractable Total identified Total characterised (by HPLC)					
$\bigcirc$					



# Table 6.6.1- 14:Distribution of radioactivity in turnips (3rd rotation) after spray application onto bare<br/>soil with [pyrazole-4-14C]BCS-CN88460

son with [pyrazole-4- C]DCS-C100400		<i>a</i> .° ×
	turnip	leaves
	TRR =	0.026
Report name	and ma	/kg L
	%.	mg/kg
Conventional extract	92.3	0.024 4
Conventional extract – analysed by HPLC	52.3	× 0024 \$
Conventional extract - losses	Q n.a.	
Identified Compounds		
BCS-CN88460		
BCS-CR60082 (M49)	× 9.4	<u>√</u> ≪Ø.002≈℃
	y 9.4%	
BCS-CN88460-cyclopropyl-pyrazole-carboxamide Ala (1966)	<del>~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~</del>	0.001
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Glyc (isome 1) (M62, isomer 1)	Q 5.5 Q	O ⁴ Q0001 J ⁴
BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Olyc (isomer 2)		X LO DOWN
(M62, isomer 2)		0.00
BCS-CN88460-desfluoro-N-methyl-cyc@propyl-pyrazoe-	C ~ 3 9 5	\$ <u>0</u> 9001
carboxamide-OH-Cys (M52)		∑, %9.001 ,
BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole		<u>%</u> 0.004
BCS-CN88460-cyclopropyl-pyrazole-carboxanide-OH-lactic acid		$\odot'$
(isomer 1) (M69, isomer 1) $\bigcirc$ $\bigcirc$ $\bigcirc$		b
BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pgrazole	U 5.0 25	0.001
carboxamide-mercapto-Glyc (M56) 0 0		0.001
BCS-CN88460-cyclopropyl-pylazole-carboxamide-Off-lactic acid	° 🞸	
(isomer 2) (M69, isomer 2) (M6		
(M67)	Q . 3.8	0.001
BCS-CN88460 desflugso-N-methyl-cyclopropyl-pyrazole-	2 1.8	< 0.001
carboxamideodesamino-Cys (M55) 2 A V V	1.0	<0.001
BCS-CN88460-desfluoro Manthal-cyclopropyl-pyrazole- carboxamide-mercapto-@yc-Max(M57)	3.8	0.001
carboxanite-mercapto-@yc-M@M57)	¢	
(M68)		
Characterised in the conventional extract OHPLE	36.9	0.010
Number of unknown peaks 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		9
Largest unknown peak	7.3	0.002
Exhaustiveextract	n.a.	n.a.
Total extractable	92.3	0.024
Total dentified	55.4	0.014
Total characterised (by HPI C) $e^{0}$ $a_{1}$	36.9	0.014
Total not analysed	n.a.	n.a.
Post extraction solide (PFS)	7.7	0.002
Accountability	100.0	0.026
	100.0	0.020
carboxamide-mercapto-Oyc-Max(M57) BCS-CN88460-cyclopropyl-pyrazole-carboxamide-acetic acid (M68) Characterised in the conventional extract (HPLC) Number of unknown peaks Largest unknown peak Exhaustive extract Total extractable Total extractable Total characterised (by HPLC) Total not analysed Post extraction solids (PES)		
$\bigcirc$		



#### III. Conclusions

The metabolism of the fungicide isoflucypram (BCS-CN88460) was investigated in confined rotational crops after one spray application onto bare soil. The application rate amounted to 201.9 g a.s./ha and the test compound was ¹⁴C-radiolabelled in the pyrazole mojety.

The TRRs in the raw agricultural commodities (RACs) were low and ranges from 0.004 mg/kg for wheat grain (1st rotations) to 0.340 mg/kg for wheat straw (3rd rotation). The TRR values increased slightly from the 1st to the 2nd rotation and stayed stable in the 3rd rotation, TRR values in turner roots were constantly low at 0.006 mg/kg throughout the three cotations.

Radioactive residues were first extracted with conventional methods in case of wheat has, straw and grain, solids had to be further extracted.

BCS-CN88460-N-methyl-cyclopropyl-pyrazole-carboxamide (BCS-CR60052) (M49), BCS-CN88460-cyclopropyl-pyrazole-carboxamide-Ata (M66), BCS-CN88460-cyclopropyl-pyrazolecarboxamide-Glyc (isomer 2, M62-i2), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazolecarboxamide-OH-Cys (M52), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazolecarboxamide-OH-GSH (M54), BCS-CN88460-desfluoro-Cyclopropyl-pyrazolecarboxamide-OH-GSH (M54), BCS-CN88460-desfluoro-Cyclopropyl-pyrazolecarboxamide-OH-GSH (M54), BCS-CN88460-desfluoro-Cyclopropyl-pyrazole-carboxamide-OH-lattic acid (isomer 2, M69-i2), BCS-CN88460-desfluoro-Cyclopropyl-pyrazole-carboxamide-OH-lattic acid BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-Ala (M674) and 
Parent compound and metabolites BCS-CN88460-cyclopropy Ppyratole-carboxanide-Glyc (isomer 1, M62-i1), BCS-CN88460-cyclopropyl-pyrazole-carboxamide-OH-laetic acid (isomer 1, M69-i1), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-mercapto-Glyc (M56), BCS-CN88460-desfluoro-N-methyl-cyclopropyl-pyrazole-carboxamide-desamine-Cys (M55) and BCS-CN88460-cyclopropyl-pyrazole-carboxamide-acetic acid (M68) were quantified in low amounts only (TRR <10%) in the conventional extracts of the RACs. Oll other metabolites were detected in low amounts and were characterised by their extraction and phromatographic behaviour.

The following metabolic reactions were observed:

• cleavage of the parent compound leading to BCS-@N88460-N-methyl-cyclopropylpyrazole-carboxamide (BCS-CR60982)

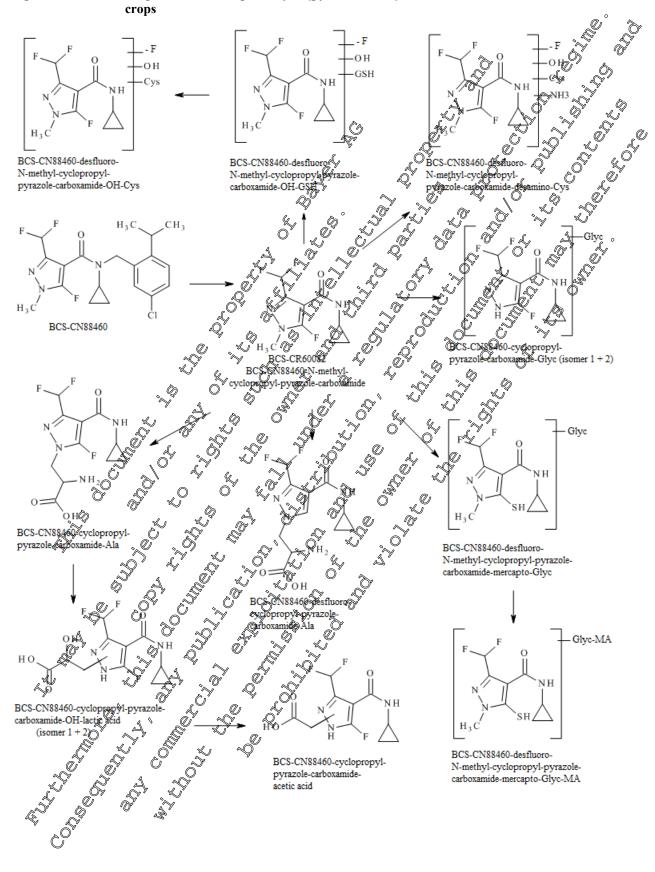
conjugation of BCS-CR 9082 with admine, Tactic acid or acetic acid with or without defluoromation of the pyrazoleging

- demeth dation of BCS CR60082 for lowed by conjugation with glucose
- hydroxylation, deamination and defluoronation of BCS-CR60082 followed by conjugation with cysteme or glutathione
- defluoronation of BES-CR60082 followed by conjugation with glucose and glutathione And degradation of the glutathione group to mercapto alcohol, additional conjugation with malonic active

Based on these results, the metabolism of [pvrazole-4-14C]BCS-CN88460 in confined rotational crops is adequately understood and the following metabolic pathway is proposed.



#### Figure 6.6.1-1: Proposed metabolic pathway of [pyrazole-4-14C]BCS-CN88460 in confined rotational





<b>Report:</b> Title: Report No.: Document No.:	KCA 6.6.1/02; Konstanting; Konstanting; 2017; M-595695-01-1 Metabolism of [phenyl-UL-14C]BCS-CN88460 in confined rotational crops EnSa-17-0128 M-595695-01-1
Guideline(s):	OECD Guideline for the Testing of Chemicals, 502: Metabolism in Rotational Crops,
	adopted 2007-01-08
	Regulation (EC) No 1107/2009 amended by Comission Regulation (EQ) No 263/2012
	(Europe)
	US EPA OCSPP Residue Chemistry Test Guideline OPPTS 860.1550: Contined
	Accumulation in Rotational Crops
Guideline deviation(s):	none
GLP/GEP:	yes

ExecutiveSummary

The metabolism of the fungicide isoflucypram (BCS-CN88460) was investigated in confined rotational crops after one spray application (no bare soil). The test compound was ¹⁴C radiolabelled in the phenyl moiety. The soil was treated with 197.7 g a.s. the according to the envisaged use pattern. Root crops are represented by turkins, leafy crops by Swiss chard and cereals by wheat. They were sown 30 days (1st rotation), 140 days (2st rotation) and 287 days (3st rotation) after soil treatment.

A sample of immature Swiss-chard was harvested at BBCH stage 45. Wheat forage was sampled at BBCH stage 29 and wheat hay at BBCH stage 78 to 83. At maturity furnin beaves, furnip roots, Swiss chard, wheat straw and wheat grain were harvested.

The TRRs in the different KACs ranged from low to very low. The TRR values increased slightly from the 1st rotation to the 2nd rotation and declined to tower values in the 3rd rotation, as shown in the following table:

Ro	
Table 6.6.1-95:	TRR values in confined rotational crops after spray application onto bare soil with
1 abic 0.0.3-13.	TRREatures to configed Totational crops ager spray application onto bare son with
@ ¹	[phearyl-UK ^{AC} ]B€S-CN88460 S
¢Q"	
12 51	

	s i s u		
Matrix	^{1 st} rotation		3 rd rotation
wheat forage starts	0 0023 0 ⁵	<del>گ</del> 0.018	0.015
wheat hay	Q 0.03	0.062	0.036
wheelestraw	Q Q Q S 1	0.070	0.055
wheat grain	0.001	0.004*	0.003*
Swiss chard (intermediate)	0.029	0.016	0.020
Swiss chard (at maturity)	¢ 0.020	0.016	0.025
turnip poots 5 2 5	~ [©] 0.003*	0.003*	0.003*
turorp leaves A	0.004*	0.006*	0.006*

TRR values were determined by LSC measurement following combustion. Samples were not extracted due to their amount being <0.01 mg/kg.

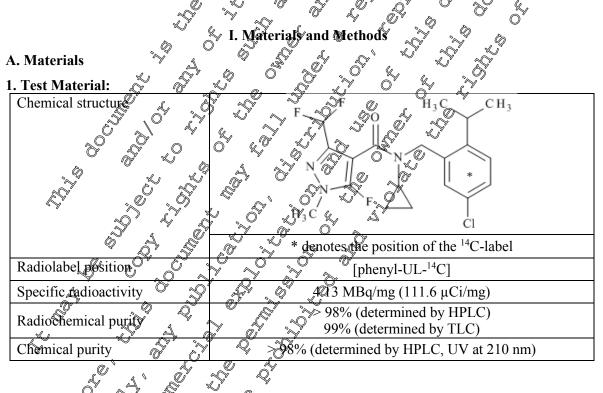
The TRRs in the raw agricultural commodities (RACs) of the current study were lower as the TRRs found in the study with the pyrazole label. The majority of the radioactive residues of all RACs was



conventionally extracted with a mixture of acetonitrile/water (8/2; v/v). The residues in the conventional extracts amounted from 78.4% to 97.7% of the TRR. Solids after extraction of wheat hay and wheat straw (1st, 2nd and 3rd rotation) were exhaustively extracted with a mixture of acetonitrile/water/formic acid (50/50/1; v/v/v) using microwave assistance. Exhaustive extracted residues were not further characterised due to low TRR values ( $\leq 0.006$  mg/kg). All RACs were sufficiently extracted. The total radioactivity in the post extraction solids (P68) amounted to  $\leq 9.6\%$  of the TRR except for wheat straw (1st rotation, 11.5% of the TRR and 0.006 mg/kg). BCS-CN88460 was the only major compound identified in the conventional extracts with up to 17% (0.004 mg/kg) of the TRR. All other metabolites were detected in the amounts and were characterised by their extraction and chromatographic behaviour

Further characterisation of residues by acidic hydrobysis of crude extracts of Swiss chard (immature and mature, 1st rotation) and wheat straw (1st rotation) indicated presence of confugates of BCS-CN88460-carboxylic acid and BCS-CN88460-propanol besides parent compound in these selected extracts.

Based on these results, the metabolism of [pheny]-CL-¹⁴CBCS-CN88460 in confine Protational crops is adequately understood. Parent compound was the only residue component dentified.



356 mg of the EQ 200 blank formulation was added to 22 mg of the radiolabelled test compound. After homogenisation a water actionitrile mixture (50/50; v/v) was added to receive the ready-to-use application suspension (total volume: 100 mL). The radioactivity in the final application suspension was determined by CSC and amounted to 0.907 MBq/mL. The formulated test compound was used as test item.

**2. Soil:** "**Constant**" 4", pH (CaCl₂) = 6.7, 15% clay, 20% silt and 65% sand 1.3% organic carbon, cation exchange capacity (CEC) of 7.5 meq/100 g



#### 3. Plants:

rotational crop	variety	representative for crop group
Spring wheat	Thasos	cereals
Swiss chard	Lucullus	leafy crops
Turnips	Rondo	root crops

#### **B. Study Design**

#### **Experimental conditions:**

The application conditions simulated the maximum@annuaDrate envisaged use pattern.

The bare soil was treated on 2014-03-25 An approximately 10% Aigher field rate (approx. 220 g a.s./ha) was used to compensate losses during the application. The application was performed with 100 mL of the application suspension (according to 90,24 MBe) using a computer white lied track sprayer fitted with a flat fan nozzle. The homogeneity of the spray application was checked by determination of the radioactivity on ten filter papers (1.5 cm diameter), which were randomly placed on the soil before application. The spray application washom beneque. After application the stock container of the application apparatus was rinsed twice with acetonitrile/water (5050; v/v). The Pinsing solution was measured for radioactivity by SC. By subtraction of all these losses from the radioactivity of the application suspension, the actual amount applied to the soft was calculated. As a result, ð, 197.7 g a.s./ha (81.63 MBq/m²) was applied C

The stability of the dest compound in the application suspension was checked before and after the application by HPSC. No degradation was observed The purity of the test compound was analysed after the application by NPLC analysis and amounted to 100%.

For ageing, the soil remained undisturbed for 90 days. The Soil was watered in order to maintain adequate mosture content. Before each sowing of the crops the upper soil layer was intensively mixed (approx, 10 cm depth) and soft cores (10 to 15 cm depth) were taken. Additional soil cores were sampled at the end of the 3rd rotation (harcest of wheat, 15-30 cm depth). The radioactivity in the airdried soil cores was determined by combustion of aliquots followed by LSC.

#### Sampling:

#### Wheat

Definition of BBCH-codes for cereals:

- BCH-codes for cereals: BBCH 29 -
- medium wilk: grain convent maky, grains reached final size BBCH 75 -
- BBCH 83 arly dough 🔍
- fully tipe: gen hard, difficult to divide with thumbnail BBCH 89 -

#### Wheat fora

Forage was taken at approx BBCH 29 (62, 175 and 335 days after application). One of five rows wheat plants was cut from the roots, which remained in the soil. The forage was cut in small pieces and homogenised with liquid nitrogen using a Polytron (Kinematica). An aliquot of the homogenised sample was used for extraction. Residual sample material was stored at approx. - 18°C.



#### Wheat hay

Hay was taken at BBCH 75 - 83 (101, 233 and 387 days after application).One of five rows wheat plants was cut from the roots, which remained in the soil. The hay sample was dried for four days. The dried hay sample was cut in small pieces and homogenised with liquid nitrogen using a Polytron (Kinematica). An aliquot of the homogenised sample was used for extraction. Residual sample material was stored at approx. - 18°C.

#### Wheat straw and grain

Straw and grain were harvested together at BBCH 89 (1, 39, 286 and 407 days after application). The wheat plants were cut shortly above soil surface. The roots remained in the soft. The seeds were of collected manually yielding the grain sample. The romaining ears and chaff were combined with the straw.

Grain and straw samples were homogenised as described for torage. The homogenised samples were stored in aliquots at approx. - 18°C. One aliquit of each sample was used for extraction.

#### Swiss chard

Definition of BBCH-codes for leaf vegetables (not forming heads): BBCH 45 - 50% of the leaf mass typical for the variety teached BBCH 49 - typical leaf mass reached

Swiss chard was harvested as an animature RAC (BBCH 45, 36, 17) and 30 days after application) and at maturity (BBCH 49; 62, 189 and 342 days after application). The samples were cut from the roots, which remained in the soil. The samples were homogenised as described for forage. The homogenised samples were stored in aliquots at approx. 18°C. One ariquot of each sample was used for extraction.

#### Turnip leaves and roots

Definition of BBCH codes for roof and stem vegetables

BBCH 49 - expansion complete; typical form and size of roots reached

Turnip leaves and roots were harvested together at maturity (BBCH 49; 79, 212 and 356 after application). The turnips were pulled out of the soil and the leaves were separated from roots. The roots were cut into slices and the leaves into small pieces Both were homogenised as described for forage and stored in alignots a approx. - 18°C. One aligned of each sample was used for extraction.

#### C. Analytical Proceduces

#### Conventional Extraction and Sample Preparation of all RACs

Aliquots of the homogenised samples were extracted 2 to 4 times with acetonitrile/water (8/2, v/v). The extraction steps were conducted using a Polytron homogeniser. The residues were -dried and weighed yielding the solids. The TRR of each RAC was calculated from the specific radioactivity of the test compound, the amount of the sample used for extraction and the sum of radioactivity, measured in the extracts and the remaining solids. The purified (solid phase extraction (SPE)) and concentrated combined extracts, were subjected to HPLC analysis based on reversed phase chromatography using an acidic water acetonitrile/THF gradient. Recoveries of the concentration processes amounted from 90.3% to 111.6%.

#### Exhaustive Extraction of Solids

Depending on the amount of residues in the solids of the conventional extraction, an exhaustive extraction was performed once with acetonitrile/water/formic acid (50/50/1; v/v/v) using microwave assistance. All samples were purified using SPE cartridges. Recoveries of the purification process amounted from 88.0% to 129.7%.



#### Hydrolysis of Extracts

For isolation of parent compound and degradation products, extracts of wheat straw and Swiss chard (immature and at maturity) of the 1st rotation were hydrolysed for 1 h in 1M HCl at 100°C.

#### Quantification:

Parent compound and metabolites were quantified in the conventional expacts by HPLC analysis based on reversed phase chromatography using an acidic water/acetonitrile/TJFF gradient. Corresponding metabolites were named with the same report name and peak ID. They were assigned to each other by comparison of the metabolite profiles and retention times based on the HPLC profiling method.

#### Identification and characterisation:

Parent compound was identified by comparison of HPLC profiles with each other.

Acidic hydrolysis of crude extracts of the 1st rotation from Swiss chard (inphature and at maturity) and wheat straw, revealed the presence of three major aglyca Paren compound and the two metabolites BCS-CN88460-carboxylic-acid and BCS-CN88460-propanol were isolated in HPLC fractions from purified and concentrated hydrolysed extract from Swiss chard (at maturity, 1st rotation).

All isolated compounds were identified by spectroscopic methods

To support metabolite identification, comparison of HBLC-profiles of isolated compounds with HPLC profiles of hydrolysed extracts of the 1st rotation from Swass chard (impature and at maturity) and wheat straw was performed.

In addition, the presence of BCS-CN88460-carboxyfic acid and BCS-CN88460-propanol in the hydrolysed extracts was confirmed by comparing these HPCC profiles with profiles from laying hen metabolism studies.

The obtained aglyce after hydrolysis, which were isolated and identified from the crude extracts after hydrolsis, were not assigned to any peaks in the native extracts. All other peaks or regions additionally detected in the respective HPLC chromatograms were assigned as "unknown" and numbered accordingly. Drey were characterised by their extraction and chromatographic behaviour.

#### Storage stability:

All samples were stored at temperatures -18 °C before extraction and analysis. All RACs were extracted within maximal & days. Within maximal 44 days after extraction, the earliest metabolite profiles (used for quantitation of metabolites) were obtained by HPLC-analysis analysis based on reversed phase chromatography using an activic water/acetonitrile/THF gradient.

Therefore, it was concluded that the results of this study were not negatively influenced by storage effects.

# II. Results and Discussion

The TRR of each raw agricultural commonly (RAC) was calculated from the specific radioactivity of the test compound, the amount of the sample used for extraction and the sum of radioactivity, measured in the conventional extracts and the remaining solids.

The TRR's in aD RACs reached from low to very low values. The TRR values in the 1st rotation ranged from 0.001 mg/kg (wheat grain) to 0.051 mg/kg (wheat straw). In the 2nd rotation, the TRR values slightly increased in wheat hay, straw, grain, turnip roots and turnip leaves and ranged from 0.004 mg/kg (wheat grain) to 0.070 mg/kg (wheat straw) whereas the TRR values in wheat forage and Swiss chard (immature and at maturity) slightly decreased to 0.016 mg/kg (Swiss chard, immature and at maturity) and 0.018 mg/kg (wheat forage). In the 3rd rotation, the TRR values for Swiss chard (immature and at maturity) increased slightly to 0.020 mg/kg and 0.025 mg/kg, respectively. The TRR



values in the other RACs decreased and ranged from 0.003 mg/kg (wheat grain) to 0.055 mg/kg (wheat straw).

RACs with an amount of >0.01 mg/kg were conventionally extracted with a mixture of acetonitrile/water (8/2, v/v). The conventional extraction rates amounted from 77.2% to 97.7% of the TRR.

Due to low extraction rates in wheat straw and hay, the solids remaining after conventional extraction. were further extracted by microwave assistance with acetonitrile/water/formic acid (50/59/1; y/6/v).

