Cyprodinil

NOTIFICATION OF AN ACTIVE SUBSTANCE UNDER COMMISSION REGULATION (EU) 844/2012

DOCUMENT M-CA, Section 6 Supplement

RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Version history[1]

Date	Data points containing amendments or additions and brief description	Document identifier and version number
20 May 2016	Amended in response to questions from the RMS: CA 6.1, 6.2.5, 6.3.1, 6.3.2, 6.4.1, 6.4.4, 6.5.3, 6.6.2 (All changes highlighted in yellow).	CGA219417_11529 8 October 2105 updated 20/5/16
31 March 2017	Inclusion of new report details in CA 6.6.2. (All changes highlighted in green)	CGA219417_11529 8 October 2105 updated 20/5/16, 31/3/17
31 May 2017	Inclusion of two additional storage stability studies in CA 6.1. (All changes highlighted in green)	CGA219417_11529 8 October 2105 updated 20/5/16, 31/3/17, 31/5/17

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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

This document supports the application for renewal of the regulatory approval of cyprodinil under Commission Implementing Regulation (EU) 844/2012 of 18 September 2012. This document reviews the residues in or on treated products, food and feed, including additional data and risk assessments, for cyprodinil.

Cyprodinil was included into Annex I of Council Directive 91/414/EEC (Commission Directive 2006/64/CE of 18 July 2006). This active substance is an approved active substance under Regulation (EC) 1107/2009 (repealing Commission Directive 91/414/EEC) as specified in Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011.

In accordance with Commission Implementing Regulation (EU) 844/2012, this document summarises new information which are relevant for the renewal of the approval of cyprodinil under Regulation (EC) 1107/2009. Where appropriate this document refers to the Commission Implementing Regulation (EU) No. 540/2011 for cyprodinil and to the EFSA report for cyprodinil (EFSA Scientific Report (2005) 51, 1-78), and in particular the endpoints provided in Appendices I and II thereof.

This document covers data and risk assessments which were not part of the original dossier and which are necessary to reflect changes:

- In requirements under Commission Regulation (EU) No 283/2013, and the associated Annex, which repeals Commission Regulation (EU) No 544/2011 which, under Regulation (EC) 1107/2009, replaced the requirements of Annex II to Directive 91/414/EEC
- In scientific and technical knowledge since the approval or last renewal of the approval
- To representative uses

Where the conclusions of the EU review had specific areas of concern on cyprodinil, new data and/or reviews and/or risk assessments have been provided. Where additional and/or new data on cyprodinil are provided, a justification has been included. Also a justification has been given if new data are required but none were provided.

Details of the literature search undertaken can be found in M-CA Section 9. If a relevant scientifically peer-reviewed open literature reference has been identified for cyprodinil or its major metabolites, it has been discussed within the relevant data point.

CA 6.1 Storage stability of Residues

EU documents: France, 2010, France, 2005

Stability of residues during storage of samples

The storage stability of cyprodinil residues in animal and plant products was evaluated under the peer review of Directive 91/414/EEC. The studies are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.7, November 2003**) and addendum (**Addendum to Volumes 3 – Annex B.7 and B.9 (post annex 1 inclusion), Section B.7.5.4, March 2010**).

Studies previously evaluated are summarised in Table 6.1.1. Reports were submitted previously for Annex I listing and are not presented in full in this dossier.

Table 6.1-1: Summary of stability data for cyprodinil

Commodity Category[1]	Commodity	Maximum Storage Period	Report Reference	Source
EU Reviewed Data				
High Water Content	Peach Fruit	26	104/92 ABR-97114	France, 2005
	Apple Fruit	26	104/92 ABR-97114	France, 2005
	Apple Pomace	26	ABR-97114	France, 2005
High Starch Content	Wheat ears	24	104/92 ABR-97114	France, 2005
	Potato	24	104/92 ABR-97114	France, 2005
High Acid Content	Grapes Berries	24	104/92	France, 2005
	Strawberries	24	104/92	France, 2005
High Oil Content	Canola	9	-	New data
	Tree Nuts	10	-	New data
Other Products	Wine	24	104/92	France, 2005
	Wheat stalks	24	104/92 ABR-97114	France, 2005
Animal Meat	Bovine muscle	18-19 months	ABR-97115	France, 2005
Animal Liver	Bovine Liver	18-19 months	ABR-97115	France, 2005
Milk	Cow's Milk	18-19 months	ABR-97115	France, 2005
Eggs	Poultry eggs	18-19 months	ABR-97115	France, 2005