After the exhaustive extraction all RACs were sufficiently extracted with total extraction roles between 87.3% (wheat straw, 1st rotation) and 97.7% (Swiss charge immature and at maturity, 1st rotation). Significant losses of radioactivity during the concentration process of the extracts of radioactivity in the distillates were not observed. The post extraction solids (PES) in the RACs ranged from 2.3% (<0.001 mg/kg) of the TRR for Swiss chard (at maturity, 1st rotation) to 14.7% (0.004 mg/kg) in wheat hay (3rd rotation). Solids were not further extracted

Parent compound and metabolites were quantified in the conventional extracts by HPLG analysis based on reversed phase chromatography using an acidie water/acetonitrile/HIF gradient They were assigned in all extracts by comparison of the metabolite profiles and retention times based on the profiling method. Corresponding metabolites were pared with the same report pare and peak ID. The identification rates in the three rotations were low A total of 1. 7% to 77.0% of the TRR was identified in RACs of the 1st rotation, up to 12,2% of the TRP in RACs of the 2% rotation and up to 5.2% of the TRR in RACs of the 3rd retation. The low identification rates are due to the generally low amounts of residues in the according RACs

Parent compound BCS-CN88460 was the only compound identified. In wheat for age it accounted for 17.0% (0.004 mg/kg) of the TRR, 122% (0.002 mg/kg) of the PRR and 5.2% (0.001 mg/kg) of the TRR in the 1st, 2nd and 3rd rotation, respectively. In wheat hay of the 1st botation and Swiss chard (immature and at maturity) of the Pt rotation it accounced for up to 6,1% (2001 mg/kg) of the TRR. In total 16 metabolities were observed with maximum amounts  $\geq 10\%$  of the TRR in different crops and rotations. Since the TRR was in the mange 00.002 to 0.007 mg/kg for all compounds, no identification was possible and they were only characterised by their characteristic behaviour via HPLC.

Further characterization by scidic hydrotysis in Acated, that the majority of these metabolites are conjugates of aglycons and parent compound topresenting up to 74.7% of TRR. Two aglyca (BCS-CN88460-carboxytic acid and BCS-CN88469-propanol) and parent compound were isolated from hydrolysed extracts and identified by EC-MS and IC-MS/MS.

The distribution of the gadioactive residues as well as the identified and characterised compounds in

The distroution of the adioactive residues as well as the identified and characterised com confined rotational crops after spray application solo bare soil is shown in the tables below.



Table 6.6.1- 16:	Distribution of radioactivity in confined rotational crops (1 st rotation) after spray
	application onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460

application onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460								
	wheat	forage	whea	t hay	wheat	t straw	whea	t grafin
	TRR =	0.023	TRR =	0.039	TRR =	TRR = 0.051		92001*
	mg	/kg	mg	/kg	mg	A Se	me	
	%	mg/kg	%	mg/kg	%	mg/kg		ông/kg
Total extractable	94.8	0.021	92 <b>,8</b> Ô	0.036	88.5	0.046	↓ n.a.	n.a
Conventional extract (analysed)	94.8	0.021	86.1	0.033	6 ⁹ 17.2	0.040	na	Ana.
Losses conventional extract	n.a.	n.a.	≰ [©] n.a.	n.a.Q	1.3.	0.001	n.a.	Un.a.
Exhaustive extract	n.a.	n.a.Q	6.7	0.003	QU.1	0.005	⁾ n.a.Q	p.g.
Post extraction solids (PES)	5.2	0.001	<b>?</b> .2	<u>૾</u> 0.003	11.5	0.006	100.0	0.001
Accountability	100.0	<u></u> 0.023	100.0°	0.039	100.0	40°	5100.05	0.061
		<u>」</u> ″√ wis≴≈chard	(i@motu	<u>~</u>		wiss Gard	(at the star	rie i
		<u> </u>			, v (	wiss equal u	ar.	
	Å.	<b>∛</b> TRR <del>,</del> ⊘	9°0.02959	$\sim$	ð,	SFRR ₹	0.020	
Ø1	<u>y y</u> V	 Or	/kġð>	<del>Å k</del>		$\sim$	g/kĝ∻yਁ k	
T + 1 + + 11	× ·			<u>g/kg 炎</u>		<u>%</u>	Ý	g/kg
Total extractable	s s	אין דאָ	@0.	028		9.7 Q		.020
Conventional extract (añalysed)	\$97 ©	1.7 S		<b>p2</b> 8	_ <i>√</i> 9	7.7~~~	0	.020
Losses conventional extract	n N	.a.	n sh	-		n av	1	n.a.
Exhaustive extract	n car	la.	n n	20 101		1.a.	1	1.a.
Post extraction solids (PES)	<u> </u>	.3	( ⁷ 0.	901 ( ¹	J I	2.3	<(	0.001
Accountability		<u>,.0</u> Ø.0 <u>Ø</u>		026		0.00	0	.020
		turnip		<u>y</u> _9	ý 	turnip	leaves	
		TRR [°]	0.003*	AN A		TRR =	0.004*	
		, inc.	/kg (	~			g/kg	
		Î Î	ing ing ing	/kg		%		g/kg
Total extractable	Y Q	a.	ý	a.		n.a.		1.a.
Conventional extract (analysed)	Ø n.	a 2 %	<b>K</b> )	a.		n.a.		1.a.
Losses convention extract	à é	xa. "N	n.	a.	r	1.a.	1	1.a.
Exhaustive extract	n.	.a. 0	n	a.	r	1.a.	1	1.a.
Post extraction solids (PES)	<u></u> 10	0.9	0.0	003	10	0.00	0.	.004
Accountability	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.0	0.0	003	1(	0.00	0	.004

* TRR values were determined to LSC measurement following combustion. Samples were not extracted due to low residue leves.



Table 6.6.1- 17:	Distribution of radioactivity in confined rotational crops (2 nd rotation) after spray
	application onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460

application onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460								
	wheat	forage	whea	t hay	wheat	straw		t gran
	TRR =	0.018	TRR =	0.062	TRR = 0.070		TRR =	9.004*
	mg	/kg	mg	/kg	mg	ð ý	me	
	%	mg/kg	%	mg/kg	%	mg/kg		ng/kg
Total extractable	93.5	0.017	91, <b>s</b> Ô	0.057	<b>9</b> 9.4	0.063	n.a.	næ
Conventional extract (analysed)	93.5	0.017	86.3	0.053	5 ⁹ 82.9	0.05	n a	ana.
Losses conventional extract	n.a.	n.a.	∫n.a.	n.a.Q	n.a.	na.	n.a. (	n.a.
Exhaustive extract	n.a.	n.a.Q	<b>5</b> .5	0.003	<u>.</u> M.6	~0.005 C	n.a.	p.a.
Post extraction solids (PES)	6.5	0.001	§.2	9.005 Č	^ل 9.6	0.007	100.0	0.004
Accountability	100.0	<u></u> 0.018	() 100.0	0.062	100.0	0.070 (	5 ⁴ 100.00	0.064
	4	J ^N N	(Company)	$\sim$		viss Qard	(aff also store	
		<u> </u>	(i@matu		v€( <u>≫</u> .0			(Carlor)
		% ¶∕RR ₹	y'0.01 <b>6</b> y	2		SFRR <del>_</del>	0.016	
		ene Amg	/kģ <del>`}</del>	<u>Å</u>			g/kĝ∻y⊂	
			ô ng			<u>%</u>	Ý	g/kg
Total extractable		9.4 °	@0.0			5?6 Q	0.	015
Conventional extract (anylysed)	\$9(	5.4	0.6	ф\$ [«]	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	5.6~~	0.	015
	, s n	a.	n.	a. 🌒 🖌	^k n	à	n	ı.a.
Exhaustive extract	D' AR	a.	<u>n</u> .	al L	n	.a.	n	i.a.
Post extraction solids (PES)		.67	<u>بې</u> کې	aØ 101 Ø	<u></u> 3	.4	0.	001
Accountability		<u>9.0                                     </u>	<u>()</u> () () () () () () () () () () () () ()	16	<i>©</i> 10	0.0	0.	016
. 9		turnin	goots 🚿	<del>y _</del>	,×	turnin	leaves	
		STDD ^S	) <del>' K'</del>	jan o'		TRR =	0.006*	
		$\sqrt{2}$ mg	0.003*				9.000 s	
	000	<u>``</u>	in the second	/kg	(	// //		g/kg
Total extractable	× Q	a.	, n.			.a.		1.a.
Conventional extract conalysed	n.		ζ γ n.			.a.		ı.a.
Losses conventional extract	à é	a. N	n.	a.	n	.a.	n	ı.a.
Exhaustive extract	n.	a.	n.	a	n	.a.	n	ı.a.
Post extraction solids (PES)	S 10	09.0	0.0	003	10	0.0	0.	006
Accountability	~	0.0	0.0	003	10	0.0	0.	006
	*				~ .			

* TRR varties were determined by LSC measurement following combustion. Samples were not extracted due to low residue leves.



Table 6.6.1- 18:	Distribution of radioactivity in confined rotational crops (3 rd rotation) after spray
	application onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460

application onto	bare sol	i with [ph	enyi-UL	- CIBCS	-UN8846	U U	<i>^</i>	
	wheat	forage	wheat hay		wheat	tstraw	wheat grain	
	TRR =	0.015	TRR = 0.036		TRR =	0055	TRR # 0.003*	
	mş	g/kg	mg	/kg	mg	Økg	mg/kg	
	%	mg/kg	%	mg/kg		mg/kg	M mg/kg	
Total extractable	90.1	0.014	88	0.032	@0.7	0.050	n a n a	
Conventional extract (analysed)	90.1	0.014	<b>\$</b> 2.0	0.030	[™] 79.9	0.644	⊿ଇଅ ା∿ଯାର ∧.∿	
Losses conventional extract	n.a.	n.a. 🛓	n.a.	n.a.	pa.	o n.a.	ç n.a. 🗘 n.aç	
Exhaustive extract	n.a.	n.a.9	6.4	<b>0</b> ,002	10.8	0.000	n.a. n.a. n.a. n.a.	
Post extraction solids (PES)	9.9	6002	011.7 ×	0.004	23	02005	100.0 0.003	
Accountability	100.0	0.0150	10090	0:936	100.0	0.055 C	100 0 0.003	
		$\sim$	<u>~</u>					
	S S	is chare	(immatu	re)	Č Sv	vies chard	(at maturity)	
	Ç (	TRR =	0,020	S.		TRR	0,025	
		or mg	Arg C				Økg	
	Č	× 4	ې سې	g/kg		<b>%</b> (	)° mg/kg	
Total extractable	Ű \$9	5.2 C	L 01	219 🖏	\$ 	, 5.6 💭	0.024	
Conventional extract (analyse)	\$ 90	59° 20	\$`	219 ぞ 019 &	9	5.6)	0.024	
Losses convention		.a. S		÷80	O´_n	.a.	n.a.	
Exhaustive extract	<u> </u>	a s	N D	a. Ó	n an	.a.	n.a.	
Post extraction polids (PES)	<u> </u>		.0%	0015	<i>≈</i> 4	.4	0.001	
Accountability	A10	0.0		)20 👗	10	0.0	0.025	
		<u> </u>	r S	<u>`````````````````````````````````````</u>				
	۲ <u> </u>	turnip	roots	AN A	turnip le		leaves	
		*@mj	0.003	r	TRR =		0.006*	
	Ŷ~	$\mathbf{\hat{PRR}} = 0.003 \mathbf{\hat{P}}$		mş		g/kg		
	R	<u>O</u>	(O) [*]	g/kg	(	%	mg/kg	
Total extractable	Ø"	% 6 3 .a. 7 .a. 7 .a. 7 .a. 7 .a.	P	.a.	n	.a.	n.a.	
Conventional extract (analysed)	× ôn	.a.	n	.a.	n	.a.	n.a.	
Losses conventional extract	© n	.a	n	.a.	n	.a.	n.a.	
Exhaustive	<u>S</u> n	.a.	n	.a.	n	.a.	n.a.	
Post extraction solids (PESO	~~10	0.0	0.0	003	10	0.0	0.006	
			1		1			

 * TRK value were determined by LSC measurement following combustion. Samples were not extracted due to low residue tevels.



soil with [phenyl-UL- ¹⁴	C]BCS-CN	88460				<b>°</b>	
	wheat	forage	whea	it hay	wheat	střaw	
	TRR =	0.023	TRR =	0.039	TRR 🛒	0.054	
Report name	mg	/kg	mg	/kg	.mg/	kg 🖉 🐁	>_
	%	mg/kg	% 5	¢mg/kg		mg/kg	2
Conventional extract	94.8	0.021	86.1	0.033	78.4	0.040	.C
Conventional extract - analysed by HPLC	94.8	0.021	86	0.033 🛫	V 77 D	0.040 (	Ő
Conventional extract - losses	n.a. 4	© n.a.	n.a.	n.a.	1.3	⊳.001 <i>@</i>	1
Identified Compounds	- The second sec	×					
BCS-CN88460	17.0	0.004	l LIY	<b>.@.</b> 001 <b>%</b>	<u> </u>	<u>_</u>	
Characterised Compounds		V N		o a		4	
unknown 5	<u>s</u> ~	<u> </u>	Q. 3.5	0.001	Ő 20	·	
unknown 6		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	8.0	<u>,</u> 0,003 ≼	9.3	0.905	
unknown 8	( <u>`</u> L	Ø <u></u>	9.6	0.00 b	, A	Ő	
unknown 9	\$~~~. \$	~~~	02.7.5	0.001	8.8 Ø	0.005	
		s &	3.2	Ø.001 å			
unknown 10 unknown 12 unknown 13		\$ <i>0</i> 7	<u>~</u>	ð <u>,</u> 0	43.6	0.007	
unknown 13	⁽	<u> </u>	Ø13.2 Ø	0.005	05.9	0.003	
	306	0.007	× -~~	×~0	b		
unknown 14 unknown 15	S.	\$ Q	9.3 ·	0.004			
unknown 16 🐇 🖉	<u> </u>		× «,		10.4	0.005	
unknown 17	9.4	0.002	9.60	0.004			
unknown 19 5 , or 29 2	² ~ ~	9° 6°	se .	<i>©</i>	8.7	0.004	
unknown 20	A17.0	0.004	2 ×	×	2.8	0.001	
unknown 21 🖉 🖉 🖉	6.50	.0001 (	14. <b>@</b>	0.006	3.8	0.002	
unknown 22	, 34	®0.002	855	0.003	2.8	0.001	
unknover 23	6.9	0,002	<i>~</i>				
unknown 24	\$ <u></u> >	( A	2.5	0.001			
unknown 25 S	″_,@~	Ő	2.5	0.001	2.9	0.001	
unknown 26	× \$	-\$			4.0	0.002	
unknown 27		~ <u>~</u>	1.7	0.001	4.3	0.002	
unknown 17 unknown 19 unknown 20 unknown 21 unknown 22 unknown 22 unknown 24 unknown 25 unknown 26 unknown 27 unknown 28 Exhaustice extract		<i>o</i> °	2.2	0.001			
Exhausti@extract	n.a. 🔪	n.a.	6.7	0.003	10.1	0.005	
Microwave extract	/ n.a. n.a.	n.a.	6.7	0.003	10.1	0.005	
Microwave extract - SPE	j jisa.	n.a.	6.7	0.003	10.1	0.005	
Exhaustice extract	""m.q.	n.q.	n.q.	n.q.	1.3	0.001	
Total extractable	[™] 94.8	0.021	92.8	0.036	88.5	0.046	
Total identified	17.0	0.004	1.1	< 0.001	n.a.	n.a.	
Total characterises (by HOLC)	77.9	0.018	85.0	0.033	77.2	0.040	
Total not analysed A 55	n.a.	n.a.	6.7	0.003	11.4	0.006	
Post extraction solids (PES)	5.2	0.001	7.2	0.003	11.5	0.006	
Accountability S	100.0	0.023	100.0	0.039	100.0	0.051	

### Table 6.6.1-19: Distribution of radioactivity in wheat (1st rotation) after spray application onto bare soil with [phenyl-UL-¹⁴C]BCS-CN88460

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Table 6.6.1- 20:	Distribution of radioactivity in Swiss chard (1 st rotation) after spray application onto	)
	bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460	0

bare son with [phenyi-OL-	-]			<u> </u>
	Swiss chard	(immature)	Swiss chard (a	at maturity)
	TRR =	0.029	TRR =	0.020
Report name	mg/	kg	mg/k	
1	%	mg/kg	\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	mg/kg 🗸
Conventional extract	97.7	0.028	97.7	<u>0.020</u>
Conventional extract - analysed by HPLC	97.7	0.028	97,7¢	5 0.020
Conventional extract - losses	n.Ø	n.a.	p.a.	Ala.
Identified Compounds				
BCS-CN88460	2.8 .	~0.001°	@ 6.th	× 0.00
Characterised Compounds				
unknown 6	3.5	Q001	<u> </u>	<u></u>
unknown 7	3.6	≈0.001	, O ^y ,	
unknown 8	້≫້2,6∕ໍຸ	0.0 <b>0</b>	J 59 ~	0.001
unknown 8 unknown 9 unknown 10	\$.0 ~~	0001	<u> </u>	<u>ہ</u>
unknown 10	7.5	20.002°	ى 10.3 كَلْ الْمَ	 ² 0.002
unknown 10 unknown 13 unknown 14	0 ² 5.5 ²	0.002	°° 2,10° ℓ	[*] 0.004
unknown 14	6.0 4	0 <del>,0</del> 702	<u>v</u> or	
unknown 14 unknown 15 unknown 16	J 4.7 O	Ø.001 ×	s	0.001
unknown 16	\$ - <del>4</del>	_≫ ∿€/ [¥] .		0.003
unknown 16 unknown 17 unknown 19	\$ <u>\$</u> .4 .0	^v 0k007	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
unknown 19		O*	2.8 گرچ	0.001
unknown 16 unknown 17 unknown 19 unknown 20 unknown 21		0.003	9.6	0.002
unknown 21 unknown 22	4.8 ~		Ş [¥]	
unknown 22 g g g g g		0.004	8.6	0.002
unknown 17 unknown 19 unknown 20 unknown 21 unknown 22 Exhaustive extract	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.0000 , 18.a.	12.1	0.002
Total attractable		• 0.028	n.a. 97.7	n.a. 0.020
Total identified		≥ 0.028 ≥ 0.001	6.1	0.020
Total characteriser by HRLC)	0 94 9 P	» 0.027	91.6	0.019
Total not analysed	Aa S	n.a.	n.a.	n.a.
Post extraction solids (PES)	2.3	0.001	2.3	< 0.001
Accountability	\$ 10 <b>%</b> 0	0.029	100.0	0.020
Exhaustive extract Total extractable Total identified Total characterised (by HRLC) Total not analysed Post extraction solids (PES) Accountability			L	<u></u>
	Ô			
	1			
A CA				
$\bigcirc$				



Table 6.6.1- 21:	Distribution of radioactivity in confined wheat (2 nd rotation) after spray applicatio	n
	onto bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460	•

onto bare son with [pite	<i>.</i>	,	1			^_^ 🖄
	wheat	forage	whe	at hay	wheat	střaví př
	TRR =	0.018	TRR =	0.062	TRR 🔊	, 0.070
Report name	mg	g/kg	m	g/kg	" <b>Ma</b> g/	kg
-	%	mg/kg	%	kg/kg	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	mg/kg
Conventional extract	93.5	0.0.7	86.3 @	0.053	82.9	0.058
Conventional extract - analysed by HPLC	93.5	0.017	86.3	0.053 🦼	© 82.90	0,058
Conventional extract - losses	n.a.	Ŵn.a.	n á!	n.a. O	n.a.	n.a.
Identified Compounds		, <b>b</b>		Q Q	. Ô ^V čo	a y
BCS-CN88460	12.2	0.002	0 X	.@- ?	<u> </u>	, Ş
Characterised Compounds		Ø ×	<u>,                                    </u>			4
unknown 3	<u>s</u> ~	@	Q	0 <u>-7</u>	02.6	0.002
unknown 6	6.4	10,001	7.3	<u>0</u> 005 ×	J 11.3	0,008
unknown 7	ve start and a start and a start a sta	¢″ 🔊	7.9	×0.005	50	0.004
unknown 8	S S	* *	<b>A</b> .2	0.00	Q 0	,
unknown 9	5,2	8,001	5.1	0,003	³ √ ³ 4.8 √ ³	0.003
unknown 9 unknown 10 unknown 11	5,2 10:3	~0.001@j		8	( (	
unknown 11	· · · · ·	°	j <u>ůž</u> (	å °	05.4	0.004
unknown 12	12	0.002	3.9	0:002	l 2 3.6	0.003
unknown 12 unknown 13	<u> </u>	S S	6.4	£9.004	5.8	0.004
unknown 14 😓 🖉	0 _{5.7} Č	7 0.00	<b>%</b> .4 %	0.004	3.9	0.003
unknown 13 unknown 14 unknown 15 unknown 16 unknown 17		× í	6.4 O	0.004		
unknown 16 5 5	A0.7	<b>\$0.002</b>	-4	"Q		
unknown 17	4.8	0.001	<b>A</b> 3.4	0.008	12.5	0.009
unknown 19 🖉 🖉 🖉	21.6	Q:904	ő", Ø			
unknown 20 K	S.	° 0	128	0.008	12.7	0.009
unknows 21 C &	<u>9.8</u>	0.002	5.9	0.004	5.5	0.004
unknown 22	·,~	<u> </u>	گ [≫] 7.2	0.004	4.1	0.003
unknown 23	<i></i>	0 [°] »			5.5	0.004
Exhaustive extract	°∼yn.a. Қ	≥ n.a.	5.5	0.003	7.6	0.005
Microwave extract - SPE Microwave extract - SPE Microwave extract - SPE Total extractable	n.å.y	n.a.	5.5	0.003	7.6	0.005
Microwave extract - SPE	toja.	©n.a.	5.5	0.003	7.6	0.005
Microwave extract - SPE Losses	n.a. 🔨	n.a.	< 0.1	< 0.001	<0.1	< 0.001
Total extractable	93.5	0.017	91.8	0.057	90.4	0.063
Total identified	£\$.2	0.002	n.a.	n.a.	n.a.	n.a.
Total characterized (by HPLC)	81.3	0.015	86.3	0.053	82.9	0.058
Total not analysed A &	🎽 n.a.	n.a.	5.5	0.003	7.6	0.005
Post extraction solids (PES & ~	6.5	0.001	8.2	0.005	9.6	0.007
Account	100.0	0.018	100.0	0.062	100.0	0.070
Microwaye extract - SPE/Losses						



Distribution of radioactivity in Swiss chard (2 nd rotation) after spray application onto	)
bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460	,

Swiss chard (immature)         Swiss chard (at maturity)           Report name         TRR = 0.016         TRR = 0.016           mg/kg         mg/kg         mg/kg           Conventional extract         96.4         0.015         96.6         0.015           Conventional extract - analysed by HPLC         96.4         0.015         96.6         0.015           Conventional extract - losses         n.a.         n.a.         n.a.         n.a.         n.a.           Wknown 7           7.0         -0.001         0.002           wknown 7           7.0         -0.001         0.002           wknown 10           28.5         0.004         11.6         0.002           wknown 12            28.5         0.004            wknown 14            28.5         0.002            wknown 18                  wknown 18                 wknown 20	<b>_</b>
Report name         mg/kg	
Report name         mg/kg	)
%         mg/kg         %         %         mg/kg         %         %         mg/kg         %         %         %         mg/kg         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %         %	
Conventional extract       96.4       0.015       96.6       0.015         Conventional extract - analysed by HPLC       96.4       0.015       96.6       0.015         Conventional extract - losses       n.a.       n.a.       n.a.       96.4       0.015       96.6       0.015         Conventional extract - losses       n.a.	, P
Conventional extract - analysed by HPLC       96.4       0.015       96.6       0.015         Conventional extract - losses       n.a.	
Conventional extract - losses       n.a.	Å
Characterised Compounds        7.0       0.001         unknown 7        7.0       0.001         unknown 9        6.0        7.9       0.001         unknown 10         9.002         0.001         unknown 11         9.002         0.002         unknown 12         28.5       0.004         0.002         unknown 14          28.5       0.001         0.002         unknown 15          0.002        0.001         0.002         0.004         0.004       0.001         0.002         0.002        0.002        0.002        0.002        0.002        0.001        0.002        0.001        0.002        0.001        0.002        0.001        0.002	w۲
unknown 9       6.0       0.004       11       0.002         unknown 10       11.2       0.001       11.4       0.002         unknown 11       11.2       0.001       11.4       0.002         unknown 12       11.2       0.002       11.4       0.002         unknown 14       12.4       0.002       28.3       0.001         unknown 15       11.4       0.002       57.0       0.002         unknown 16       12.4       0.003       12.4       0.002         unknown 18       16.7       0.003       12.4       0.002         unknown 18       16.7       0.001       56.2       0.001         unknown 20       11.6       0.002       11.6       0.002	2
unknown 9       6.0       0.004       11       0.002         unknown 10       11.2       0.001       11.4       0.002         unknown 11       11.2       0.001       11.4       0.002         unknown 12       11.2       0.002       11.4       0.002         unknown 14       12.4       0.002       28.3       0.001         unknown 15       11.4       0.002       57.0       0.002         unknown 16       12.4       0.003       12.4       0.002         unknown 18       16.7       0.003       12.4       0.002         unknown 18       16.7       0.001       56.2       0.001         unknown 20       11.6       0.002       11.6       0.002	
unknown 11       unknown 12         unknown 14       unknown 15         unknown 16       unknown 18         unknown 20       y         unknown 22       y	
unknown 11       unknown 12         unknown 14       unknown 15         unknown 16       unknown 18         unknown 20       y         unknown 22       y	c
unknown 14         unknown 15         unknown 16         unknown 18         unknown 20         unknown 22	
unknown 14         unknown 15         unknown 16         unknown 18         unknown 20         unknown 22	
unknown 15       unknown 16         unknown 16       unknown 20         unknown 22       unknown 20         unknown 20       u	
unknown 20 unknown 22	
unknown 20 unknown 22	
unknown 20 unknown 22	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	
Full contribution of the section of	
Exhaustive extract $n_{a}$ $n_{a}$ $n_{a}$ $n_{a}$ $n_{a}$ $n_{a}$ $n_{a}$	-
Tatal automatable $\mathcal{O}$	-
Total identified	
Total characterised (by HPLC) $\sqrt{2}$ $\sqrt{96.4}$ $\sqrt{96.4}$ $\sqrt{2}$ $0.06$ $\sqrt{2}$ $96.6$ $0.015$	
Total not analysed of new new n.a. n.a.	
Post extraction solids(PES) 2 2 3.6 7 0.001 3.4 0.001	
Accountability 2 2 100.0 100.0 0.016 100.0 0.016	
Total identified Total identified Total characterised (by HPLC) 4, 4, 96.4, 0.015 Total not analysed Post extraction solid (PES) Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accountability Accounta	



soil with [phenyl-UL- ¹⁴	C]BCS-CN	88460				~ °	
	whea	t forage	whe	at hay	wheat	střavů	
	TRR =	0.015	TRR =	0.036	TRR =	0.055	
Report name	m	g/kg	mg	g/kg	mg	/kg v	Pa.
	%	mg/kg	%	©mg/kg		, mg/kg≪	2
Conventional extract	90.1	0,014	82.0	0.030	°,79.9 [∧]	0.044	R
Conventional extract - analysed by HPLC	90.1	0.014	82	0.030 🛒	V 79.90	0,044	Ő
Conventional extract - losses	n.a.	Ø n.a.	A.A.	n.a.	n.a.	n.a.	1
Identified Compounds		, <b>b</b>		? Q.		<u> </u>	
BCS-CN88460	5.2	0.001	¥	<i>_0</i> ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		<u> </u>	
Characterised Compounds	Ô,	Ø ×		T A		1	
unknown 1	A 0	, e	Q 5.2	0.002	Ő 2	× ×	
unknown 2		Š 2		, 0 ² - x		£₽	
unknown 4	,			× · 6		0	
unknown 5	3.9	0.001	Ø, S	-5	, , ¢		
unknown 6	10,1	~0.002 ×	8.8	Q.003	16:0	0.009	
unknown 8	œ-	S 0	5.1	00.0020	Q.5	0.002	
unknown 9	· ···· ·		@Ť.3 ¢	0.003	O5.8	0.003	
unknown 10 unknown 11	15	69002			þ		
unknown 11		\$ \$`	4.3	0.002			
unknown 11 unknown 12 unknown 13 unknown 14 unknown 15	0	<u>*</u>	[∞] /5.9 ‰	0.002			
unknown 13	🖗 15.2 ³	\$,002	5.10	0.002	13.0	0.007	
unknown 14	´	Ş Ş		Q	2.9	0.002	
unknown 15	×4.9	0.001	<b>4.5</b> ⊀	J [™] 0.002			
unknown 16 O	¥\$	0.002	4.9	0.002	11.7	0.007	
unknown 10 S	<b>10</b> .4	0.002	96 <b>7</b>	0.003			
unknow 18	<u> </u>	T.	0 [%]				
unknown 19		\$~~~ A	Y		12.2	0.007	
unknown 20	18:7	00.003	17.3	0.006	3.1	0.002	
unknown 21	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		4.2	0.002			
unknown 22		0.001			5.1	0.003	
unknown 25		<i>o</i>			3.1	0.002	
unknown 14 unknown 15 unknown 16 unknown 10 unknown 19 unknown 20 unknown 21 unknown 22 unknown 25 unknown 25 unknown 27 Exhaustive extract					3.6	0.002	
Exhaustive extract	n.a.	n.a.	6.4	0.002	10.8	0.006	
Microwave extract 5 5	jer.	n.a.	6.4	0.002	10.8	0.006	
Microwave extract - SPE	n.a.	n.a.	5.5	0.002	10.1	0.006	
Microwave extract - SPE Microwave extract - SPE Losses Total extractable Total identified Total characterised (by HPLC) Total not analysed Post extraction solids (PES) Accountability	[≫] n.a.	n.a.	0.8	< 0.001	0.7	< 0.001	
Total extractable 2 5 2 ~	90.1	0.014	88.3	0.032	90.7	0.050	
Total identified	5.2	0.001	n.a.	n.a.	n.a.	n.a.	
Total characterised (by HPLC)	84.9	0.013	82.0	0.030	79.9	0.044	
Total not adalysed of	n.a.	n.a.	6.4	0.002	10.8	0.006	
Post extraction solids (PES)	9.9	0.002	11.7	0.004	9.3	0.005	
Accountability	100.0	0.015	100.0	0.036	100.0	0.055	

## Table 6.6.1- 23: Distribution of radioactivity in wheat (3rd rotation) after spray application onto bare soil with [phenyl-UL-¹⁴C]BCS-CN88460



Table 6.6.1- 24:	Distribution of radioactivity in Swiss chard (3 rd rotation) after spray application onto
	bare soil with [phenyl-UL- ¹⁴ C]BCS-CN88460

bare son with [pricity]	-			
	swiss char	d immature	swiss chard	at matuřný
	TRR =	0.020	STRR =	0.0\$\$
Report name	mg	/kg	mg	/kgy ~ ~
	%	mg/kg	× % ×	mgkg 📈
Conventional extract	96.2	0.019	95.6	<u>0.024</u>
Conventional extract - analysed by HPLC	96.2 d	0.019	95.6 C	30024 6
Conventional extract - losses	n.a.	n.a.	n.a.	
Identified Compounds				à. Â.
BCS-CN88460				
Characterised Compounds				
unknown 2				
unknown 4		× 20001 A		
unknown 4 unknown 5			× 2 2 4 5 /	× 0 <b>0</b> 01
unknown 5 unknown 6				\$ 00001 \$20.001
unknown 8				0.001
V (			4.7 č	0.001
unknown 9	Ø6.2 S			0.001
unknown 10	× 1.4		0.8	
unknown 11		0.001 \$0.001	\$ 0.4 \$	0.002
unknown 12		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		
unknown 13			(A):3	0.004
unknown 14		0,001 O	[*] 7.3	0.002
unknown 12 unknown 13 unknown 14 unknown 15 unknown 16 unknown 18 unknown 19 unknown 21 unknown 22	$\gamma_{12}$		4.9	0.001
unknown 16			² 10.6	0.003
unknown 18 ° ° v			4.4	0.001
unknown 18 unknown 19 unknown 20 unknown 21				
unknown 00	6.2		11.6	0.003
unknown ² 21	0 ³ 2,87 ( 7 <u>0</u> 7.2 0 ⁷	0,001		
unknown 22	<u> </u>	<u> </u>	10.4	0.003
Exhaustive extract	°∼y n.a. √y	of n.a.	n.a.	n.a.
Microwave extract - SPE		n.a.	n.a.	n.a.
Microwave extract - SPE	🖓 🖉 🖉 . a. 🚬 🖉	n.a.	n.a.	n.a.
Microway Cextract - SPE Cosses	n.a. s	n.a.	n.a.	n.a.
Total extractable	96 yr F 96 yr Fra.	0.019	95.6	0.024
Totalsdentified	Va.	n.a.	n.a.	n.a.
Total characterised (by HPLC)	Q ^{≫96.2}	0.019	95.6	0.024
Total not analysed	n.a.	n.a.	n.a.	n.a.
Post extraction solids (PES)	3.8	0.001	4.4	0.001
Accountabulity	100.0	0.020	100.0	0.025
Microway Pextract - SPE Posses 2				



#### III. Conclusions

The metabolism of the fungicide isoflucypram (BCS-CN88460) was investigated in confined or rotational crops after one spray application onto bare soil. The application rate amounted to 197.7 g a.s./ha and the test compound was ¹⁴C-radiolabelled in the phenyl moiet.

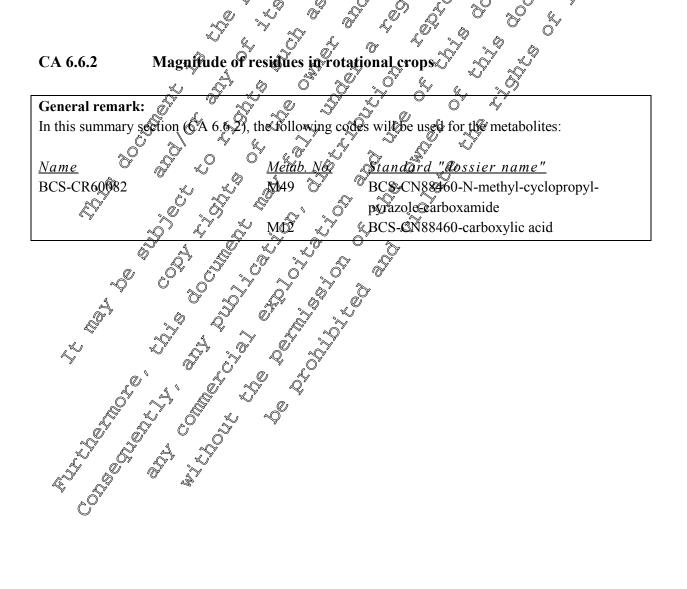
The TRRs in the raw agricultural commodities (RACs) ranged from very low to low with values between 0.001 mg/kg in wheat grain (1st rotation) to 0.070 mg/kg in wheat straw (2nd rotation).

Radioactive residues were extracted with conventional methods. In case of wheat hav and straw, solids had to be further extracted.

BCS-CN88460 was the only compound identified in the conventional extracts amounting for up to 17.0% (0.004 mg/kg) of the TRR.

Further characterisation of residues by acidic hydrolesis of order extracts of Swiss chard (immuture and mature, 1st rotation) and wheat straw (st rotation) indicated presence of conjugates of BCS-CN88460-carboxylic acid (M12) and BCS-CN88460-propanol (M01) besides parent compound in these selected extracts.

Based on these results, the metabolism of [phenyl-UL-¹⁴C]BCS-CD88460 in contined stational crops is adequately understood. Parent compound was the only residue component identified.





Report:	KCA 6.6.2/01; , , , , , , , , , , , , , , , , , , ,
Title:	Determination of the residues of BCS-CN88460 in/on soil and the field rotational
The.	crops barley, carrot, turnip and lettuce after spray application of BCS-CN88460 E $\mathbb{Q}^{\circ}$
	050 to bare soil in Germany, the Netherlands, southern France and Italy
Report No.:	15-2502
Document No.:	M-605725-01-1
Guideline(s):	Regulation (EC) No 1107/2009 of the European Parliamen@and of the Council of 21
	October 2009 concerning the placing of plant protection products on the placet of the
	OECD Guidelines for the Testing of Chemicals. Residues in Rotational Crops
	(Limited Field Studies), 504, 2007-0 $0$
	October 2009 concerning the placing of plant protection products on the market OECD Guidelines for the Testing of Chemicals. Residues in Rotational Crops (Limited Field Studies). 504. 2007-01-08 OECD Guideline for the Testing of Chemicals on Crop Field Triate TG 509 published in September 2009) US EPA OCSPP Guideline No 860.1900, Field Accumulation in Rotational Crops
	in September 2009)
	US EPA OCSPP Guideline No 60 1900 Field Accumulation Rotational Cross
	US EPA OCSPP Guideline No. 860.1500 on Crop Field Trice
Guideline deviation(s):	yes, see report
GLP/GEP:	yes the second s

I. Materials and Methods

The purpose of the study 15-2502 was to determine the magnitude of the relevant residues of BCS-CN88460 in/on barley, lettuce and carrot or turnip grown as rotational crops after one spray application to bare soil with BCS CN88460 EC 050 an empisifiable concentrate (EC) formulation containing 50 g/L BCS-CN88460, followed by plant back intervals of 21 to 34 days (1st rotation), 100 to 201 days (2nd rotation) and 299 to 370 days (3rd rotation).

The study included four supervised residue trials conducted in northern Europe (Germany and the Netherlands) and southern Europe (France and Italy) during the 2015 and 2016 growing seasons.

One spray application of BCS-CN88460 EC 050 was made to bare soil at an application rate of 3.6 L/ha (equivalent to @18 kg/ha active substance) with a water rate of 300 to 400 L/ha. The application procedure was followed by incorporation of the test frem into the soil via following to a depth of  $\leq 8$  cm. All treatments were made at the scheduled rates

At various intervals props were planted onto the lest area in order to simulate a crop failure ("rotation 1", plant-back interval [PBI] 21-34 days), a second use of the ploton the same year ("rotation 2", PBI 100-201 days), or use of the same plot in the succeeding year ("rotation 3", PBI 299-370 days). In each rotation, 3 different crops representing different botanical groups were planted: a root crop (carrots or turnips), a leafy crop (lettuce), or a small grain cereal darley).

Samples of representative soil commodities were taken on the day after sowing/planting the crop for each individual rotation from each of the subplots. Moreover, samples of the rotational crops were taken at their respective harvest times, as well as at one earlier interval (immature RACs for lettuce and root crops, or green material (where plant without roots) for barley).

Each field sample was placed in double tabelled bags and stored deep-frozen within 24 hours after sampling and until dispatch to the Laboratory for Sampling, Preparation Technique and Sample Logistics (PVTL), Bayer AG, Crop Science Division, BAG-CS-HSRA in D-**Constant and and Second Second** and Rhein. All field samples were shipped deep-frozen under monitored conditions during shipment and arrived at PVFL in good condition. The field samples were stored in a freezer at -18°C or below until preparation of the examination samples.

For the preparation of the soft examination samples, the deep-frozen field samples were grounded with dry-ice and homogenized in a Stephan mill. Representative parts of the homogenized samples were transferred into polystyrene boxes and stored at -18°C or below until analysis. For the preparation of examination samples, the deep-frozen field samples were shredded and homogenized with dry ice in a cutter. Representative parts of the shredded samples were transferred into polystyrene boxes and stored at -18°C or below until analysis.



Residues of BCS-CN88460 and its metabolite BCS-CN88460-carboxylic acid were determined in soil using method 01432 (2014; M-499794-01-1; referenced in MCA Section 4 under Point 4.1.2). The LOQs for each analyte were 0.001 mg/kg, the metabolite being not expressed in patient of equivalents.

The samples of the rotational crops were analyzed for the parent compound and its metabolite BCS-CR60082 using method 01475 (2016; M-558986-01-1; referenced MCA Section 4 under Point 4.1.2) which was validated prior to the residue analysis of the samples. Additional validation recoveries were conducted for all sample materials in the study 15-2502. Samples of barley (grain straw and green material) were analyzed according to the procedure described in the method for dry matrices (soaking step before extraction) and the samples of carrot root and leaf), turnip (root and leaf) and lettuce (head) were prepared according to the procedure for higher-water containing commodities (no soaking step before extraction). The LOQs for each analyte over 0.01 mg/kg (all in parent equivalents).

# Concurrent recoveries for BCS-CN88460 and its metabolite BCS-CN88460-carboxylic acid were obtained from samples of soil. The recovery samples were spiked at levels of 0001 mg/kg and up to 0.01 mg/kg. Details of concurrent recovery data are shown in Table 6.6.2- 2 for BCS-CN88460 carboxylic acid. The average recoveries were within the acceptable range of 70 – 110%. The RSD values were below 20%

II. Findings

Besides, concurrent recoveries for BCS-CN88460 and its metabolite BCS-CR60082 were obtained from samples of carrots, turnips, bettuce, and barley. The recovery samples were spiked at levels of 0.01 mg/kg and up to 0.10 mg/kg. Details of concurrent recovery data are shown in Table 6.6.2-3 for BCS-CN88460 and in Table 6.6.2-4 for BCS-CR60082. The average recoveries were within the acceptable range of 70 - 110%. The RSD values were below 20% for each compound and all sample materials.

No residues above the DOQs were found in the control samples. The detailed results obtained for soil samples are summarised below in Oable 6.2- 7 and the results obtained for rotational crop samples are summarised in Table 6.6.2-6 to Table 6.5.2-8. The results were not corrected for concurrent recoveries.

The residues of BCS CN88460 and BCS CR60082 in the treated rotational crops were always found < LOQ with one exception.

In the trial 15-2501-01 (Germany), residues of BCS-CN88460 reached levels of 0.057 to 0.075 mg/kg only in carrot leaves  $(2^{nd}$  (diation, plot P-2A). These results – confirmed with re-analyses- were illogical because no residues were found in carrot root from the same plot and no residues were found in the 1st rotation for carrot.

It appears that five days before the first harvest of carrot leafs in plot T-2A, the adjoining plot dedicated to barley (T-1C) was sprayed with BCS-CN88460 EC 050. There was no buffer zone between the two plots, the carrot plot was not protected during the spray of the plot T-1C, and there was a very light wind in the direction of the carrot plot. This explanation supports the fact that the residue level of BCS-CN8460 found in carrot leaves in the plot T-2A are the result of a spray drift. These residue levels should not be considered because they are not attributable to residues arising from soil freatment.

Based on all fire other results, it is concluded, that after an application of BCS-CN88460 EC 050 on bare soil at a rate of 180 g a.s./ha, the residues of BCS-CN88460 and BCS-CR60082 are expected to be <0.01 mg/kg in barley, lettuce and carrot or turnip grown as rotational crops.

The analyses of soil were done after a maximum frozen storage period of 320 days and the analyses of plant commodities after a maximum frozen storage period of 341 days. For crop commodities, the time between the beginning of the sample preparation and the sample analysis did not exceed 24



hours. For soil, all final extracts were analysed within 8 days. This storage period of soil extracts is covered by storage stability experiments conducted in the method 01432 (2014; M-499794-01-1; referenced in MCA Section 4 under Point 4.1.2).

#### **III.** Conclusions

In order to support the use of BCS-CN88460 in the EU for non-perennial crops, four multi-plant back, multi-crop rotational crop trials were conducted in Europe (2 each in the northern and southern residue regions) in 2015-2016. BCS-CN88460 was applied once as an EC 050 formulation be bare soil at an application rate of 3.6 L/ha (corresponding to 180 g active substance/ha). Crops representing 3 different botanical groups (roots, leafy vegetables, small grain cereals) were planted on the plots at \$ intervals thereafter. All applications were at the required rates, and all trials were conducted according to GLP.

The residues of BCS-CN88460 and BCS-CR60082 in the rotational crops were provide to the rotational crops were provided to the rotational crotation

In the trial 15-2501-01 (Germany), residues of BCS-CN88460 reached levels of 0.057 to 0.075 mg/kg only in carrot leaves (2nd rotation, plot T-2A). These results – confirmed with re-analyses were illogical because no residues were found in carrot roots from the same plot and no residues were found in the 1st rotation for carrot.

It appears that five days before the first harvest of carry leafs in plot T-2A, the adjoining plot dedicated to barley (T-1C) was sprayed with BCS-CN88460 fc 050. There was no buffer zone between the two plots, the carrot plot was not protected during the spray of the plot T-1C, and there was a very light wind in the direction of the carrot plot. This explanation supports the fact that the residue levels of BCS-CN88460 found in carrot leaves in the plot T-2A are the fesult of a spray drift. These residue levels should not be considered because they are not attributable to residues arising from soil treatment.

Based on all the other results, it is concluded, that after an application of BCS-CN88460 EC 050 on bare soil at a rate of (80 g a s./ha, the residues of BCS-CN88460 and BCS-CR60082 are expected to be <0.01 mg/kg in barley, lettuce and carrot or turnip grown as obtational crops.

The dose rate of 180 g active subtrance/ha tested in this study adequately covers the plateau concentration of isoflucypramin soil overtime. Indeed, the maximum seasonal rate for isoflucypram is 75 g as/ha. The accumulation factor for isoflucypram parent compound in soil was calculated to be 1.5 for parent (please refer to **Example**, G.; **Example**, W. 2017; M-608723-01-1 in MCA 7 Point 7.1.2.2.2). Considering a crop interception of 80% applicable for cereals growth stages ranging from BBCH 30 to BBCH 69, the plateau n soil corresponds to 22.5 g as/ha x 1.5 x 0.2).

When this plateau is added to a last application tate of 75 g as/ha the appropriate dose to be investigated is 97.5 g as/ha (plateau of 22,5 g as/ha + seasonal rate of 75 g as/ha), below what was actually tested in the study 15-2502

It is also highlighted that, for the  $2^{nQ}$  and  $3^{rd}$  rotations, it would be relevant to apply the crop interception of 80% to the last seasonal rate as well since for normal rotations the treated crops are harvested and not re-incorporated into the soil. Proceeding so, the appropriate dose rate to be investigated for the  $2^{nd}$  and  $3^{rd}$  rotations is 37.5 g as/ha (plateau of 22.5 g as/ha+ 75 x 0.2), a dose rate far below the one tested in the study 15-2502.