[1] Crop commodities according to the categories described in OECD 506

Storage stability of cyprodinil in crop commodities was demonstrated for a period of 26 months at -18°C in commodities with high water content (three diverse commodities), and 24 months at -18°C in commodities with high acid content (two diverse commodities) ~~and~~, high starch content (two diverse commodities), and in dry commodities, and for 9 months in high oil content (two diverse commodities). No decrease of residues was observed with time for cyprodinil in any of the matrices tested. According to the OECD guideline no. 506 on stability of pesticide residue in stored commodities "*if the stability of test substance in three diverse commodities in this category* [high water] *is confirmed, further examination with other crops that belong to this category is unnecessary*." The stability of cyprodinil in wheat ears, wheat stalks (straw) and high water content category has been demonstrated and would therefore cover the representative use on barley including grain, straw and forage. Storage stability of cyprodinil in apple fruit and pomace has been demonstrated for the representative use on apples. Stability of cyprodinil in the matrices included in this submission have therefore been adequately demonstrated.

Storage stability of cyprodinil in milk, muscle, fat, liver and eggs at -18°C or below for up to 18-19 months.

Of the commodities tested in freezer stability studies, the results in high water (apple), high protein (wheat) and the animal commodities (meat, liver, milk and eggs) are directly relevant to the representative uses in this submission.

A summary of the studies demonstrating storage stability of free and conjugated metabolite CGA304075 in animal commodities are given in Table 6.1.2. It is not clear whether the studies have been peer-reviewed in the EU. A full summary of the first study (T008935-03) is presented below. A full summary of the second study (T001784-05, a feeding study in dairy cattle) is presented in Section CA 6.4.2.

Table 6.1-2: Summary of stability data for metabolite CGA304075 (free and conjugated)

Commodity Category	Commodity	Maximum Storage Period	Report Reference	Source/ Dossier Reference
New Data				
Milk	Cow's milk	3 months	T008935-03	France, 2010 KCA 6.1/01
Animal Liver	Bovine Liver	6 months	T001784-05	France, 2010 KCA 6.4.2/01
Animal Kidney	Bovine Kidney	6 months	T001784-05	France, 2010 KCA 6.4.2/01

In the first study with CGA304075 (T008935-03), residues of free CGA304075 were found to be stable in milk but unstable in liver, kidney, muscle and fat after 3 months in frozen storage. However, in a second study (T001784-05), incurred residues of CGA304075, both free and conjugated, in samples from a three-level dairy feeding study were found to be stable in liver and kidney for at least 6 months of frozen storage.

Report:	K-CA 6.1/01. Joseph T (2006). Cyprodinil: Stability of CGA304075 in animal tissues and milk under freezer storage conditions. Syngenta Crop Protection Inc., USA. Study Dates: August 2005 – March 2006. Report No: T008935-03 (Syngenta Regulatory Document CGA304075/0005)

Report:	K-CA 6.1/02. Hamilton L, Joseph T (2006). Cyprodinil: Validation of analytical method GRM010.01A for the determination of residues of cyprodinil and its metabolite, CGA304075 in ruminant livestock commodities. Syngenta Crop Protection Inc., USA. Study Dates: June 2005 – December 2005. Report No: T001771-05 (Syngenta Regulatory Document CGA219417/1527)

Guidelines

Residue Chemistry Test Guidelines, OPPTS 860.1380. Storage Stability Data. United States Environmental Protection Agency, August 1996.

GLP

The study is fully compliant with the principles of Good Laboratory Practice standards.

EXECUTIVE SUMMARY

A study to demonstrate the stability of CGA304075 residues in animal commodities was conducted during 2005 and 2006.