The plateau is soil for the metabolite M12 (BCS-CN88460-carboxylic acid) does not need to be considered since its  $DT_{50}$  value is < 150 days (worst case laboratory  $DT_{50}$  of 112 days).

It is conduded that plant-back restrictions and MRL proposals above 0.01 mg/kg based on rotational crops are not necessary.



	·				
Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	
	0.001	95; 96; 97; 97; 98; 98; 98; 99; 99; 100; 100; 100; 101; 102; 102; 102; 104	99	2.4	
soil / soil 0-30 cm	0.01	97; 97; 97; 97; 99; 99; 99; 99; 99; 99; 99; 100; 100; 100; 100; 102; 102; 102			
		Overall recovery (a ≠ 34)	⁹⁹	2.1	

Table 6.6.2- 1:	Recovery da	ata for BCS-	CN88460 in soil
1 4010 01012 11	iteeo, er y u		CI (OO IOO III SOII

FL = Fortification level, RSD = Relative standard deviation, 1000 = Practical limit of quantification Fortified with BCS-CN88460, determined as BCS-CN88460 and calculated as BCS-CN88460 and calculat

	-	tive standard deviation, $\mu_{OO} = Practical limit of quantification$	
Fortified with BCS-CN	88460, detern		
			à a
Table 6.6.2- 2:	Recovery d	ata for BCS-CN88460-carboxylic acid in soil	
Crop / Sample	FL	Single values [%]	['] LOQ
material	[mg/kg]		[mg/kg]
	0.001	735 77; 84; 89; 89; 91; 95; 95; 96 97; 98; 99; 102; 902; 109 104; 005	L V V
soil / soil 0-30 cm	0.01 🔌	\$90; 93;97; 97; 97; 98; 98; 98; 100; 104; 101; 102; 102; 105; 196; 106; 4,7	0.001

		4	<u>.</u>	$\overline{\alpha}$	()	C
Table 6.6.2- 2:	<b>Recovery data for</b>	BCS-EN88	460-ca	rboxvlic	acid in	n soil

FL = Fortification level, R\$D = Relative standard deviation COQ = Practical limit of quantification Fortified with BCS-CN88460-carboxylic acid, determined as BCSaCN88460-carboxylic acid and calculated as BCS-CN88460-carboxylic acid

Overall recovery  $n = 30^{\circ}$ 

97

6) 8.1

Table 6.6,2,2,3:	Recevery data for BCS-CN8840	60 in rotational crop matrices (root, leafy, and cereal	
10 m	croops)		

Crop / Sample 🧙 material 🖗	FL [mg/kg]	Single Values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]
	0.01	92; 9 <del>9</del> , 95; 26, 97; 99	96	2.5	
barley Agrain	0.00	296; 9 <b>8</b> , 98; 100	98	1.7	0.01
		Overall recovery (n = 10)	97	2.5	
barley / green	0.00	91692; 9266; 97 98; 99; 101; 101; 104; 07; 108	99	5.7	
material	Q.10	7; 105 103; 106; 117	105	7.0	0.01
		Overall recovery (n = 17)	101	6.6	
Û AŞ	0:01	S 93; 95; 96; 97; 100; 100; 103	98	3.5	
barloy / straw	0.10~∽	87; 98; 100	95	7.4	0.01
barley / strass		Overall recovery (n = 10)	97	4.7	
	0.01	93; 93; 98; 104; 107; 107	100	6.5	
carrot / leaf	0.10	101; 102; 103; 105; 105; 106	104	1.9	0.01
		Overall recovery (n = 12)	102	4.8	

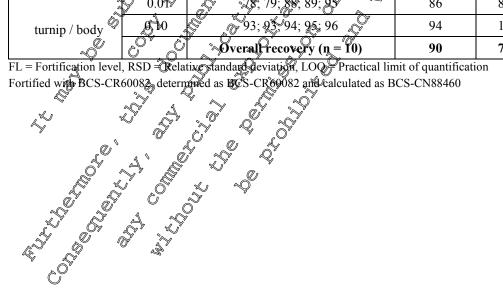


material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD [%]	LOQ [mg/kg]
	0.01	92; 92; 100; 100; 100; 101	98	4.4	
carrot / root	0.10	102; 103; 107; 107; 107	105	2.4	<b>2</b> 01
		Overall recovery (n = 11)	101	5.2	
	0.01	82; 95; 96; 98; 101; 102	96 🔬	7.6	
lettuce / head	0.10	98; 100; 101; 104 💍	96 A 101 98	2.5	~ <u>Ø</u> .01 ~
		Overall recovery (n = 10)	<b>298</b>	63	\$ \$
	0.01	99; 99; 99; 103, 04	101 🖌	02.5	
turnip / leaf	0.10	94; 99; 100; 105; 109		5.54	© 0.01
-		<b>Overall recovery (n = 10)</b> 88; 89,96; 98,904	× 101 0	<b>34.2</b>	
	0.01	88; 89,96; 98,904	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	\$ 7.0 J	
turnip / body	0.10	102; 103; 103; 105; 106	A104 \$	1.6	0.01
		Overall recovery (@=10)	6 ⁹ 99, 7	<b>\$6.5</b> *	
Š					
		102; 103; 103; 105; 406 Overall recovery (a = 10) 4 ve standad deviation, LOC = Parentical lip incl as BCS-CA88460 and calculated as a a b b b b b b b b b b b b b b b b b b b			



abic 0.0.2- 4.	crops)		- op (		, una con cui Ø
Crop / Sample material	FL [mg/kg]	Single values [%]	Mean value [%]	RSD	
	0.01	86; 91; 92; 92; 92; 93	91	2.8	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
barley / grain	0.10	92; 95; 95; 95	94	1.6	
		Overall recovery (n = 10)	90	2.9	
barley / green	0.01	83; 84; 85; 87; 88; 89; 89; 90; 90; 90; 91; 93	6 ⁹ 88	2.4 0	
material	0.10	92; 96; 98; 99, 109	S 99°	6.4	9.01
		Overall recovery (n = 17)	Q Q 2 2 91 Q	~7.0	
	0.01	81; 89; 90090; 92092; 94	L 200	\$4.7	4
barley / straw	0.10	\$7; 96; <b>98</b>	94	6. <b>D</b>	© 0.01 ° °
-		Over fill recovery $(\mathbf{n} \neq 10)$	<b>91</b>	<b>\$</b> 3.3	
	0.01	<b>26</b> ; 88; 91; 92; 94; 95	V 90	<b>3.8</b>	0
carrot / leaf	0.10	\$ 88; 91(96; 96; 103; 103	<u></u> 896 E	<u></u>	0.01
		Overall recovery (0 = 12)	<u>م</u> ج 94	05.8 _(k)	· ¥
	0.01 🔬	86; 87,92; 94; 94; 96	⁵ .92	4.5°	
carrot / root	0.10	0 93094; 99099; 101	\$97 \$ <del>`</del>	<b>\$</b> 9.6	0.01
		A Overall recovery (n = 1)	94	õ ⁵ 5.0	
	\$0.01 Ô	76; <b>8</b> 8; 89; <b>20</b> ; 95; <b>2</b> 7 O	89	8.3	
lettuce / head 🦼	0.16	\$93; <u>24</u> ; 94; 95	£ 94 @	0.9	0.01
Ú		Qyerall recovery (n = 10)	<b>9</b> 1	6.6	
Ĩ,	\$0.0K	92,93;93,93,94	<b>2</b> 93	0.8	
turniằ∳leaf	0,4,0	ين ⁽¹⁾ (90; 91, 91; 98; 98 (1)	or 94	4.3	0.01
<i>K</i>		Overall recovery (n = 10)	93	2.9	
	0.01	Overal recovery (n = 10)	86	8.4	
turnip / body	of B.	§ 93; 93; 94; 95; 96	94	1.4	0.01
~0		Overall recovery (n = 10)	90	7.3	

Table 6.6.2- 4:	Recovery data for BCS-CR60082 in rotational crop matrices (root, leafy, a	nd cereal
	crops)	°





Trial No./		Applicati	on rate per <u>on bare soi</u> l		Dates of treatment		Residue	(figg/kg)	109	· ptot	ender of	CREP
Location/ Year	Plot (Commodity)	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and last date	Portion analyzed	Analyte 1 BCS-CN88460	Amalyte 2 BCS C 888460- carboxylic acid	C D'ÁLT (days) N	De <b>E Detti</b> Detti	id 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20tion 20	efor
	(a)				(e) \$		ar and	<u>au²0-</u> au	C (a)	ert -	100-7 · · ·	-
5-2502-01	Plot T-1A (carrot)	180	300	60	2015-03-12	Soil 0-30 cm	0.023 0.026 \$			(g) EC (GO g/L)	O _{Ma} .	
Germany	Plot T-1B (lettuce)	180	300	60C Uller	2015-03-12	Soil 0-30 cm	0.024	\$ < 0.001 \$	28	(i) 0 001 an o ko	2	
orthern Europe	Plot T-1C (barley)	180	300 \$	60 J.L.O	2015-08-26	Soil & 30 cm	0.009 0.014	<0.001 < 0.001	\$ 34	(k) Method Val 01432 (l) 253 days	idation Data in	
015	Plot T-2A (carrot)	180	300	60 t	2015-03-12	Soil 0-30 cm	0.020	> < 0.001 < 0.001 < 0.001	JY94 S	(-) _ = = = = = = = = = = = = = = = = = =		
	Plot T-2B (lettuce)	180	300		2008-03-12	501 0-30 cm		<0.001 <0.001	144			
	Plot T-2C (barley)	180	300		2015 09-12	Soil 0+30 cm	0.025	₹0:001 < 0.001	201			
	Plot T-3A (carrot)	180 J	300 Ĉ	60 00	2015-03-12	Soil 0-30 cm	0.025 0.029	<pre>&lt; 0.001 &lt; 0.001</pre>	369			
	Plot T-3B (lettuce)		300	60	2015-03-12	Soil 0-30 em	<10:028 0.017	< 0.001 < 0.001	369			
	Plot T-3C (barley)	180	306-	2 ° 2	2018-03-12	89170-30 cm	0.002 0.020	< 0.001 < 0.001	369			
- (a) Accor - (b) Only i - (c) Year r - (d) Days a - (e) Reman inform - (f) Study - (g) Formu - G green	ling to CODEX Cla frelevant sust be indicated frer last application ks may include: Cla work which mean reference lation track	(Laber pre-ha (Laber pre-ha intrute condition thes are inch	iuide 1 ivide 1 irvest inforval, ons deterence ded	PHI, uncertaine to analytical m	Performance of the second seco	Sphol-30 cm	<ul> <li>(i) Method</li> <li>(j) LOQ</li> <li>(k) Method</li> <li>(l) Storage</li> <li>* prior to</li> <li>* residue</li> </ul>	ation method d information e validation e (max) last treatment in control available				

- -
- -
- -

- (h) Application method
- (i) Method information (j) LOQ

- (k) Method validation (l) Storage (max)
- * prior to last treatment
- ** residue in control



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	1							in the same in the		
Trial No./		Applicat	ion rate per <u>on bare soi</u>		Dates of treatment		Residues (mg/kg)	atty as 2001 and		
Location/ Year	Plot (Commodity)	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and last date	Portion analyzed	Analyte 1 BCS-CO888460 BCS-CN88460 BCS-CN88460 BCS-CN88460	DALT (day) $Details on trial The		
	(a)				(c)	<u> </u>	et 1 at Carboxylic for			
15-2502-02	Plot T-1A (carrot)	180	400	45	2015-04-15		0.030 C < 0.001 0.020 001	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} $		
	Plot T-1B (lettuce)	180	400	45	2015-04-15	Soil 0-30 cha	0.034 0.030 <0.001 <0.001 <0.001	(i) 01432 (i) 01432		
The Netherlands Northern Europe	Plot T-1C (barley)	180	400	45	2015-09-21	Soil -30 cm	0.035	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} $		
F 2015	Plot T-2A (carrot)	180	400	45 JIM	2015-04-95	Soil 050 cm	0.027 0.031 0.031 0.001	COLOR COLORS		
	Plot T-2B (lettuce)	180	. Ĝ	45	2015-04-13	Soil 0-30 Ga	2007 20001 20001 20001 20001 20001			
	Plot T-2C (barley)	180	100	45	2019-04-15	Soil 0-30 cm	₩ 0.036 0.036 0.001 0.001 0.001 0.001 0.001			
	Plot T-3A (carrot)	180	400	45 60	2015-04-15	Soil 0-30 cm	0.025 0.001 0.001	3 366		
	Plot T-3B (lettuce)	180	400 Ş ^V	45 5	2015-04-13	Soil 0-30 cm	0.017 10 < 0.001 0.065 0.001	365		
	Plot T-3C (barley)	180	900 C	939 × ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	\$015-04-15	Soil 0-30 km ^{OLL}	0.017 < 0.001 < 0.001	366		
<ul> <li>(a) Accord</li> <li>(b) Only i</li> <li>(c) Year n</li> <li>(d) Days a</li> <li>(e) Rematinform</li> <li>(f) Study</li> <li>(g) Formu</li> <li>G greend</li> </ul>	$\begin{array}{c c c c c c c c c c c c c c c c c c c $									



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						-				
Trial No./		Applicat	ion rate per <u>on bare soi</u>		Dates of treatment		Residues (mg/kg) 12 and and and and and	9		
Location/ Year	Plot (Commodity)	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and last date	Portion analyzed	Residues (mg/kg)Analyte 1Analyte 2BCS-C088460BCS-CN88460BCS-C088460BCS-CN88460Colspan="2"> $(d_0, 0)$ BCS-C088460BCS-CN88460Colspan="2"> $(d_0, 0)$ Colspan="2"> $(d_0, 0)$ <tr< th=""><th></th></tr<>			
	(a)				(c)	a pe	$\left\{ \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \end{array} \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \end{array} \\ \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \left\{ \begin{array}{c} \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$			
15-2502-03	Plot T-1A (turnip)	180	300	60	2015-08-07		$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			
	Plot T-1B (lettuce)	180	400	45	2015-04-10	Soil 0-30 cm	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			
France Southern Europe	Plot T-1C (barley)	180	300	60	2015-09-18	Soil@-30 cm C				
F 2015	Plot T-2A (turnip)	180	300	60 JICE	2015-04-40	Soil 050 cm				
	Plot T-2B (lettuce)	180	. G		2015-04-18	- K. ^{B.}				
	Plot T-2C (barley)	180	<b>\$90</b>	60	2019-04-10	Soil 0-30 cm				
	Plot T-3A (turnip)	180	300	69 C	2015-04-10	Soil 0-30 cm	$\begin{array}{c} 0.049 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\ 0.001 \\$			
	Plot T-3B (lettuce)	180	300 GV	60 5	2015-04-10	Soil 0-30 cm	0.012 0.012 0.001 229			
	Plot T-3C (barley)	180	300 C		\$015-04-10 ⁵	Soil 0-30 km	$\begin{array}{c c c c c c c c c c c c c c c c c c c $			
	$\frac{1}{100} \frac{100}{100} \frac{100}$									
- (a) Accorr - (b) Only i - (c) Year r - (d) Days a - (e) Remar	ding to CODEX Cla f relevant nust be indicated after last application ks maximclude: Cli	(Label pre-ha	Guide arvest interval, onst Reference	PHI, uncertaine	P ) ) hethod and	LDL	<ul> <li>(h) Application method</li> <li>(i) Method information</li> <li>(j) LOQ</li> <li>(k) Method validation</li> <li>(l) Storage (max)</li> </ul>			
- (f) Study - (g) Formu - G green	neon which meres reference llation type house I	F field	nded	J.C. Y			<ul> <li>* prior to last treatment</li> <li>** residue in control</li> <li># no data available</li> </ul>			



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					1		and international internationa
Trial No./		Applicati	ion rate per <u>on bare soi</u>		Dates of treatment		Residues (mg/kg) The albert albert albert
Location/ Year	Plot (Commodity)	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and last date	Portion analyzed	Residues (mg/kg)Analyte 1Analyte 2DAL TBCS-C 888460BCS-C N88460DAL TBCS-C 888460BCS-C N88460Colspan="2"> $(d_0 y)$ DAL TDetails on trialBCS-C 888460BCS-C N88460Colspan="2"> $(d_0 y)$ DAL TDetails on trialDAL TDetails on trialColspan="2"> $(d_0 y)$ DAL TDetails on trialBCS-C 888460BCS-C N88460Colspan="2"> $(d_0 y)$ Colspan="2"> $(d_0 y)$ <
	(a)				(c)	<u> </u>	$\left[ \left( \frac{1}{2} \right)^{\frac{1}{2}} \left$
15-2502-04	Plot T-1A (carrot)	180	300	60	2015-04-14		$ \begin{array}{c} & & & & \\ & & & & \\ & & & & \\ & & & & $
Italy	Plot T-1B (lettuce)	180	300	60	2015-04-14	Soil 0-30 cm	$ \begin{array}{c} 0.029 \\ 0.022 \\ 0.022 \\ 0.022 \\ \end{array} \begin{array}{c} 0.001 \\ 0.001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.00001 \\ 0.00001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.0001 \\ 0.00001 \\ 0.00001 \\ 0.00001 \\ 0.00000 \\ 0.00001 \\ 0.0000 \\ 0.000$
Southern Europe	Plot T-1C (barley)	180	300	60	2015-09-22	Soil 0-30 cm	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
F 2015	Plot T-2A (carrot)	180	300	60 UIRE	2015-04-94	Soil 030 cm	$0.020$ $0.021$ $0.001$ $0.125$ $0.110$ $0^{\circ}$
	Plot T-2B (lettuce)	180	. Ĝ	60 01	2015-04-14	Soil 0-30 Ga	
	Plot T-2C (barley)	180	200	60	2015-04-14	Spil 0-30 cm	$\sim 0.017$ $0^{\vee}$ $0.001^{\vee}$ $1.001^{\vee}$
	Plot T-3A (carrot)	180	300	69.C	2015-04-14	Soil 0-30 cm	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
	Plot T-3B (lettuce)	180	300 Ş ^{V)}	60 \$	2015-04-14	Soil 0-30 cm	0.017 10 < 0.001 0.025 10 < 0.001 353
	Plot T-3C (barley)	180	300 Ĉ		2015-04-14	Soil 0-30 km	0.015 < 0.001 345 < 0.001 345
<ul> <li>- (a) Accor</li> <li>- (b) Only i</li> <li>- (c) Year r</li> <li>- (d) Days a</li> <li>- (e) Remaninform</li> <li>- (f) Study</li> <li>- (g) Formu</li> <li>- G green</li> </ul>	ding to CODEX Cla frelevant nust be indicated frelevant inter last sourcation rks mount which mean reference lation types	a (Laber pre-ha in (Laber pre-ha in the condition prices are inclu- fr field	Suide 1 Suide 1 Arvest informal, ons Geterence ded with DO	DO DI DI CL CL PHI, uncertific to analytical n		Soil 0-30 cm Soil 0-30 cm Soil 0-30 cm	<ul> <li>(h) Application method</li> <li>(i) Method information</li> <li>(j) LOQ</li> <li>(k) Method validation</li> <li>(l) Storage (max)</li> <li>* prior to last treatment</li> <li>** residue in control</li> <li># no data available</li> </ul>



Table 6.6.2- 6 Analyte 1: BC Analyte 2: BC	S-CN88460	(determi		CN88460,	calculated	as BCS-0	CN88460)	Â	Jer Pc	ert	CI and	1 0 ^D	egine and
Trial No./	Commodity/	PBI	Date of 1.Sowing or		on rate per t on bare soil		Dates of treatment	B ⁰	Growth		(mg/kg)		ant s
Location/ Year	Variety (Plot)	(days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (l/ha)	g a.s./hl	or no. of treatments and St	Portion C analyzed	stage of stoppling	1 × 0 × 0 ×	Qualyte 2 BC&CR60082	(days)	Details on trial
	(a)	(b)				* DC		1 DE				*W	(e)
15-2502-01	Carrot/ Bolero F1 (Plot T-1A)	28	1) 2015-04-09 3) 2015-07-15 - 2015-08-15	180	300 1 5	60 A	2015-03-120 5 V.C.I.	Root Leaf	BBC1047 BBCH 49 BBCH 40 BBC1749	U.G.0.01 <0.001/10/01		D125	(f) 15-2502 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg
Germany Northern Europe F 2015	Carrot/ Laguna (Plot T-2A)	106	1) 2015-06-26 3) 2015-09-10 - 2015-09-30	180 July		69 CC	2015 (9) 12 C J.D.C	Root Leaf Of I	BBCH 47 BBCH 47 BBCH 49 BBCH 47 BBCH 49	<ul> <li>&lt;0.01</li> <li>&lt;0.02</li> <li>&lt;0.05</li> <li>a</li> <li>0.057 c</li> <li>&lt;0.057 c</li> </ul>	<0.01 b <0.01 d		(k) Method Validatior Data in 01475 and study 15-2502 (l) root: 300 days leaf: 299 days
	Carrot/ Laguna (Plot T-3A)	368*	1) 2016-03-14 3) 2016-07-15 - 2016-08-15		300 SDE		2015-03-12	Root Leaf	BBCH 47 BBCH 49 BBCH 47 BBCH 47 BBCH 49	<pre> 0.01</pre>	<0.01 <0.01 <0.01 <0.01	491 505 491 505	

PBI = plant-back interval DALT: days after the last treatment a Mean of three replicates: (0.077; 0.077 and 0070 mg/kg) b Mean of three replicates: (<0.01; <0.01 and <0.01 mg/kg) c Mean of three replicates: (<0.01; <0.01 and <0.060 mg/kg) d Mean of three replicates: (<0.01; <0.01 and <0.01 mg/kg) * Plant back interval is slightly longer as reqested in the study protocol However, the timing for the last interval is considered to be in an acceptable range.

	e' all' al alt chit rea			
- (a)	According to CODEX Classification / Guide	-	(h)	Application method Method information
- (0) - (c)	Year must be indicated by the second se	-	(j) (k)	LOQ Method validation
- (e)	Remarks may include: Climite conditions Geterence to analytical method and	-	(l)	Storage (max)
- (f) - (g)	Study reference	-	* **	prior to last treatment residue in control
- G	greenhouse F field	-	#	no data available



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											3		F
Trial No./	Commodity/		Date of 1.Sowing or	Applicati	on rate per on bare soil		Dates of treatment		e Sowth	Residues	(mg/kg)	~	egine and
Location/ Year	Variety (Plot)	PBI (days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (l/ha)	g a.s./hl	or no. of treatments and last	Portion analyze	A TALANA	Analojed BCS-CN88460	Analyte 2	DAILT (days)	Derails on trial
	(a)	(b)	5. narvest				date (c)			BCS-CN88460	Analyte 2 BCS-CR00082	(d) (	C9 all Details on trial
15-2502-02	Carrot/ Napa Washing (Plot T-1A)	22	1) 2015-05-07 3) 2015-08-10 - 2015-08-20	180	400	Ø	20 <b>0-0</b> 4-15	Röd	BBCH 480 BBCH 49 BBCH 49 BBCH 48 BBCH 49 BBCH 49 BBCH 49 BBCH 49 BBCH 49 BBCH 49 BBCH 49 BBCH 49 BBCH 48			106 120 106	(f) 5/2502 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg
The Netherlands Northern Europe F 2015	Carrot/ Nerja late (Plot T-2A)	100	1) 2015-07-24 3) 2015-11-09 - 2015-11-16	180	400 j.S D ^T DI	45 OF	2015-04-15 GULC	Root Alla Leaf	BBCH 47 BBCH 49 BBCH 49 BBCH 49				(k) Method Validation Data in 01475 and study 15-2502 (l) root: 285 days leaf: 284 days
	Carrot/ Nerac Orange (Plot T-3A)	365	1) 2016-04-14 3) 2016-08-10 - 2016-08-20	OSC DID			BUCL BUCL 201504-15 201504-15 DUD DUD DUD DUD DUD DUD DUD DU	Bain Lear D	BBCH 48 BBCH 48 BBCH 48 BBCH 48 BBCH 48		>0.01 <0.01 <0.01 <0.01	471 485 471 485	
			S ^{JI}		JUL S	1004	diet TI	d use	er the ?	ci gu			
	« »	t TAR		30CUI	Dell'	LOIL'		A ^e J2	^E				
	>	-¢	6 1 91 F.D.J.S	r Pul	e the		eg Ir Srg						
<ul> <li>(a) Accor</li> <li>(b) Only</li> <li>(c) Year</li> <li>(d) Days</li> <li>(e) Rema</li> </ul>	ding to CODEX C if relevant must be indicated after last application rks may include: C	Clasenteatio	n / Guide e-harvest inforval, 1 ditions Generence	PHI, underline	P C C	n'i D'i	- - - -	<ul> <li>(h) App</li> <li>(i) Meti</li> <li>(j) LOO</li> <li>(k) Meti</li> <li>(l) Store</li> </ul>	lication method hod information } hod validation age (max)				
- (f) Study - (g) Form - G green	reference ulation type	F field	AND TO AND	»- ~¢	) ^{EC}		- - -	* prio: ** resic # no d	r to last treatment lue in control ata available				



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												3			
Trial No./	Commodity/		Date of 1.Sowing or	Applicati	on rate per <u>on bare soil</u>		Dates of treatment			P Fowth	Residues	(mĝ/kg)	~	egine and	ŀ
Location/ Year	Variety (Plot)	PBI (days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (l/ha)	g a.s./hl	or no. of treatments and last date		rtion lyzeeb 🔊	stage at sampling	Analoje BCS-CN88460	Analyte 2	DAD T (days)	Details on trial	
	(a)	(b)	5. narvest				(c)_~( [*]	Z,	Jates		BCS-CN88460	Analyte 2 BCS-CR00082		ECOLO ECOLO (Del ESO)	
15-2502-03	Turnip/ Navet rave d'auvergne (Plot T-1A)	20	1) 2015-08-27 3) 2015-11-05 - 2015-11-15	180	300	a.	29 0 98-07	Body	LL LL	BBCH 480 BBCH 49 BBCH 49 BBCH 49 BBCH 49	<0.01 <004 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 0.01	83 97 83 83 83 97	(i) (j) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg	
France Southern Europe F 2015	Turnip/ Navet rave d'auvergne (Plot T-2A)	139	1) 2015-08-27 3) 2015-11-05 - 2015-11-15	180	300 <u>,</u> S	60 (F	2015-04-10 G	4	² ² e ⁶	BBCH 48 BBCH 49 BBCH 48 BBCH 49	2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 200 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2		83 o 1 83 83 97	(k) Method Validation Data in 01475 and study 15-2502 (l) body: 194 days leaf: 193 days	n
	Turnip/ Navet de Croissy (Plot T-3A)	350	- 2015-11-05 - 2015-11-15 1) 2016-03-25 3) 2016-06-10 - 2016-06-20 - 2016-06-20 - 2016-06-20 - 2016-06-20 - 2016-06-10 - 2016-06-20 - 2015-11-15	O.L.J.	13000 ² 200 ²	State of the second sec	2015-04-10 JID	Bosty Leaf		BBCH 48 BBCH 49 BBCH 48 BBCH 48 BBCH 48	<pre></pre>	<0.01 <0.01 <0.01 <0.01	298 311 298 311		
			ll a		J'ALL'S	L. L.	dilstri i	J. V.	,e "De ^T	o ^f	19110				
		1. Sult	1 ^{oe} c	) ²¹		LOR ,			)79 _{fc} e	ж.»					
	Ţ		EDÌÓ	eule t	exer?	0 ² ,5 ⁵ ,0	A ALA	AJ 12							
<ul> <li>(a) Accor</li> <li>(b) Only</li> <li>(c) Year</li> <li>(d) Days</li> <li>(e) Rema</li> </ul>	ding to CODEX ( if relevant must be indicated after last application rks may include: (	Clasenteatio	n / Guide 1 e-harvest inforval, 1 Iditions & eterence	PHI, undervine			- - - - - -	(h) (i) (j) (k) (l)	Application Method in LOQ Method val Storage (ma	n method formation lidation ax)					
- (f) Study - (g) Form - G green	reference	F field	N L L L L	), Å	SC			* ** #	prior to last residue in c no data ava	t treatment control ilable					



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				A						AC		- Old		egine and	
Trial No./	Commodity/	PBI	Date of 1.Sowing or	Аррисан	on rate per on bare soil		Dates of treatment or no. of	Por	tion 🧳	Growth	Residues	(mg/kg)	DAN) T	. C 9 01	
Location/ Year	Variety (Plot)	(days)	planting 2.Flowering	g a.s./ ha	Water (l/ha)	g a.s./hl	treatments and last		lyzee 🔊	stage at sampling	Anakoje BCS-CN88460	Analyte 2 BCS-CROU082	(days)	E9 July Details on trial	
			3. Harvest				date	, A	×,e ^r		BCS-CN88460	BCS-CR60082	UD L-	K. Chtr	
	(a)	(b)					(c) (°			ect	2 ^{till}	V of I	(d) ()	e of the second se	
15-2502-04	Carrot/ Nantes Clodia 2	28	1) 2016-05-12 3) 2015-08-03 - 2015-08-11	180	300	7	2005-04-14	Rôm	rel	BBCH 460 BBCH 49			93 107	(1) \$2502 (2) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg	
Italy	(Plot T-1A)					*De	1 K B	Lear	<u>*</u> **	BBCH 46 BBCH 49	<0.01 <0.01 \$	<0.01 ©.01	107	(i) 01475 (j) 0.01 mg/kg (k) Method Validatio	n
Southern Europe	Carrot/ Nantes Clodia 2	125	1) 2015-08-17 3) 2015-10-26 - 2015-11-10	180	300 5 \$	60 F	2015-04-14	Root	ġ.	BBCH 46	U-<0.01	0.01 0.01 0.01 0.01 0.01 0.01 0.01	195 o	Data in 01475 and study 15-2502 (1) root: 299 days	.1
F 2015	(Plot T-2A)		2013 11 10	J.M.C	9. Pr	N * 9	TO B	6			3.001 3.0		195 209	(1) foot: 299 days leaf: 298 days	
	Carrot/ Nantes Clodia 2	353	1) 2016-04-01 3) 2016-06-01	0.86	3000	80.	2015-04-14	Boot		BBCH 45 BBCH 49	<0.01 <0.01 <0.04 <0.04	0.01	419 433		
	(Plot T-3A)		TAL	Organ	to "	OF V	12 1	Leaf 1	5	BBCH 45 BBCH 49	<0.01 <0.01 <0.01	<0.01 <0.01	419 433		
PBI = plant-back	interval	DALT: da	iys after the last t	reatment &	- MES	- 4 C		I DE	,C A	0 ⁵	1 JUL				
			GV ^J				972 92	jð.	WD.e."	the .					
			1 ²⁰⁶ C ⁽	DPI AU	RELL'S		10 ⁵⁰ x	,n ^e ,	N O ^{te}	, 1					
	« ²	C TAIO	*	300	1 ¹ Car	O ^{LE®}	0 ^f	J'LO	7						
	*		- 2015-11-10 1) 2016-04-01 3) 2016-06-0 - 2016-06-0 - 2016-06-20 - 2016-06-20 - 2016-06-20 - 2016-06-20 - 2016-06-20 - 2015-11-10	al PUL	exe		I OILO	>							
	L' CODEV (						e ^{o,}		A 11 - 41						
- (a) Accor - (b) Only - (c) Year	if relevant must be indicated		n / Guide	300-708			-	(h) (i) (j)	Method ir LOQ	nformation					
- (d) Days - (e) Rema inform	after last application include: Contract of the second sec	on (Label ) Climatic con bolites are i	re-harvest interval, 1 nditions (Reference in included	PHI, underhine to analytical m	ethod and		-	(k) (l)	Method va Storage (n	alidation nax)					
- (f) Study - (g) Form - G greer	reference ulation type	F field	L'IL DO	y 'Y	y-		- -	* ** #	prior to las residue in no data ava	st treatment control ailable					
0	×		SM -												



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Analyte 1: BC Analyte 2: BC									L CON	ș¢ I c	Derry .		an ring
Trial No./	Commodity/	PBI	Date of 1.Sowing or		on rate per <mark>on bare soi</mark>		Dates of treatment	Rortion	Grewch	Résidues	(mg/kg)	C ^{CC}	
Location/ Year	Variety (Plot)	(days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and late	DY la	Stage at Sampling	Analyte 4	AnalyttQ ² BCS-CR6082	DAL Ĉ (days)	COLL CELOS
	(a)	(b)				+ DC		j.ľ		·	to to	(d)	к. "Ш." (e)
15-2502-01	Lettuce/ Aleppo (Plot T-1B)	28	1) 2015-04-09 3) 2015-06-01 - 2015-06-30	180	300 je		20 12 12	Head D.C.	BBCH 46 BBCH 49 BBCH 49			00 ³ 90	(f) 15-2502 (g)CEC (50 g/L) (h) Spraying
Germany	Lettuce/ Aleppo (Plot T-2B)	144	1) 2015-08-03 3) 2015-09-10 - 2015-09-21	180 CUIRC	900 S	CON M ^{ES}	2025-03-12	Albead	BBCH 47 BBCH 49		CUPICIE	9 ⁸² 186	<ul> <li>(i) 01475</li> <li>(j) 0.01 mg/kg</li> <li>(k) Method Validation Data in</li> </ul>
Northern Europe F 2015	Lettuce/ Aleppo (Plot T-3B)	370*		180 J.L.J.	300 x	SO E E	2015-03-12	Head	BBCH 45 BBCH 49 ×	20.01 <0.01	<0401 50.94	424 438	01475 and study 15-2502 (1) 341 days
15-2502-02	Lettuce/ Salanova Butterhead (Plot T-1B)	21	1) 2015-05-06 3) 2015-07-01 - 2015-07-08		400 Sht B	45 E	2015-04-15	Pread	BBCH 45 BBCH 49 (		<0.01 <0.01	65 79	(f) 15-2502 (g) EC (50 g/L) (h) Spraying (i) 01475
The Netherlands Northern Europe	Lettuce/ Nadine Butterhead (Plot T-2B)	131	1) 2015-08-24 3) 2005-10-13 - 2015-10-20 C		400 K.		2015-04-19	Head O	BBCH 46 BBCH 49	<0.01 <0.01	<0.01 <0.01	170 184	(j) 0.01 mg/kg (k) Method Validation Data in 01475 and study 15-2502 (l) 318 days
F 2015	Lettuce/ Nadine Butterhead (Plot T-3B)	369	1) 2016-04-14 3) 2016-06-03 - 2016-06-00	BP .	400 CO	45 ° ° °	2015-00-75	Head's O	BBCH 45 BBCH 49	<0.01 <0.01	<0.01 <0.01	404 418	

* Plant back interval is slightly longer as requested in the study protocol. However the time for replacting of rotational crops as given in the OECD guideline on residues in rotational crops (limited fieldstudies) 504 suggests 270 to 365 days for crops rotated the following gar. Thus, the actual plant fact interval is considered to be in an acceptable range.

-	(a)	According to CODEX Classification / Guide 1	-	(h)	Application method
-	(b)	Only if relevant	-	(i)	Method information
-	(c)	Year must be indicated a start of the start	-	(j)	LOQ
-	(d)	Days after last application (Labor pre-harvest inforval, PHI, underhine)	-	(k)	Method validation
-	(e)	Remarks may include: Climate conditions Beference to analytical method and	-	(l)	Storage (max)
		information which metabolities are included			
-	(f)	Study reference	-	*	prior to last treatment
-	(g)	Formulation type and the former of the forme	-	**	residue in control
-	G	greenhouse F field	-	#	no data available



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										Ċ	A.C	9	in the o
Trial No./	Commodity/		Date of 1.Sowing or		on rate per <u>on bare soi</u>	treatment <mark>1</mark>	Dates of treatment		Growth		s (mg/kg)		AR TEST BURN
Location/ Year	Variety (Plot)	PBI (days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (L/ha)	g a.s./hL	or no. of treatments and last date	Portion analyzed	stage at sampling	Analyte 1	Analyte 2	DAET (days)	Di Gerails on trial
	(a)	(b)	5. Hai vest				(c) ©Î	r4 	ate ^{\$}	BCS 6188460	BCS-CR60082	(d)	
15-2502-03	Lettuce/ Kiribati loose leaf lettuce (Plot T-1B)	26	1) 2015-05-06 3) 2015-06-10 - 2015-06-20	180	400	45 * D [©]	20\$5-04-10	erland J.C.	BBCH 47 BBCH 49	0.01 x 01 x 01 x 0 x 0 x 0 x 0 x 0 x 0 x 0 x 0 x 0 x 0	<0.004e. <0.004e.	69	(f) 15-2602 (g) FC (50 g/L) (h) Spraying (i) 01475
France Southern Europe	Lettuce/ Kirinia loose leaf lettuce (Plot T-2B)	139	1) 2015-08-27 3) 2015-10-10 - 2015-10-20	180	300 je	60 of	auch	Plead	BBCH 48 BBCH 48 BBCH 495		~0 ⁵ 0 h	Ort	(j) 0.01 mg/kg (k) Method Validation Data in @1475 and study 15-2502 (l) 333 days
F 2015	Lettuce/ Kiribati loose leaf lettuce (Plot T-3B)	348	1) 2016-03-23 3) 2016-05-10 - 2016-05-20	1800Ills	300		2015-04 50 2	Head	BBCH 48 BBCH 49			266 279	
15-2502-04	Lettuce/ Gentile Estony Loose leaf (Plot T-1B)	28	1+2015-05-12 3-2015-05-12 - 2015-06-30	2 CCE	2000		2015-04-14	Head D	BBCH 46 BBCH 49		<0.01 <0.01	55 69	(f) 15-2502 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg
Southern Europe	Lettuce/ Gentile Estony Loose leaf (Plot T-2B)	125	1) 2015-08-17 3) 2015-06-28 - 2015-10-05	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ant			~~C	BROH 45 SBCH 49	0.01 0.01	<0.01 <0.01	146 160	(k) Method Validation Data in 01475 and study 15-2502 (l) 329 days
2015	Lettuce/ Gentile Estony Loose leaf (Plot T-3B)	35800	1) 2016-04-04 3) 2016-05-11 - 2016-05-20			160 × 02	2015-04-14 *		BBCH 45 BBCH 49	<0.01 <0.01	<0.01 <0.01	392 406	
PBI = plant-back int	erval D	ALT: days	after the tast freatr	nent P	exer t		ed all	<i></i>					
<ul> <li>(a) Accor</li> <li>(b) Only</li> <li>(c) Year</li> <li>(d) Days</li> <li>(e) Rema</li> </ul>	Loose leaf (Plot T-3B) erval D ding to CODEX Cla frelevant must be indicated after last soparation rks may include: Cl maon which methy reference lation type	(Label)	/ Guide -harvest inforval, I litions Beterence t	PHI, underline q analytical m	Der C	MIN		- (h) - (i) - (j) - (k) - (l)	Application me Method inform LOQ Method validat Storage (max)	nation			
- (f) Study - (g) Formu - G green	reference lation types	F field	AN DE LEO	)>	) ^e			- * - ** - #	prior to last tre residue in conti no data availab	rol			



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Table 6.6.2- 8 Analyte 1: BC Analyte 2: BC	S-CN88460 (	determi		CN8846	0, calcula	ated as BCS			1er p	j	TTA SUG	, 0 [°]	regine ond
Trial No./	Commodity/	PBI	Date of 1.Sowing or	Applicat	ion rate pe on bare s	er treatment <u>oil</u>	Dates of treatment or	Al Portion	Growth	Residues	s (mg/kg)	BADT	
Location/ Year	Variety (Plot)	(days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (L/ha)	g a.s./hL	no. of treatments and las Quate	Portion		Agalyte 1 BCS-CN86960	Anglyte 2 BCS-@60082	(Mays)	Det Details on trial
	(a)	(b)				, DC			DITO.	ori , or	OT I	(d)	(e)
15-2502-01 Germany	Barley/ Lomerit (Plot T-1C)	34*	1) 2015-09-29 2) 2016-05-15 - 2016-05-20 3) 2016-07-01 - 2016-07-15	180	300 CD	ALAN S	2013208-26	Green material	BBCH 30 BBCH 75 BBCH 89 BBCH 89 BBCH 89	0.01 0.01 0.01 0.01 0.01 0.01	11 0.01 11 0.01 11 0.01 11 0.01	222 279 316	(f) 15-2502 (g) EC (50 g/L) (h) Spraying (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data
Northern Europe F 2015	Barley/ Lomerit (Plot T-2C)	201	1) 2015-09-29 2) 2016-05-15 - 2016-05-20 3) 2016-07-01 -2016-07-15		3900× 200×		2015-03-12	Grand	BBCH 30 BBCN 33 BBCH 89 BBCF 89		<0.01 <0.01 <0.01 <0.01	389 446 483 483	in 01475 and study 15-2502 (1) green material: 169 days grain: 74 days straw: 78 days
	Barley/ Vespa (Plot T-3C)	369*	1) 2016-03-15 2) 2016-06-06 - 2016-06-16 3) 2016-08-01 - 2016-08-31		300 70 °	60 TRAY	2015-03 12 0 2	Green oraterial Grain	BBCH 29 BBCH 75 BBCH 89 BBCH 89	<pre></pre> <pre>&lt; 0.01 &lt;0.01 &lt;0.01 &lt;0.01 &lt;0.01 </pre>	<0.01 <0.01 <0.01 <0.01	425 466 515 515	

* Plant back intervals are slightly longer as requested in the study protocol. However the timing for replanting of replanting of rotational crops and at 270 to 365 days for crops rotated the following year. Thus, the actual plant back intervals are considered to be in an acceptable range.
 (a) According to CODEX Classification / Guider 1
 (b) Only if relevant
 (c) Paramets be indication
 (d) Days after last topication (Later bre-harvest interval, PHI, uncefine)
 (e) Remarks methodic: Classification (Later bre-harvest interval, PHI, uncefine)
 (f) Study reference
 (g) Formulation type
 (g) Formulation type
 (g) Formulation type
 (g) Formulation type
 (h) Application type
 (h) Application type
 (h) Application type
 (h) Application method
 (h) Application type
 (h) Application type
 (h) Application method
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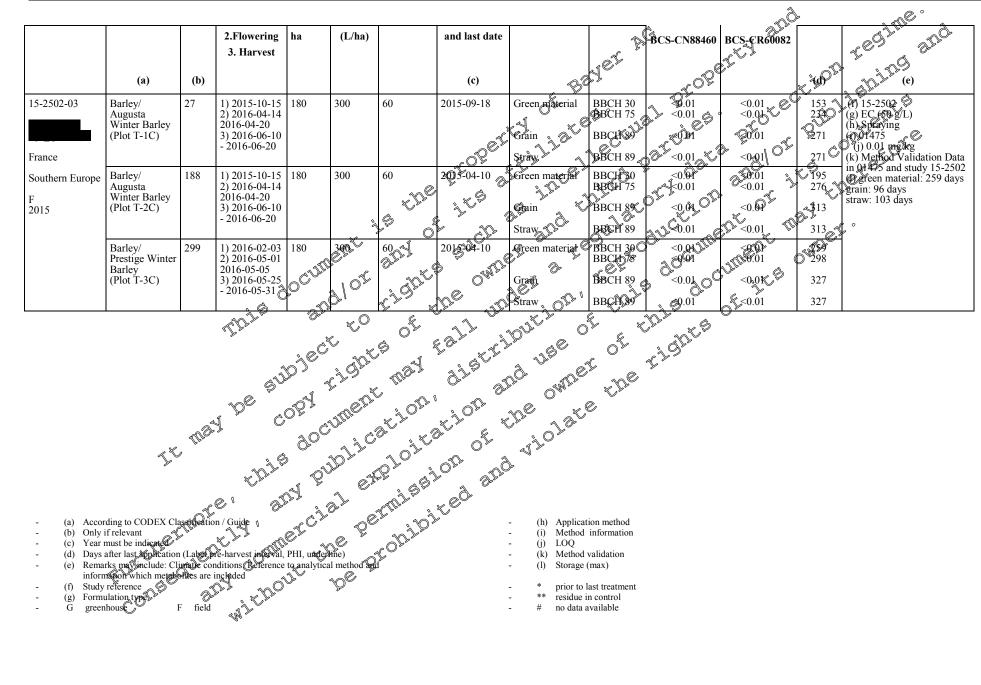


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											j	Þ	
	(a)	(b)					(c)		Þ		r A Orte	(d)	egine, and
15-2502-02 D The Netherlands	Barley/ Naomi Winter (Plot T-1C)	22	1) 2015-10-13 2) 2016-05-15 2016-06-01 3) 2016-07-09 - 2016-07-16	180	400	45	2015-09-21	Green material Grain	BRCH 30 BBCH 75 BBCH 89	<0.01 <0.01 <0.01 <0.01 <0.01	<0.01 <0.01 <0.01 <0.00	5205	(f) 15-2502 (f) (g) EC (50 g/L) (h) Staving (i) 01475 (j) 0.01 mg/kg (k) Method Validation Data
Northern Europe F 2015	Barley/ Naomi Winter (Plot T-2C)	181	1) 2015-10-13 2) 2016-05-15 2016-06-01 3) 2016-07-09 - 2016-07-16	180	400	45	2015-04-15	Strawe 1	BBCH 30 BBCH 75 BBCH 89 BBCH 89	0.01		357 439 a	in 01 475 and study 15-2502 Opereen material: 170 days grain: 69 (a) straw K days
	Barley/ Tipple Summer (Plot T-3C)	365*	1) 2016-04-14 2) 2016-06-01 2016-06-15 3) 2016-08-09 - 2016-08-16	180	400		Engle	Grain ^{DD} Straw	BBCID89	20.02 200 200 200 200 200 200 200 200 20	<0.04 200.01	485 485	0
* Plant back inter suggests 270 to 30	val is slightly long		, De	0 ⁶ 1	MACLE	1 JOIL	Treplanting of rot ars considered	ational crops as gi be in an acceptat but use of the optimized of the opti	ven in the Off ble range by 5 5 5 0 5 5 5 5 5 6 5 6 5 6 5 7	ed guidelagen		nal crops (l	imited field studies) 504
Trial No./ Location/	Commodity Variety (Plot)	PBI (days)	Date of 1.Sowing or	Appucat	on rate pe	or treatment	$O^{\otimes}$ no. of $A^{\bigcirc}$	Portion analyzed	Growth stage at sampling	Residue	s (mg/kg)	DALT (days)	Details on trial
- (a) Accor	ding to CODEX Cla	savertic	planting	g.a.s.P	Water		treatmonts"	- (h) Applicat		Analyte 1	Analyte 2		
- (b) Only - (c) Year - (d) Days - (e) Rema inform	ding to CODEX Cla if relevant must be indicated after last to breation rks ma vinclude: Cli manon which metabolic reference ulation type.	(Label) maile con	re-harvest poweral, nditions (Bererence included	CHI, under to analytical	ine) I method Sod	CORTA		- (i) Method - (j) LOQ - (k) Method - (l) Storage	information validation				
- (g) Form - G greer	ulation types in the second se	field	WI THO		¥				n control				