The stability of CGA304075 was determined in dairy cow tissues and milk under freezer conditions (approximately –20°C) over a storage period of three months. For each of the commodities, samples were fortified with 0.50 mg/kg of CGA304075. The samples were immediately stored frozen under conditions identical to those used to store residue samples prior to analysis. After a storage interval of three months, the stored samples were analysed by Analytical Method GRM010.01A. The limit of quantification (LOQ) for the analytical method is 0.01 mg/kg for all substrates.

The study demonstrated that residues of free CGA304075 fortified into matrix are stable in milk (101% of fortification), relatively unstable in liver and fat (48% and 49% respectively), and unstable in kidney and muscle (19% and 3%) after three months in frozen storage.

Incurred residues of CGA304075 in animal tissues were stable for a period of at least 2 months as demonstrated by reanalysis of ^{14}C-residues from the goat metabolism study (Study T019338-04, see CA 6.2.3/01). The results of the reanalysis were in good agreement with the initial results, demonstrating stability of incurred CGA304075 in frozen liver for at least 2 months.

Further work was therefore conducted in the storage stability study using samples containing incurred residues of CGA304075 (not radio-labelled) obtained from a ruminant feeding study (Study T001784-05, see Section CA 6.4.2). Kidney and liver samples were re-extracted more than six months after the original analyses. Results from the re-analysis were in good agreement with the original results, further demonstrating stability of incurred residues in tissues.

CGA304075, when generated as an incurred in-vivo residue, has been shown to be stable in stored, frozen animal tissues (ruminant muscle, fat, liver and kidney) and in milk for at least two months, and for six months in liver and kidney, but free, fortified CGA304075 is not stable and declines rapidly (within 3 months).

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Test Material	CGA304075
Lot No.	WFH-IX-46
Purity	96.4%

A2. Test Commodities

The test commodities used were: muscle (round), fat (omental), liver, kidney and milk.

A3. Test Facility

This study was performed at Syngenta Crop Protection, Inc., 410 Swing Road, Post Office Box 18300, Greensboro, NC 27419, USA.

B. STUDY DESIGN AND METHODS

B1.Test Procedures

Tissue samples (10 g) were fortified with CGA304075 at 0.5 mg/kg. Immediately after fortification, sample sets were stored in a freezer at approximately -20°C until analysed. At the desired storage interval of approximately three months, a sample set of each substrate, consisting of a control sample, two freshly-fortified samples and two freezer-stored fortified samples were analysed for residues of CGA304075.

For the additional work using samples from the ruminant feeding study (Study T001784-05, see Section CA 6.4.2) kidney and liver samples were taken from the 25X feeding rate of this study and analysed for residues of CGA304075.

B2. Analytical Procedures

Method GRM010.01A was used to determine the residues of CGA304075 in the test commodities. The method includes an acid hydrolysis step and therefore determines conjugated as well as free CGA304075. The LOQ for CGA304075 in milk and tissues is 0.01 mg/kg.

II. RESULTS AND DISCUSSION

Results from the first experiment with fortified CGA304075 residues in stored animal commodities are detailed in Table 6.1-3. After storage for three months, there was no significant change in the concentration of free CGA304075 in milk, but over that storage period, losses of CGA304075 ranged from 52% in liver to 97% in muscle.

Table 6.1-4 is a summary of the results obtained by comparison of the incurred radio-labelled CGA304075 residue found in the goat metabolism study (Study T019338-04, see KCA 6.2.3/01) with results from the re-analysis of the same samples as part of a method validation study (T001771-05).

In this study (Ref: Hamilton, L. Joseph T., 2006; T001771-05) samples of liver from the metabolism study that had been subjected to acid hydrolysis were re-analysed after 2 months of frozen storage using method GRM010.01A. After 2 months (71 days) frozen storage, the residue was essentially unchanged (94% recovery).

Table 6.1-5 contains results obtained in this study from re-analysis of liver and kidney samples containing incurred residues of CGA304075 taken from the dairy cow feeding study (T001784-05, see section KCA 6.4.2/01) conducted with CGA304075 in dairy cows. After 6 months (188/189 days) frozen storage, the residues were essentially unchanged (114% recovery from liver, 113% recovery from kidney).

After 2 months (71 days) frozen storage, the residue was essentially unchanged (94% recovery).

The combined data clearly demonstrate rapid decline of CGA304075 residues in frozen storage of animal tissues when it is *fortified* into untreated samples, though it is stable in milk under these conditions. Losses up to 97% occurred after 3 months. In contrast, *incurred* residues of CGA304075 in animal commodities (liver and kidney) are stable for at least 6 months in frozen storage.

Table 6.1-3: Stability of fortified (free) CGA304075 residues in animal commodities following storage at -20ºC

Commodity	Storage Period (months)	Mean Procedural Recovery (%)[1]	Recovery from stored samples (mg/kg)			% of Fortification Level[4]
			Individual stored samples[2]		Mean[3]	
Milk	3 (92 days)	87	0.46	0.42	0.51	101
Liver	3 (90 days)	90	0.20	0.19	0.24	48
Kidney	3 (91 days)	81	0.07	0.09	0.10	19
Muscle	3 (83 days)	73	0.02	0.02	0.02	3
Fat	3 (91 days)	73	0.15	0.21	0.25	49

[1] – Mean of two recoveries.
[2]– Uncorrected for procedural recoveries.
[3] – Corrected for procedural recoveries.
[4] –Percentage of nominal fortification level (0.5 mg/kg).

Table 6.1-4: Stability of incurred (conjugated) CGA304075 residues in goat liver following storage at -20ºC

Commodity	Initial Concentration (mg/kg)[1]	Storage Period (days)	Final Concentration (mg/kg)[2]	Percentage Recovery[3]
Liver	0.37	71	0.35[4] (0.32, 0.37, 0.35)	94

[1] – Determined in the goat feeding study T019338-04 (see CA 6.2.3/01).
[2] – Determined in the validation study T001771-05 (see CA 6.1/02).
[3] – Percentage of initial concentration = (final concentration / initial concentration x 100).
[4] – Mean of three determinations (individual results in parentheses).

Table 6.1-5: Stability of incurred (conjugated) CGA304075 residues in bovine tissues and milk following storage at -20ºC

Commodity	Initial Concentration (mg/kg)[1]	Storage Period (days)	Final Concentration (mg/kg)[2]	Percentage Recovery[3]
Liver	0.07[4] (0.07, 0.07, 0.07)	188	0.08[4] (0.09, 0.08, 0.07)	114
Kidney	0.12[4] (0.12, 0.12, 0.11)	189	0.13[4] (0.11, 0.17, 0.11)	113

[1] – Determined in the cow residue-transfer study T001784-05 (see CA 6.4.2/01).and reported in Study T008935-03
[2] – Determined in this study.
[3] – Percentage of initial concentration = (final concentration / initial concentration x 100).
[4] – Mean of three determinations (individual results in parentheses).

III. CONCLUSIONS

The study demonstrated rapid decline of CGA304075 residues in frozen storage of animal tissues when it is fortified into untreated samples, though it is stable in milk under these conditions. In contrast, incurred residues of CGA304075 in animal commodities (liver and kidney) are stable for at least 6 months in frozen storage. Thus, milk and tissue samples from metabolism and feeding studies with CGA304075 may be stored deep-frozen for periods of at least 6 months.

Stability of residues in sample extracts

Procedural recoveries obtained during residue analysis demonstrate the stability of residues of cyprodinil and CGA304075 in sample extracts and fully support the residue data presented in the submission.

The stability of cyprodinil (CGA219417) stored in oily matrices has been investigated in two studies which have not previously been reviewed in the EU. A summary of the studies conducted on tree nuts and canola seed is shown below. Although the studies were conducted in North America they are submitted as supporting data to demonstrate that samples collected as part of the crop rotation study on oilseed rape were stable for the maximum storage period of 7 months and 8 days.