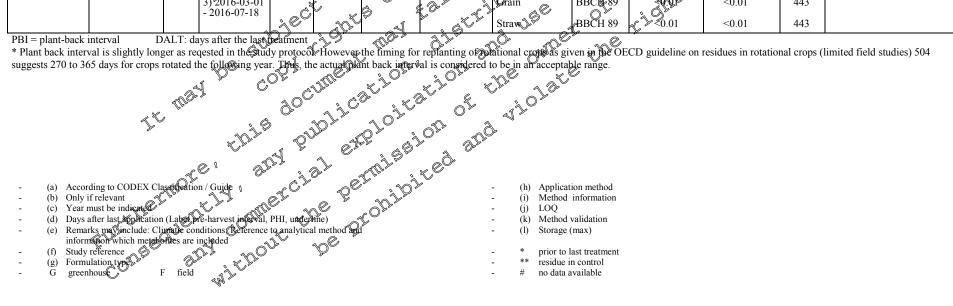
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											, ô	þ	
Trial No./	Commodity/		Date of 1.Sowing or	Applica	tion rate pe on bare s	er treatment <u>oil</u>	Dates of treatment or		(Growth	Residue	s (mg/kg)		Tegine and
Location/ Year	Variety (Plot)	PBI (days)	planting 2.Flowering 3. Harvest	g a.s./ ha	Water (L/ha)	g a.s./hL	no. of treatments and last date	Portion analyzed	Stage at sampling		Analyte 2	DALT (days)	A Charles on trial
	(a)	(b)	5. narvest				(c) (c)	t'I viate		18CS-ČN88460	°° a	P(d)	ja enta
15-2502-04 Italy Southern Europe	Barley/ Ketos (Plot T-1C)	34	1) 2015-10-26 2) 2016-04-20 2016-04-27 3) 2016-06-26 - 2016-06-30		300	60 *100	2015-00-92 2015-00-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20-92 20	Grain D	BBCH 29 BBCH 75 BBCH 89 BBCH 89	2001 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -00 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -000 -		275 275	(f) 15,2502 (g) CC (50 g/L) (i) Spraying (j) 0.01 mg/kg (k) Method Validation Data
F 2015	Barley/ Ketos (Plot T-2C)	195	1) 2015-10-26 2) 2016-04-20 2016-04-27 3) 2016-06-26 - 2016-06-30		300 ED ¹ C	any	2015-04.00	Green juniterial	BBCH 30 BBCH 75 BBCH 89 BBCH 89	0.01 0.01 0.01 0.01 0.01 0.01 0.01	<0.01 ×	275 325 436 436	(k) Welhod Vandation Data in 01475 and study 15-2502 *(1) green material: 258 days grain: 89 days straw: 96 days
	Barley/ Concerto (Plot T-3C)	345*	1) 2016-03-24 2) 2016-06-12 2016-06-19 3) 2016-03-01 - 2016-07-18			Solution of the second	15-04-14,5 22,22 6,572	Green material	BBCH 29 BBCH 75 BBCH 89 BBCH 89	0.01 0.01 0.01	<pre>0.01 &lt;0.01 &lt;0.01 &lt;0.01 &lt;0.01</pre>	378 420 443 443	





### CA 6.7 Proposed residue definitions and maximum residue levels

### CA 6.7.1 Proposed residue definitions

, E.; 2018, M-612432-01 **Report:** KCA 6.7.1/01; , R.; Title: Isoflucypram (BCS-CN88460): Evaluation of dietary metabolites and residue definition proposals M-612432-01-1 Report No .: Document No .: M-612432-01-1 Guideline(s): none Guideline deviation(s): **GLP/GEP:** no

For the discussion on the residues of isoflucyprame potentially relevant for risk assessment as a first step, consideration was given to the residue levels found in the available metabolism studies

Conclusively identified metabolites were considered for potential inclusion into the residue definition for risk assessment, if they exceeded the lever of significance of  $\gtrsim 10\%$  of the RR and  $\ge 0.01$  mg/kg in food of plant origin from the metabolism studies. If they represented less than \$0% of the TRR, only metabolites reaching levels 20.05 mg/kg were selected. For plant feed items the criterion for consideration was  $\geq 10\%$  of the TRR and  $\mathcal{D} 0.01$  mg/kg for food opaning origin, metabolites representing  $\geq 10\%$  of the TRR were selected.

The consumer exposure was further refined based on the field Studies from representative uses (cereals), the field rotational crops study and the livestock ceeding studies. The pre-dominance of the metabolites in food versus feed was considered a well as their contribution to the overall consumer exposure.  $\cap$ 

The assessment of the metabolities toxicity indicated that they are not expected to exert a higher toxicity or additional hazards beyond those identified for isothecypraph. They are considered nonrelevant based on the toxicological and structural considerations and are as well covered by the toxicological endpoints for the parent compound Ŵ

Besides as shown in the following table, the consumer exposure to these metabolites is far below the chronic and acute Tox cological Threshold of Concern (TYC) for Cramer class III compounds. . 0 Q, ×1'

		0 [×] &	
Metabolite	Grame Class	× ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	%
	Class	🏷 of the chronic	of the acute
4 7 7		TTC of 1.5 μg/kg bw/d	TTC of 5 µg/kg bw/d
BCS-CN88460-propared (M01) and its		1.3	4.7
BCS-CN88460-2-propanol (M02) and its conjugates	Ĥ	0.85	1.7
conjugates	Q,		
BCS-CN88400-desmethyl-propanol	۲. III	0.61	0.63
(M06) and its comprises			
BCS-QN8846Q-desmethyl-1,2propandiol	III	0.02	0.14
(M03) and its conjugate			
BCS-CNS8460-desmethyl-carboxylic acid	III	0.02	0.21
(M11)			
BCS-CN88460-carboxylic acid (M12)	III	1.1	1.2

Therefore, it is concluded that further toxicity studies are not needed for the metabolites.



Based on all this information the residue definition for risk assessment and for monitoring in plant and animal commodities is proposed as follows: Isoflucypram parent only.

### CA 6.7.2 Proposed maximum residue levels (MRLs) and justification of th acceptability of the levels proposed

### Plant matrices

The proposed residue definition for MRL setting in plant in the EU is softucypram parent only.

MRLs are calculated and proposed based on the available residue data in support of the representative uses of BCS-CN88460 in cereals (see Table 6.2.1-7 for barley and Table 6.3.2-7 for wheat). Calculations of MRLs were carried out using the OECD MRL@calculator (ENV/JNLMONO(201))2 of 01-Mar-2011.

### **Barley (extrapolated to oat)**

Residue data from northern Europe were compared to residue data from softhern Europe Since residues in grain at harvest are often 0.01 mg/kg, the comparison was some using the results in straw at harvest.

The results of the statistical tests Kruskal-Wath's H-Dest and Mann-Whitteey U Qest,  $\alpha = 0.05$  indicate that the straw residue data from northern Europe are not significantly different from the straw residue data in southern Europe. Thus it is suitable to combine the straw data from both regions.

Shows the roults of the MRL carculations for barley grain using the OECD MRL calculator, including the residue endpoints (STMR and FIR) for barley grain and straw.

southern and rowthern Europe southern and rowthern Europe is do the WRL Scienciations for bar indue eadpoints (STMR and FIR) for barre indue eadpoints (STMR and



Сгор	Region/Indoor (a)	Trial results relevant to the critical GAP	MRL calculation (d)	STMR (b)	
	NEU	10 × <0.01; 0.013; 0.020; 0.041	0.05	< 0.01	~Q.041
Grain	SEU	9×<0.01; 0.022; 0.027; 0.037	0.05	<0.01	\$ 0.0 <b>3</b>
	N+SEU	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0(05	<u>&lt;0.01</u>	<u>0.941</u>
	NEU	0.049; 0.11; 0.13; 0.16; 0.20 0.24; 0.32; 0.40; 0.44; 0.51; 0.94; 0.96; 12		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	
Straw	SEU	0.021; 0.13; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 1.0; 34			
~	N+SEU	0.049; 0.11; 0.13; 0.16; 0.20; 0.24; 0.32 0.40; 0.44; 0.51; 0.94; 0.96; 4.2, 0.021; 0.13; 0.16; 0.18; 0.24; 0.29; 0.29; 0.31; 0.85; 0.96; 1.02.1		0.29 0.29 0 0 0 0 0 0 0 0 0 0 0 0 0	

(a) NEU or SEU for northern or southern outdoor Phales in EV member states. A SEU if Both zones), Indoo For glasshouse/protected crops (b) STMR: Supervised Trials Median Residue

(c) **HR**: Highest residue

(d) using OECD MRL calculator

An <u>MRL of 0.05 mg/kg</u> is therefore proposed for <u>barley grain</u> (code 0500010), based on all European residue data.

An extrapolation of this <u>MRL of 005 mg/kg</u> to <u>ont grain</u> (code 0500050) is requested, as permitted by the Guidance document SANCO 75250 1/95 Rev. 102 dated of 23 September 2016 (Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs).

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# Wheat (extrapolated to rye, spelt and triticales

Residue tata from northern Enrope were compared to tesidue data from southern Europe. Since residues in grain at harvest are often <0.01 mg/kg the comparison was done using the results in straw at harvest.

C

The results of the statistical tests Kruskal-Wallis H-Test and Mann-Whitney U-test,  $\alpha = 0.05$  indicate that the straw desidue data from northern Europe are not significantly different from the straw residue data in southern Europe. Thus it is suitable to combine the straw data from both regions.

Three MR calculations were made using:

- Grain residue data from southern Furope
- Grain residue data from northern Europe
- Grain residue data from both Southern and northern Europe

Table 6.7.2- D shows the results of the MRL calculations using the OECD MRL calculator, including the residue endpoints (STDIR and HR) for barley grain.

the residue (endpoints (STONR and HR) for barley grain.



Сгор	Region/Indoor (a)	Trial results relevant to the critical GAP	MRL calcula- tion (d)	STMR (b)	HR O° (c) C C C C C C C C C C C C C C C C C C C
	NEU	12 × <0.01	0.01	< 0.01	
Grain	SEU	11 × <0.010; 0.042	<u>\$\$.05</u>	<u>&lt;0.01</u>	- <u>0.042</u>
	N+SEU	23 × <0.01; 0.042	<b>©0.05</b>	<0001	0.042 ⁰
	NEU	0.054; 0.071; 0.12; 0.19; 0.38; 0.40; 0.82; 0.94; 1.5; 1.7; 3.3; 3.6	) - &	×0.61	
Straw	SEU	0.22; 0.33; 0.41; 0.87; 13; 1.4; 1.6; 1.8; 1.9; 4 1.9; 2.3; 2.4		¥.3°	
	N+SEU	0.054; 0.071; 0.12; 0.19; 0.38; 0(40; 0.82; 0.94; 1.5; 1.7; 3:3; 3:6; 0.22; 9:33; 0.41; 0.87; 1.3; 1.4; 1.6; 1.8; 9; 1.9; 2.3; 2		0.29	3.6 5 5 5 5 5 6 5 6 5 6 5 6 5 6 5 6 5 6 5

(a) NEU or SEU for northern or southern **outdoor trais** in Exprember states (N*SEU if tooh zones) indoor & glasshouse/protected crops (b) STMR: Supervised Trials Median Residue

(d) using OECD MRL calculator * code according to Annex 1 of Regulation @6/2005

An <u>MRL of 0.05 mg/kg</u> is therefore proposed for <u>wheat grain</u> (code 0500090) based on southern European residue data

An extrapolation of this <u>MRL of 005 mg/kg</u> to <u>the grain</u> (code 0500070) is requested, as permitted by the Guidance document SANCO 7525071/95 Rev. 102 dated of 23 September 2016 (Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs).

### Other crops

Residues of BCS-CN82460 parent compound in rotational crops are expected to be <0.01 mg/kg. Thus, for all other crops that barley, oat, wheat type, spelt and triticale, an MRL of 0.01 mg/kg (at the LOQ level of the enforcement method) appropried.

# ► Apimal matrices

The proposed residue definition for MIRL setting in animal commodities in the EU is isoflucypram parent only.



Based on the laying hen feeding study (see **Construction**); **Construction**, E.; 2017; M-605909-01-1; KCA 6.4.1), at the feeding dose of 0.03 mg/kg bw/d, residues of isoflucypram (BCS-CN88460) parent compound were found <0.01 mg/kg (LOQ) in eggs and poultry tissues. Considering the maximum European anticipated dietary burden of 0.029 mg/kg bw/d for laying poultry (see Table 6.4-2), it is concluded that residues of parent compound are expected to be <LOQ in eggs and poultry tissues.

Therefore the European MRLs in animal commodities resulting from exposure of livestock to seed crops treated with BCS-CN88460 are proposed in Table 6.7.2-3.

	nounces	¥.	Đ.	0,	9 4 4
Commodities	Code No. **	MRL prôposal	STMR Qa)	اللہ اللہ اللہ (b) ک	
Tissues from swine, bovine, sheep, goat, equine, poultry and other farmed terrestrial animals	1010000	\$0.01 *		9 50,01 8 50,01	
Milk	1020000	~~Ø.005*\$	₹0.005	\$ <0.005	
Birds'eggs	1030000		<001		
			$\sim$ 0		<u>v</u> –

Ö

* at the limit of quantification of the enforcement method &

** code according to Annex 1 of Regulation 396/2005

(a) STMR: Supervised Trials Median Residue

(b) **HR**: Highest residue

# CA 6.7.3 Proposed maximum residue levels (MRLs) and fustification of the acceptability of the levels proposed for imported products (import toferance)

Since imported products are not considered in this dossier submission MRL settings for import tolerances are not required.

# CA 6.8 Proposed Safety Intervals

Pre-harvest intervals are not proposed since the application timing is defined by the crop growth stage (latest BBCH 61 for barley & outs and latest BBCH 69 for wheat, rye, spelt and triticale).

Further safety intervals are not necessary.

# CA 6.9 Estimation of the potential and actual exposure through diet and other

In order to evaluate the potential chronic and acute exposures to BCS-CN88460 residues through the diet, calculations were done using the EFSA PRIMo model (revision 2) and the following toxicological endpoints.

Table 6.9.1:	Toxicological	endpoints for	BCS-CN88460
	~ ¥ ~		

Active Substance	Toxicological End-Point	Proposed Value (mg/kg bw/day)
Isoflucypram	Acceptable Daily Intake (ADI)	0.063
(BCS-CN88460)	Acute Reference Dose (ARfD)	1.25



### Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

### TMDI

The TMDI calculations were conducted based on the residue values presented in Table 6.9-2.

Table 6.9- 2:Input va	lues for the chroni	ic consumer risk assessment (TMDA)
	Chronic risk a	assessment
Commodity	Input value (mg/kg)	Assessment (TMD4)
Barley grain	0.05	Proposed MRL
Oat grain	0.05	Proposed MRL
Wheat grain	0.05	
Rye grain	0.05	
All other crops	0.01 *	Propesed MRD OF STORE STORES
Milks and cream	0.005 *	Proposed MBL = $LQQ$ of the method for the
Bird's Eggs	0.01	Proposed MBL = LOO of the method for the parent compound
Meat, preparation of meat, offals,	0,01 * 2	
* At the limit of quantification	of the method S	

#### Input values for the chronic consumer risk asso Table ( 0 ).

As shown in Table 69-4, Osing the EFSA PROMo model (nevision 2), the highest TMDI was calculated for the WHO Cluster Diet@B" and represents 1.3% of the ADI with the highest contributors being wheat, we getables and fruits.

The TMDI calculations were far below the ADI. Therefore, a tong-term intake of residues of BCS-CN88460 is utilikely to present a public block and the state of t

EDI Since the TMDI calculations demonstrate a late margin of safety the IEDI was not used for refinement.



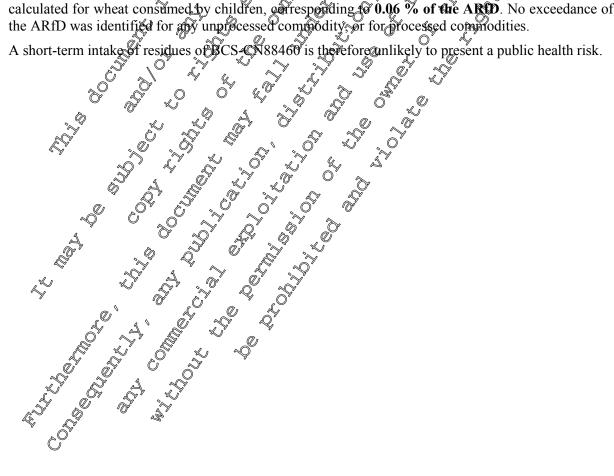
### Acute Reference Dose (ARfD) and Dietary Exposure Calculation

The IESTI/NESTI calculations were conducted based on the residue values presented in Table 6.9 3. Proposed MRLs were used as input values for cereals in a very conservative approach since usedally median residues can be applied for such blended commodities.

Table 0.3- 5. Input v	alues for the acute	
	Acute risk ass	essment
Commodity	Input value (mg/kg)	consumer risk assessment     o       vessment     o       Comment     o       Proposed MRL     o       O     o       Proposed MRL     o       O     o       O     o       V     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o       O     o <tr< th=""></tr<>
Barley grain	0.05	Proposed MRL Q o L L
Oat grain	0.05	Proposed MRL
Wheat grain	0.05	Proposed MRL
Rye grain	0.05	Propased Mat of of of of a
Milks and cream	0.005	
Bird's Eggs	0.01	
Meat, preparation of meat, offals,	0.00	Proposed MRC = LOG of the method for the parent compound

consumer risk assessment

As shown in Table 6.9-4, using the FSA FRIMO model (revision 2), the highest IESTI was calculated for wheat consumed by children, corresponding to 0.06 % of the ARCD. No exceedance of the ARfD was identified for any unprocessed compodity or for processed compodities.



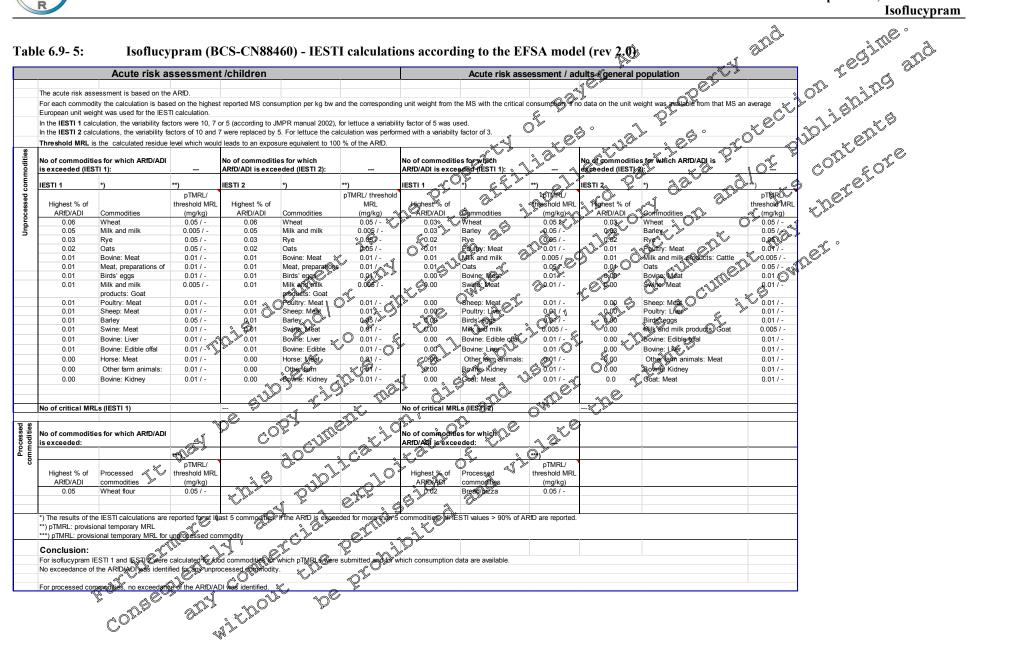


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				Born	Prepa	workbook for refined	ST SD
			isoflucypram	E.		eworkbook for refined calculations	d trion regime of trion trion treptor trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice trice
		Status of the active substance: LOQ (mg/kg bw):	Code no. proposed LOQ				
			Toxicological end points		AU LINE		
		ADI (mg/kg bw/day):	0.063 ARfD (mg/kg b				- CO* 60 [%]
		Source of ADI: Year of evaluation:	isoflucypram Source of ARC	isoftuexpram	~ °C°	20 V 01	
choice of toxicologi	cal reference values.		Isoflucypram Source of Art Year of worked April 2006. For each pesticide/commodity Chronic Kisk assessment MDI (range) i6% of ADI minimum Daximum		~ ð 1.	Open Street	L'E CI
assessment has b IRLs have been sub	een performed on the basis of the omitted to EFSA in September 2	e MRLs collected from Member States in 006.	April 2006. For each pestacide/commodity	the mignest national and the was identified the	(Noposed temporary r	ARL = pIMRL).	No. No.
			Chronic hisk assessmen	it G V		10° 0°	Real of a
					10		
				The Street of the	p 207	Che K	, er
		No of diets exceeding ADI:				ADILLE AD	AND
Highest calculated TMDI values in %		Highest contributor	2nd contributo MS diet	r to OF Sommodity / OF group of commodities S VEGETABLES	MS die (in % of ADI)	Commoditud TIDE	MIRLs at LOQ
of ADI	MS Diet	to MS diet conversely / (in % of ADI) Coroup of com	impolities (in % of Apr	group of commodities	(in % of ADI)		(in % of ADI)
1.3	WHO Cluster diet B	0.7 () Wheat		VECETABLIES	s (201	FREID (PRESH OR FROZEN)	
1.2	DK child	0.0 Wheat	2 0 0 A	Viteat	0.1	VEGETABLES	
1.2	UK Toddler	0.4 SUGARPLA		Wheat OF	0.2	Milk and cream,	
1.1	NL child	0.4 Oveat		V/host		VEGEABLES	
1.1	DE child FR toddler	0.4 FRUIT (FRE	et or frozen	VEODBLES	X 0,4	Wheat	+
1.0	UK Infant	0.3 Milkand crea		Wheat Q.		SOGAR PLANTS	
0.9	FR infant	0.3 AFGETABLE		Vicet VERUIT (FRESH GB) FROZEN)		Milk and cream.	
0.9	WHO cluster diet D	0.5 Wheat	10 A 816	VEGETABLES	656	FRUIT (FRESH OR FROZEN)	
0.8	WHO cluster diet E	0.3 Wheat 🐒 🖉		VEGETABLES FRONTRESH OR FROZEN) ØK and cream	0.1	FRUIT (FRESH OR FROZEN)	
0.8	IE adult	Wheat Wheat		FROM FRESH OR FROZEN)	0.9 0.1 0.1	VEGETABLES	
0.7	ES child	Q.4 Wheat	0.1	Book and cream, N S	0.1	FRUIT (FRESH OR FROZEN)	
0.7	SE general population 90th pe	rcentile 0.3 //heat	1 0.2 The 1 0.2 The	VEGETABLES	0.1	Milk and cream,	
0.7	WHO Cluster diet F	rcentile 0.3 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	6×. 10×. 00×	VEGETA BARES	0.1	FRUIT (FRESH OR FROZEN)	
0.7	IT kids/toddler	Wheat The	××××××××××××××××××××××××××××××××××××××		0.1	FRUIT (FRESH OR FROZEN)	
0.6	WHO regional European diet	0.2 Wheat 0.3 Deat 0.3 Wheat			0.1	Meat, preparations of meat,	
0.6	PT General population	0.3 Wheat		FRUIT (FRESHOR FROZEN) FRUIT (FRESHOR FROZEN) VEGETABLES	0.1	VEGETABLES VEGETABLES	+
0.5		0.2 Wheat		VEGETARIES	0.1	FRUIT (FRESH OR FROZEN)	+
0.5	NL general	0.2 Wheat		FROM (FRESH OR FROZEN)	0.1	VEGETABLES	1
0.5	IT adult	20.2 Wheat 0.3 Wheat	1 Q 1 1 0.1	(NEGETABLES	0.0	FRUIT (FRESH OR FROZEN)	
0.4	UK vegetarian	0.2 Wheat	0,1	SUGAR PLANTS	0.1	VEGETABLES	
0.4	DK adult	0.2 Wheat	y jor a	VEGETABLES	0.1	Rye	
0.4	UK Adult	B B Wheat		SUGAR PLANTS	0.0	VEGETABLES	
0.4	LT adult	€ Get Rige O	~~~~ s ~~ 0.1	Wheat	0.1	VEGETABLES	
0.3	FI adult	0.1 VegetAble	0.1	Rye	0.0	Milk and cream,	<b></b>
0.2	PL general population	0.1 VEGETABLE	<u> </u>	FRUIT (FRESH OR FROZEN)	0.0	PULSES, DRY	<u>+</u>
			· · · · · · · · · · · · · · · · · · ·				
Conclusion:	H. K. ST	TMDI), based on pTMRLs were below the likely to present a public health concern	~ ·				
The estimated The	oretical Maximum Daily fighters	TMDI), based on pTMRLs were below the	ADI. 🔿 🎾				
A long-term intake	on relations of isofly of pram is u	nlikely to present a public health concern,	» ^V				



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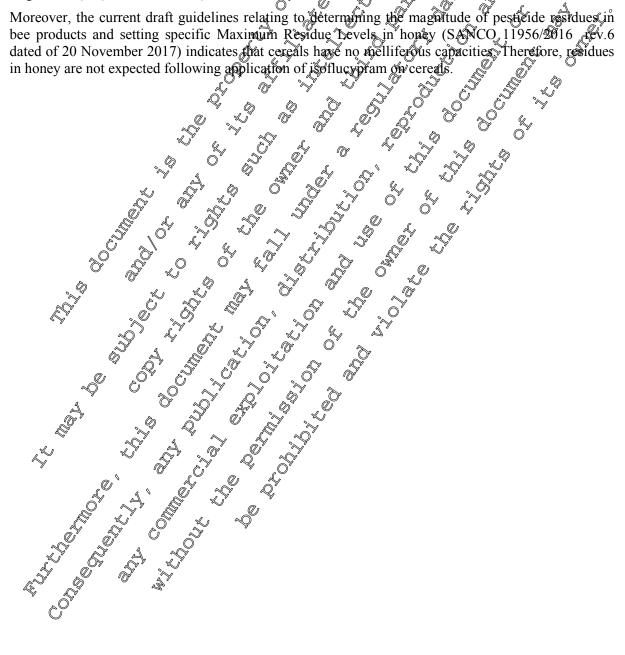


CA 6.10 Other studies No further residue studies were deemed necessary to support the registration of the active substance

### CA 6.10.1 Effect on the residue level in pollen and bee products

No residue study in pollen and bee products was conducted. Currently, no test method of Guidance document is available for conducting residue studies in pollen or be products. In these cases, waiving of this particular data requirement is considered acceptable according to the "Godance" document for applicants on preparing dossiers for the approval of a chemical new active substance and the renewal of approval of the chemical active substance according to Regulation (EU) No 28372013 and Regulation (EU) No 284/2013" (SANCO/101%1/2013 gev.2 of 2-May-2013).

Moreover, the current draft guidelines relating to determining the magnitude of pesticide residuestin bee products and setting specific Maximum Residue Devels in honey (SANCO 11956/2016 ev.6





•	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)	<u>~</u>	in:
		isoflucypram	N-(5-chloro-2-	Compound found in: animal 4 rat (faeces) live kidney); hen (eggs) fat); goat (milk, muscle, dat live
	F F H ₃ C CH ₃	BCS-CN88460	isopropylbenzyl)-	(faeces)
	$-\gamma$	CAS: 1255734-28-1	N-cyclopropyl-3- (difluoromethyl)-5-	kidney)
		ISY 🖉	fluoro, I-methyl-	then (eggs
	N N N N	LYAM823-12	1H gyrazole-4-	muscledeg,
		smiles code:	carbóxamide	fat); eoat
	$\downarrow \qquad F \bigtriangleup \qquad \downarrow$	C1(C(E)F)C(C(=O)	[QUPAC] .	muscle
	H ₃ C	$N(CCC) \stackrel{=}{=} C(C(C)C)C_{\wedge}$	1H-pyražole-4-	O gat, liver
		$C(C) = C(FON(C)N \neq 0)$	Carboxamige, N-	kidney
			methyle of	faeces)
	C19 H21 Cl F3 N3 O		Q ethyl)phenyl]methy	O gedible
	[399] nominal mass		1]-Mcyclopropyl-3-	parts Q
	399.84 g/mol (molecular weight)		(chiluoromythyl)->	viscera)
			CAL ~	Dant: soybean
				Gorage,
		\$ \$ S		hay, straw, seed);
				wheat
				(hay,
				straw, grain);
	A A	S O S		CRC
				(wheat
		Ĵ J "	0.4	forage,
	5 , 0 '2 4	~~~~?~~ <i>\</i>		Swiss chard,
				turnip
				leaves);
		N O .	N.	oilseed
			$\sim$	rape (intermedia
				te harvest,
			1	mature
				plants,
				seeds), tomatoes
				soil: aerobic &
	$A$ $\circ$ $\circ$ $\circ$			anaerobic,
				field
		, °°,		dissipation, photolysis
4		S'		water: hydrolysis,
		€		photolysis,
				water-
				sediment
	C19 H21 CI F3 N3 O [399] nominal mass 399.84 g/mol (molecular weight)			
	Ly Or Ly Ly			
p. R	y Q 'Q' LY			

## Isoflucypram: substances and metabolites; structures, codes, synonyms



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)	-	in:
M01	Empirical formula / nominal mass $F \rightarrow F \rightarrow H_3C \rightarrow OH$ $N \rightarrow F \rightarrow C \rightarrow CI$		N-[5-chloro-2-(1- hydroxypropan-2- yl)benzyl]-N- cyclopropyl-3- (difluorometh))-5- fluoro-1-methyl-1H- pyrazole	in: animal: rat (fae c8); hey (eggs fat, liver fat, liver fa
M02		Brohands Os	Released and the second	seqt: - O vater: animal: rat (faeces); goat (milk, muscle, fat, liver, kidney,
M03	H,C F, C19 H21 CI F253 02 4 [415] C19 H21 CI F253 02 4 C19 H21 CI F253 02 4 (415) C19 H21 CI F253 02 4 C19 H21 CI F253 02 4	BCS-CN88400-1,2 BCS-CN88400-1,2	pyrazole-4 earboxamide [IUPAC] N-[5cchloro-2-(1,2-	faeces, urine) plant: - soil: - water: - animal: hen
	$H_3C$ $F$		dilyaroxypropan-2- y(benzyl]-N- cyclopropyl-3- (difluoromethyl)-5- fluoro-1-methyl-1H- pyrazole-4- carboxamide [IUPAC]	(excreta) plant: - soil: - water: -
M04	[431] F O N C C C C C C C C C C C C C	RES-CN88460- Hydroxyphenyl	N-(5-chloro-4- hydroxy-2- isopropylbenzyl)-N- cyclopropyl-3- (difluoromethyl)-5- fluoro-1-methyl-1H- pyrazole-4- carboxamide <i>[IUPAC]</i>	animal: goat (urine) plant: - soil: - water: -



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M05		BCS-CN88460-	N-[5-chloro-2-(prop-	animal: rat
1105	F F CH ₃ C CH ₂	olefine	1-en-2-yl)benzyl]-N-	(factor
		ROI 2	cyclopropyl-3-	bite
			(difluoromethy) 5-	plant:
		CAS: 1471984-41-4	fluoro-1-methyf-1H-	soil 2 -
	N IIII		pyrazole-4z	water: -
		Ča	carboxannde	plant:
	F / F		[IUPAO]	
	H ₃ C	1	1H-Byrazole-4-	
	° Cl	,Ô ^Y	catboxamide, N-[[5	
			Quoro-2-(1-	4 V 4
	C19 H19 Cl F3 N3 O		methylethenyl)phenyl	
	[397]		]meihyl]-N-	
		or or so	M . 1	e 4
	4			
			ICAPA S	
107	F F H ₃ C	BCS-CN98460	NDs-chloro-2-(1- NDs-chloro-2-(1- hydroxypropan-2- yl)benzyl]-N- cyclopropyl (dtbuoromethyl)-5 Hooro-1H-pyrazol 4-carboxamide	anifali
M06	F F O H ₃ C QOH	desmethyl-	droxybronan-2	aipulai. Ta
		propanol 🗸 🔨	(VI)besz VII-N-	S (lacces,
			cyclopropyl	eggs,
	N N Q Q	ACS DESD055	(dituoromethyl)-5	muscle,
		ØCS-DC22055	ficoro-1H-pyrazo@-	fat, liver,
	$\mathbf{H} \to \mathbf{F} \longrightarrow \mathbf{F} $		4-carbowamide	excreta);
				goat (milk,
				muscle, fat, liver,
				kidney,
	C18 H19 Cl F3 N2 02 0 2			faeces,
			S. 01	
			Ŭ N	sunfish
				(edible
			s "Ø	parts,
				viscera)
			$\searrow$	plant: wheat
			0	(straw)
	$\mathbf{H} = \mathbf{F} \qquad	N & A		soil: -
				water: -
<b>M</b> 07		MOCO GNOOLOG	N-[5-chloro-2-(1,2-	animal: hen (eggs,
		desmethyl-1,0-	dihydroxypropan-2-	muscle,
		propandia	yl)benzyl]-N- cyclopropyl-3-	fat, liver,
			(difluoromethyl)-5-	excreta)
		× ~~	fluoro-1H-pyrazole-	plant: -
			4-carboxamide	soil: -
A	F H F Q	Å.	[IUPAC]	water: -
		¢		
	C18 H10Cl F3A3703			
	$F \rightarrow O \rightarrow H \rightarrow O			
	N R A N			
\$				
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ν	»Č ^y			
	$\bigcirc$			



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)	_	in:
M08	$\begin{bmatrix} F & H_3C & CH_3 \\ 0 & H_3C & CH_3 \\ 0 & H $	BCS-CN88460- desmethyl-diOH (isomers)		animal: rat (faces) plant: - soil: - wates - wates - of of of of of of of of of of of of of
	C18 H19 Cl F3 N3 O3 [417]			
M09	F F O H ₃ C O H ₃ C O H ₃ C O H ₃ C O C I C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S C I S S C I S S C I S S C I S C I S C I S C I S S C I S S C S C I S S C S C S C S S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S C S S C S S C S S S S S S S S S		[reyclopropy] {[3- difluor@nethyl)-9- fluoro_1H-pyr2col-4- y]carbonyl}amino)m/ etto[]phenyl]-2- hydroxycopanoic acid [IUDIC]	(facces, prayma, vver, kidnov bilo pant: soil:
M10	F F 5 0 0 H 5 0 0 H 5 0 0 H 5 0 0 H 5 0 0 H 5 0 0 H 5 0 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H 5 0 H	BCS-CN88460- lactic acid ROI 3 MI0	2-{4-choro-2- [(cyclopropyl{{3- (difluorom@hyl)-5-	animal: rat (faeces, plasma, liver, kidney, bile); goat (liver, kidney, faeces, urine) plant: - soil: met., aerobic water: -
M11	F CI8 P677 CI F3 N3 O3	BCS-C/988460- desmethyl- carbaxylic acid BCS-CX99799 ROI 5 M11	2-{4-chloro-2- [(cyclopropyl{[3- (difluoromethyl)-5- fluoro-1H-pyrazol-4- yl]carbonyl}amino)m ethyl]phenyl}propano ic acid [IUPAC]	animal: rat (urine, faeces, plasma, liver, kidney, bile); hen (muscle, fat, liver, excreta); goat (liver, kidney, faeces, urine) plant: - soil: met., aerobic water: -



No.	Structure	Name / Code no.	Description	Compound found
		(synonyms)		in:
M12	Empirical formula / nominal mass $F \rightarrow F \rightarrow H_3C \rightarrow OH$ $H_3C \rightarrow OH$	BCS-CN88460- carboxylic acid	2-{4-chloro-2- [(cyclopropyl{[3- (difluoromethyl)& fluoro-1-methyl)H- pyrazol-4-yl]- carbonyl}athino)- methyl]phenyl}- propandie acid [IUPQC]	animal: rat (uche, faces,
M13	N J S S		(difteoromethyl)-5- ( fluoro-1H-forazole 4-carboxamide )[IUP.46]	apimal: rat (faeces, plasma, liver, kidney); sunfish (edible parts, viscera) plant: - soil: - water: -
M14	H CI8 HI9 CIF3 N3 O [385] F F CI8 HI9 CIF3 N3 O3 CI8 HI9 CIF	BCS N88460- desmethyl- hydroxyphenyl-2- propanol	N-[5-chloro-4- hydroxy-2-(2- hydroxypropan-2- yl)benzyl]-N- cyclopropyl-3- (difluoromethyl)-5- fluoro-1H-pyrazole- 4-carboxamide [IUPAC]	animal: rat (urine, faeces, liver, bile) plant: - soil: - water: -



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M15		BCS-CN88460-	N-[5-chloro-2-(1,2-	animal: rat
	OH	desmethyl-	dihydroxypropan-2-	(factor)
	F F H ₃ C	hydroxyphenyl-	vl)-4-	
		1,2-propandiol	hydroxybenzyl	plant: -
		1,2 propulator	cyclopropyl-3-0	soil: - 🔊
			(difluoromethyl)-5-	water - 🔨 🖒
	<b>N</b> ´ }{		fluoro-11Kpyrazole-	
		<u>ک</u>	4-carboxamide	
	й у он	- The second sec	[IUPQC] @	
		L,		
	Cl	40″		
				4 4
	C18 H19 Cl F3 N3 O4		7 ° ° '	
	[433]			plant:
M16		BCS-C888460	2-14-chlog-2- Cycloptopyl{[5- fluorg-3-	animal: rat (urine, proces)
	Q ,	desmethyl-	Arcycloneonyl [5-	faseces)
		hydroxymethyl-	fluoro-3-	plant:
	OH H ₃ C	carboxylic acid	(hydroxymethyl)-1H	piant. 🐱
			pyrazol-4	soit -
	OH O H ₃ C OH		anitarbow Baming m	soft -
	N Y N Y		ethylastenvl}propano	
			ic action of the contract of t	
			IATPACIO ~O	
	Ĥ F A AT Y			фу О
		Ô O Â		
	C18 H19 CLF N3 Q4. 🔊 🔊 🤇		&, [~] , ⁶	
	C18 H19 CI F N3 Q4	BCS-CN88460- Versmethyl- hydrøxymethyl- diQH		
M17		BCS-CN88460- @/	0 9	animal: rat
	OH S HIC SCH,	desmethyl-		(faeces,
		hvdrøxvmethvl-		bile)
		diQN 💍 🔬		plant: -
			×,	1
		$\mathcal{D}^{I}$ $\mathcal{O}^{I}$ $\mathcal{O}^{I}$	Ő	soil: -
		\$ \$	Ň	water: -
		, O′ ∜` ,	0	
			7	
		o o		
	C18 H21 QI F N3. Q4 6 . 0 0			
	C18 H21 @ F N3 04 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5			
M18		BCS-C188460-	N-{5-chloro-2-[1-	animal: -
VII0	F O H ₃ C ØGlye	propanol-Glyc	(hexopyranosyloxy)p	
		propanol-Glyc	ropan-2-yl]benzyl}-	plant: wheat
		N. N	N-cyclopropyl-3-	(hay,
A		and a second sec	(difluoromethyl)-5-	straw)
	$N \rightarrow N$		fluoro-1-methyl-1H-	soil: -
		r I	pyrazole-4-	water: -
			carboxamide	
		1	[IUPAC]	
	СЭ H31 СФГ3 N3407 ~~		[ICI IC]	
	C ³³ H31 CFF3 N3 O7			
^^	C H31 CF3 N3 O7 C T1 CF3 N3 O7 C T1 CF3 N3 O7			
Le la	H ₃ C F C C C C C C C C C C C C C C C C C C			



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M19	F H ₃ C Gluc A	BCS-CN88460-	2-{4-chloro-2-	animal: rat
		propanol-GlucA	[(cyclopropyl{[3-	(faeces, o
		(isomer 1 and 2)	(difluoromethyl)	bite, goat
		· · · · · · · · · · · · · · · · · · ·	fluoro-1-methyl H-	spilk,
			pyrazol-4-	muscle
			yl]carbonyl_amino)m	ov liver v
	H ₃ C F	<i>⊳</i> ∧	ethyl]phenyl}propyl	kidney, 👋
		S S	glucopyranosiduronic	fareces,
		8	acid	garine);
	C25 H29 Cl F3 N3 O8		[ILPAC]	sunfish
	[591]	A.	$Q' \sim Q'$	(edible
			, az Qʻ	giscera)
		· ~ · · · · · · · · · · · · · · · · · ·		
				planty - 📣
			a so a	soil: - 4
	4		<u> </u>	Gwater:
M20	GhucA	BCS-CN88460-2-0	2-{ <b>4</b> -chloro- <b>2</b> [(Ocloprop)1{[3-	animal: goat
		propanol GlucA	[(Ocloprop/1{[3- (Hfluor@nethyl)] fluoroPmethyDH-	
	F H ₃ C O CH ₃ (		(chfluoromethyl)	kidney,
	F Q			acces,
		6 8 R	pyrazol-4-	" vrine)
			yllcarbon aminom	plant: - ©il: -
	N I N N N	"0" ~~	etbyl]phenyl}propan- 2-vl beta-D-	©vil: -
			glucopyranosiduronic	water: -
	H ₁ C F Log O S		acid acid	
		BY OF AT	(JUPAC)	
	C25 H29 CI F3 6 08	S' S' -	o' s'	
	C25 H29 CI F3 CO 08		L O	
M21	F C ARC & C	No an formation	&-{4-chforo-2-	animal: -
		PBCS-CN88460- propanol-GDc-MA	[(cyclopropyl{[3-	plant: wheat
			(diffuoromethyl)-5-	(hay,
	N KAL		flooro-1-methyl-1H-	(nay, straw);
		\$7. \$8	pyrazol-4-	oilseed
			yl]carbonyl}amino)m	rape
			ethyl]phenyl}propyl	(intermedia
			6-O-	te harvest,
		ž S Š	(carboxyacetyl)hexop yranoside	mature
	C28 H33 CH F3 NSO10 C			plants)
		, çi î	[IUPAC]	soil: -
				water: -
M22		BCSCN88460-2-	2-{4-chloro-2-	animal: -
	F F S A C BCH3	BCSCN88460-2- prepanol-Glyc-MA	[(cyclopropyl{[3-	plant: oilseed
A			(difluoromethyl)-5-	rape
		C	fluoro-1-methyl-1H-	(intermedia
			pyrazol-4-yl]-	te harvest,
			carbonyl}amino)-	mature
			methyl]phenyl}propa	plants)
			n-2-yl 6-O-(carboxy- acetyl)hexopyranosid	soil: -
			e acetyi)nexopyranosid	water: -
			-	
n. M	C1 C280433 C1 F3 N3 OTO (60)		[IUPAC]	
42	C280#33 Cl F3 N3 OTO			



No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M23		BCS-CN88460-	2-chloro-4-	animal: -
10125	$F $ $F $ $H_3C $ $CH_3$	hydroxyphenyl-	[(cyclopropyl{[3-	
	Υ Ϊ	Gluc-MA	(difluoromethyl)	plant: oilseed
		Gluc-MA	fluoro-1-methyl H-	rape
			pyrazol-4-yl]-	(intermedra
	N-1 L L Contra Ma		carbonyl}amino)-	te harvest,
	$H_3C$ $F$ $C$ $OGlue-MA$		methyl]-5 isopropyl-	O' matare
	ľ ³ C Ćl	ĈĄ		playats)
		A.	(carbovyacetyl)-beta-	Csoil:
	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	, r	(carboxyacetyl)-beta- D-gOcopyranoside $\ll$	water - C
	C28 H33 Cl F3 N3 O10	a y	[DPAC] o	
	[663]	A	DUPACI .	
M24	F H ₃ C CH ₃	BCS CN88460- ~	2-chlogo-4-	o ^v mataré y pitanis) wate ³ - y onimalo
	$F \sim 0$ $H_3 \sim CH_3$	hydroxyphenyl- 🔗	[(cychopropy]]3-	plant. oilsead
		Glyc-MA	(diffuoromethyl)-5	rane
			fuoro-1-thethyl-1/b-	rape (intermedia °
			Opyrazol-4-yll-	O harvest
	F O-MalonylGlycovide		carbonyl}amino)-	mature
	H ₃ C Cl		methyl]-5-isopropy	↓ plants)
			phenyl 6.04	
	64 X	BCS CN88460-	(carboxyacetyl)	(0)1: -
	C28 H33 Cl F3 N3 O10		hexopyranoside	Swater _X
	[663]		[IIIPAC] O	
	[663] $F = F = O = O = O = O = O = O = O = O =$	V. S. O		
M25	F_{-} F_{-} H_2C H_2C H_2C	BCS-@8846@-	4-chloro-2-	animal: goat
		propenol-GlucA	(cycloprop yl)[3-	(kidney,
		<i>0</i> '0'	(difleoromethyl)-5-	urine)
	N N N N		flatoro-1-methyl-1H	plant: -
	H ₃ C F C C C		pyrazol-4-	soil: -
			yl]carbonyl}amigo)m	
	H ₃ C F A CI	N N a	ethyl prop-2-	water: -
		L	en 1-yl beta D-	
			gycopyranosiduronic	
	C25 H2772 F3 NF08 0 0 4		Gicid V	
	C25 H27 F3 N508	propenoi-Giuca	[©] [IUPQC]	
M26	F F HC F	BCS-CN88460 propariol-SA	2-94-chloro-2-	animal: hen (liver,
		propariol-SA	o[(cyclopropyl{[3-	excreta)
		× 6 4	(difluoromethyl)-5-	plant: -
			fluoro-1-methyl-1H-	soil: -
	I VI SIAL S V.		pyrazol-4-	
			yl]carbonyl}amino)m	water: -
			ethyl]phenyl}propyl	
			hydrogen sulfate	
		Q* _Q	[IUPAC]	
	CIQUIZI CI F3 N3 @5 S 🖉 🖉			
		~0″		
M27		BCS-CN88460-1,2-		animal: hen
	F F H ₃ Q	Oropandiol-SA		(excreta)
		Ĩ		plant: -
	N D N ISI N .			soil: -
				water: -
	TAL OT S			
4				
~	VICTY 1678/1CTE39/13 (06:337	1		
Br.				



Empirical formula / nominal mass (synonyms) in: 128 $I = I = I = I = I = I = I = I = I = I =$	(http://
$\begin{bmatrix} 28 \\ F \\ N \\ H_{3}C \\ F \\ H_{4}C \\ C \\$	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	
GlucA GluCA GluCA GluCA GluCA GluCA GluCA GluCA GluCA GluCA Gl	
$ \begin{array}{ c c } \hline \\ \hline $	
$\begin{bmatrix} \mathbf{N}_{\mathbf{N}} & \mathbf{N}_{\mathbf{N}} & \mathbf{N}_{\mathbf{N}} \\ \mathbf{H}_{\mathbf{N}} & \mathbf{F} & \mathbf{C}_{\mathbf{I}} \end{bmatrix} \begin{bmatrix} \mathbf{N}_{\mathbf{N}} & \mathbf{V}_{\mathbf{N}} \\ \mathbf{V}_{\mathbf{N}} & \mathbf{V}_{\mathbf{N}} \\ \mathbf{V}_{\mathbf{N}} & V$	
	S O
	j d
C25 H27 Cl F3 N3 O9	Ĩ
$\begin{array}{c} C25 H27 Cl F3 N3 O9 \\ \hline [605] \end{array}$	<u> </u>
$\begin{bmatrix} 129 \\ F \\ F \\ O \end{bmatrix} \begin{bmatrix} F \\ G \\ H_3C \\ C \\ CH_3 \\ OH \end{bmatrix} \begin{bmatrix} BCS-CN88460 \\ C \\ OH \\ CHucA \\ C \\ CHucA \\ C \\ $	ces,
$\begin{array}{c c} \mathbf{P} & \mathbf{O} \\ \mathbf{P} & \mathbf{O} \\ \mathbf{H} & \mathbf{H} \\ \mathbf{H} \\ \mathbf{H} & \mathbf{H} \\ $) s
Plant:	
$ \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1$	je j
H,C F C C Cater: 6	9
F O OH OH OH OH (isomer 1 and 2) H, C C1 D OF OF OH	
C25 H29 CI F3 N3 O9	
C25 H29 Cl F3 N3 O9	
$\begin{array}{c} C25 H27 Cl F3 N3 O9 \\ [605] \hline \\ 129 \hline \\ \hline $	
$\mathbf{F} = \mathbf{O} \qquad \mathbf{H} \mathbf{C} \qquad \mathbf{C} \mathbf{H}_{3} \qquad \mathbf{H} \mathbf{C} \qquad \mathbf{C} \mathbf{H}_{3} \qquad \mathbf{H} \mathbf{C} \qquad \mathbf{C} \mathbf{H}_{3} \qquad \mathbf{H} \mathbf{C} \qquad \mathbf{C} \mathbf{H} \mathbf{H} \mathbf{C} \qquad \mathbf{C} \mathbf{H} \mathbf{H} \mathbf{H} \mathbf{H} \mathbf{H} \mathbf{H} \mathbf{H} H$	eces,
F o hor GlacA or hor hor bild N of the chiral of the chir	*)
soil: -	
H,C O O O Water: -	
C2\$\$H27 CI F3 N3 68 65 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	
H,C OCI Water: - H,C OCI H,C	
$[31] \mathbf{F} \mathbf{F} \mathbf{F} \mathbf{F} \mathbf{F} \mathbf{F} \mathbf{F} \mathbf{F}$	eces,
propanol-GlucA (difluoromethyl)-5-	
(isomer 1 and 2) fluoro-1H-pyrazol-4- sun	nfish
N yl]carbonyl}amino)m (ed	ible
ethyl]phenyl}propyl par	ts, cera)
🛛 🖌 🖓 👘 🖤 🖓 🛸 👘 I gluconvranosiduronic 👘 viso	
F C C C C C C C C C C	
glucopyranosiduronic viso acid [IUPAC] soil: -	
F 0 1/2 </td <td></td>	
Image: Classic state Image: Classic state <td></td>	
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F F <td></td>	
Image: Classic state F Image: Classic state glucopyranosiduronic acid plant: - Image: Classic state F Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic state Image: Classic state plant: - Image: Classic state Image: Classic	
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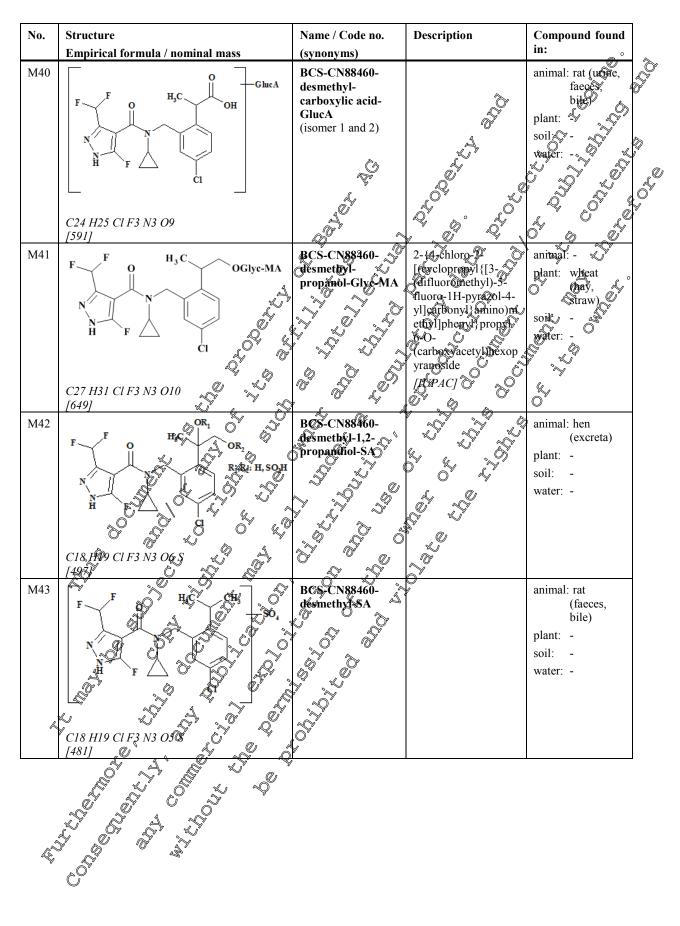


No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M32	$\begin{bmatrix} F & H_3C & CH_3 \\ & & \\ & & \\ & & \\ & & \\ & & \\ & H & F \\ & & $	BCS-CN88460- desmethyl-OH- GlucA (isomer 1 to 2)		animal: rat (utbre, faeces, bits) plant: soil: water:
	C24 H27 Cl F3 N3 O8 [577]			
M33	F O H ₃ C CH ₃ OH OH OH G bret H F Cl	BCS-CN88460- desmether diOH- Gluc A (isomer 1 to 6)		soil: -
	C24 H27 Cl F3 N3 O9			
M34	F = F = O + O + O + O + O + O + O + O + O + O	Bos-CN88460- Acsmethyl-triOH- GlucA		water: -
M35	C224 H27 CI F3 N3 QF0 F GincA C24 H27 CF3 N3 Q7 C24 H27 CF3 N3 Q7 C24 H27 CF3 N3 Q7 C24 H27 CF3 N3 Q7 C24 H27 CF3 N3 Q7 C4 C4 C24 H27 CF3 N3 Q7 C4 C4 C4 C4 C4 C4 C4 C4 C4 C4	BCS-CN88460- desmethol-GlucA (isomer 1 and 2) (isomer 1) (isomer 1) (isom	N-(5-chloro-2-iso- propylbenzyl)-N- cyclopropyl-3- (difluoromethyl)-5- fluoro-1-(beta-D- glucopyranuronosyl)- 1H-pyrazole-4- carboxamide [IUPAC]	animal: rat (bile); sunfish (edible parts, viscera) plant: - soil: - water: -
les and a second		1	1	



No.	Structure	Name / Code no.	Description	Compound found
1 10.	Empirical formula / nominal mass	(synonyms)	2000 prion	in:
M36		BCS-CN88460-	N-[5-chloro-2-(1,2-	animal: hen
10130	F H ₃ C	desmethyl-1,2-	dihydroxypropan-2-	(muscle
	F O OH	propandiol-N-	yl)benzyl]-N-	leg, hver,
		GlucA	cyclopropyl-3-	(xcreta)
			(difluoromethy)-5-	plant
			fluoro-1-	
		(CA	(glucopyranuronosyl) -1H-pyrgzole-4-	soi? - 6
	ci	- The second sec	carboxamide	
		L	[Il@PAC]	
	C24 H27 Cl F3 N3 O9	4 ⁰		
	[593]			
M37	F H ₃ C	BCS-CN88460-	N-[5-shloro-2-(1-	animal hen (eggs,
		desmeth 2	hydroxypropan-2-	muscle leg,
		propanol-N-GłucA	Abenzy YON-	livter,
			Cyclopropyl-3-	O (Socreta)
			(difluoromethy)-5-	plant: -
			(glucopyranuronogyl)	sout - O
			H-pyrazole-4	Water:
			carboxamide	Chater:
	C24 H27 Cl F3 N3 O8		[III]PAC] O	×
		O A L		Sec. 1
M38		BC&/CN88460-		animal: hen (liver,
1110 0	F F O B H3G G	desmethyl-2-	N-[5-cploro-242- hydroxypropan-2-	excreta)
		propanol N-GlucA	yi)oenzyig-iv-	plant: -
			cyclopropyl-3-	soil: -
	N IS NO IS IC		O(difluoromethyl) 5- fluoro-1-	water: -
	N		(glucopyraturonosyl)	Water.
	GlucA & F		-H-pyrazole-4-	
			Carboxamide	
			[IUPAC]	
	C244P7 CIF3 N3 Of	ð ^v	~ O Š	
	C244527 CI F3 N3 OS		0 ^Y	
M39		BCS-CN88460-	/	animal: rat (bile)
		desmethol-oxo-		plant: -
				soil: -
		, Ö ^v Öv		water: -
		an a		Water.
	F A S A .	Q [*] Q		
A		S.		
	$\begin{bmatrix} C24H25 CIF3 N3 O8''O' & Cj^{*} & \downarrow \\ I5751 & a_{1} & a_{2} & a_{3} & a_{4} & a_{5}			
	$C24AH27 CI F3 N3 OK F \rightarrow 0	<u>,</u>		
n P	Y 6 O' X			
NG.	A A			
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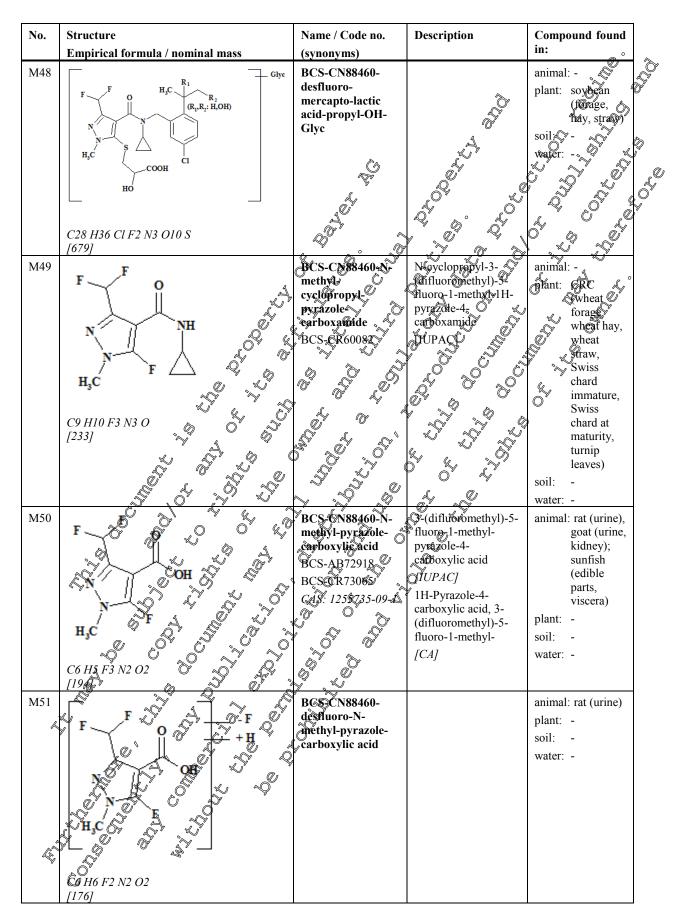




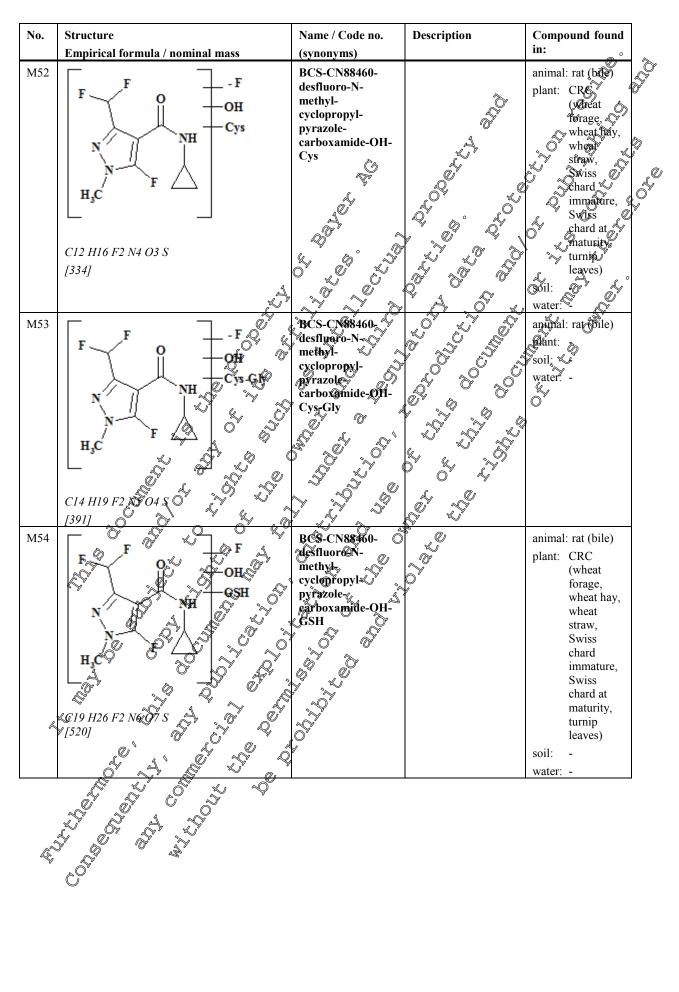


No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)		in:
M44	$F \xrightarrow{F}_{hGSH} H_3C \xrightarrow{CH_3}_{C1}$	BCS-CN88460- desfluoro- homoGSH	gamma-glutamyl-S- {4-[(5-chloro-2- isopropylbenzyl)(cycl opropyl)carbantov]]- 3-(difluoromethyl)-1- methyl-1H-ftyrazol- 5-yl}cystsunyl-beta- alaninov [IUPQC]	animal: -
M45	C30 H39 Cl F2 N6 O7 S [700]	00 ⁰ 000 000 000 000 000 000 000	Ne (coarbourgenetul)	
M143	C25 H29 CI F2 N4 O6 SQ	desflition - CysellA	3 Gifluoronethyl) hethyl-U-pyrach- 5-yl) sylcine [IUDAC]	animal: - Diant: Oybean (Forage hay straw) solt Svater: (
M46		BCSON88460		animal: -
	C22 H2OCI F2 NO 05 S			
M47	[517] F F H COO COO	BCS-CN88460- destruoro- meycapto-lactic Seld-Glyc	3-({4-[(5-chloro-2- isopropylbenzyl)(cycl opropyl)carbamoyl]- 3-(difluoromethyl)-1- methyl-1H-pyrazol- 5-yl}sulfanyl)-2- (hexopyranosyloxy)p ropanoic acid <i>[IUPAC]</i>	animal: - plant: soybean (forage, hay, straw) soil: - water: -

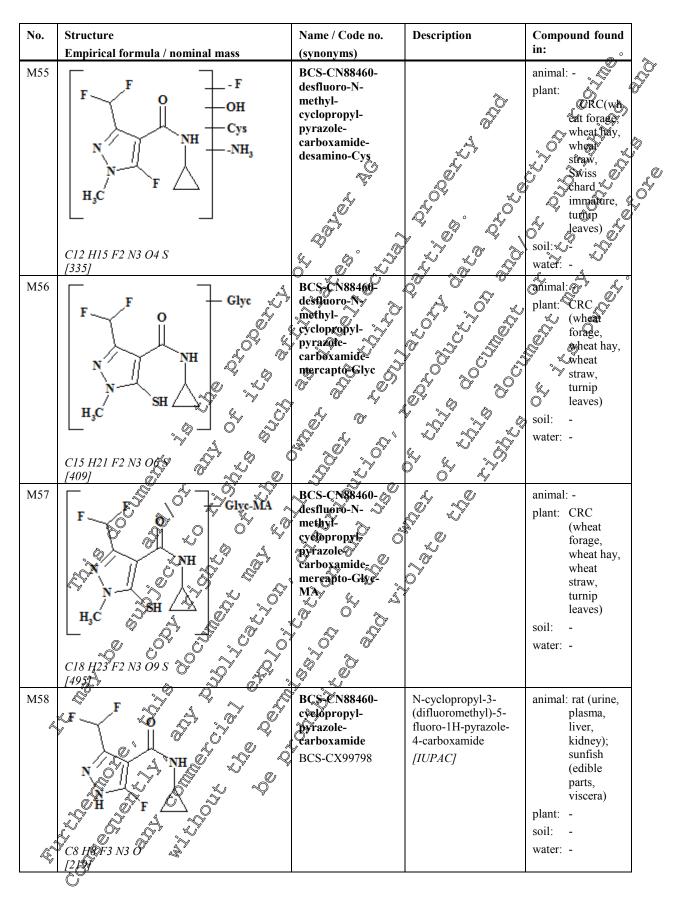




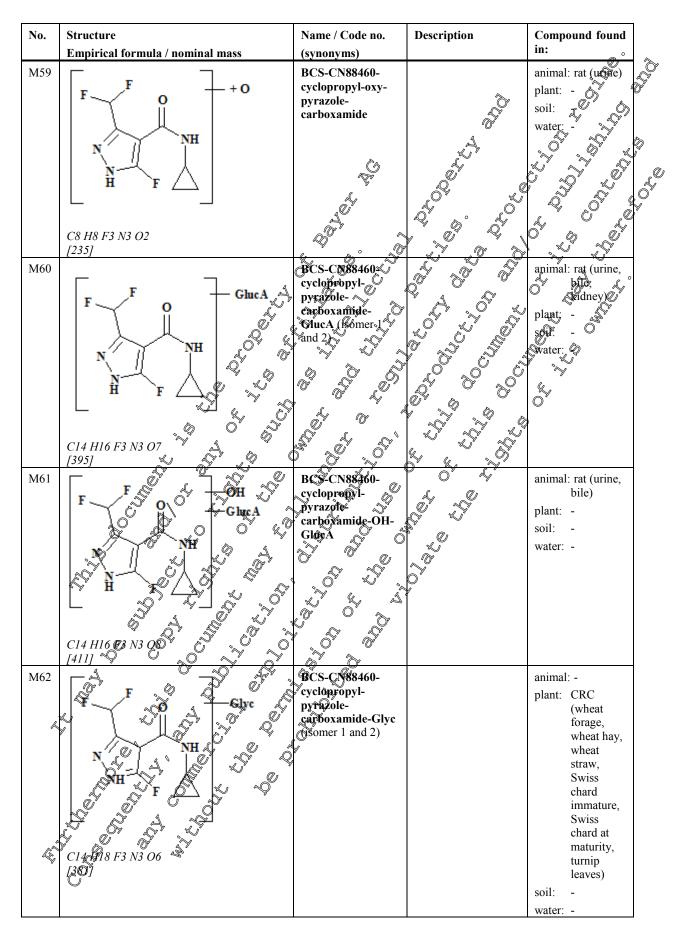














No.	Structure	Name / Code no.	Description	Compound found
	Empirical formula / nominal mass	(synonyms)	Ĩ	in:
M63	F F O	BCS-CN88460- pyrazole- carboxylic acid	3-(difluoromethyl)-5- fluoro-1H-pyrazole- 4-carboxylic acid [IUPAC]	animal: rat (utbre, faeces, kieney, kure,
	N OH H F			plant $ +$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
	C5 H3 F3 N2 O2 [180]			
M64	F O NH ₂	BCS-CN88460-	3-(difluoronethyl).	animăl: rat (urine) Stant:
	N H H K K H F C5 H4 F3 N3 O	BCS-CN88460-2 pyrazole-amide	Q-carboxamide [IUFAC] O + + + + + + + + + + + + + + + + + + +	
M65		Bes-CN88460- Ayrazole Carbox Dic acie Ala		animal: rat (urine, bile) plant: - soil: - water: -
	HO 10 10 10 10 10 10 10 10 10 10 10 10 10			
M66		BCS-CN88460 cyclopropyl- pyrazole- carboxaniude-Ala	3-[4- (cyclopropylcarbamo yl)-3- (difluoromethyl)-5- fluoro-1H-pyrazol-1- yl]alanine <i>[IUPAC]</i>	animal: - plant: CRC(wh eat forage, wheat hay, wheat straw,
Å	H C5 H4 F3 N3 O [179] F O H C5 H4 F3 N3 O [179] F O C N H C C C C C C C C C C C C C		-	wheat grain, Swiss chard immature, Swiss chard at maturity,
A. J.	C11493 F3 N4 O3			turnip leaves) soil: - water: -