Report:	K-CA 6.1/03: Sagen K. (2009). Fludioxonil/Cyprodinil WG (A9219B) - Residue Levels on Canola Seed and Processed Fractions, Meal and Refined Oil, from Trials Conducted with SWITCH® 62.5 WG in Canada During 2007 (MRID 47644301) Final Report Amendment 1. Task Number: T008682-08; Report Number: CER04169/07 Syngenta File Number: A9219B_50006

Guidelines

Canadian OECD GLP regulations Codex “Guidelines on Minimum Sample Sizes for Agricultural Commodities from Supervised Field Trials for Residue Analysis”, ALINORM 87/24A (1987) PMRA Regulatory Directive DIR98-02 “Residue Chemistry Guidelines”.

PMRA Regulatory Directive DIR98-01

GLP

The study is fully compliant with the principles of Good Laboratory Practice standards.

Executive Summary

Samples of canola seed, meal and oil for cyprodinil were stored under freezer conditions of -20°C and were shown to be stable for at least 9 months.

Storage stability was set up for cyprodinil in canola seed, meal and oil. Sampling periods consisted of 0 days, 3 month, 6 month and 9 months. The storage stability results generated demonstrate no significant differences in the recoveries of cyprodinil in freezer storage samples versus the freshly fortified procedural recovery samples or the designated 0 day analyses which are to serve as a benchmark for the study results.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

A cyprodinil standard was used to fortify storage stability samples, concurrent recovery samples and to prepare calibration standard solutions. Information pertaining to the cyprodinil standard is given below.

Test Material	CGA219417
Lot No.	410442
Purity	99.5%

A2. Test Commodities

Canola seed is a representative of the high oil content commodity category (OECD 506 – Stability of Pesticide Residues in Stored Commodities).

A3. Test Facility

The Performing Laboratory was located at: ALS Laboratory Group 9936-67 Avenue, Edmonton, Alberta, T6E 0PS, Canada.

B. STUDY DESIGN

B1.Test Procedures

The canola commodity samples were fortified with cyprodinil standard at 0.2 ppm for seed and meal samples or 0.1 ppm for oil samples. These were then stored frozen under conditions identical to those used to store residue samples prior to analysis. Freezer storage temperatures were monitored daily and were between -41ºC to -15ºC.

For cyprodinil, the stored samples were analysed at storage intervals of approximately 0, 3, 6, and 9 months.

Cyprodinil samples were removed from the freezer to warm up prior to extraction in 80:20 (v:v) methanol:water.

B2. Analysis

Residues of cyprodinil were analysed with Novartis method AG-631B with the following modifications for canola seed and meal samples:

1. The extracts were centrifuged at 5000 rpm instead of being filtered
2. Diethylene glycol diethyl ether was not added.

3. Extracts were brought to 10mL final volume instead of 2mL final volume.

Cyprodinil (CGA 219417) was analysed for canola refined oil samples using Syngenta method AG-597B with the following modifications made to them:

1. 10g sample was extracted instead of 25g sample.
2. Hexane, florisil and phyenyl column clean-ups were not performed.

This method addressed the complications of extraction from an oily matrix and produced suitable recoveries at the LOQ.

II. RESULTS AND DISCUSSION

The table below summarises the storage stability for cyprodinil in canola commodities.

Table 6.1-6: Stability of cyprodinil residues in canola commodities following storage at -20ºC

Average Recovery for Aged samples- Cyprodinil					
Matrix	Interval (Months)				Overall Average
	0	3	6	9	
Seed	74	89	80	101	86
Meal	99	107	97	78	95
Oil	102	100	106	105	103

The tables below summarises the individual results for each storage period and expresses these as a corrected percentage of the nominal. The results generated demonstrate no significant differences in the recoveries of cyprodinil in freezer storage samples versus the freshly fortified procedural recovery samples or the designated 0 day analyses which are to serve as a benchmark for the study results.

The results show that residues of cyprodinil are stable for up to at least 9 months in tested canola commodities under freezer conditions of -20°C.

Table 6.1-7: Cyprodinil sample recovery results in canola commodities following storage at -20ºC

Commodity	Storage Interval	Nominal Fortification Level (Procedural Recovery Samples)	[1]Average Recovery for Aged Samples	Uncorrected Stored Sample Residue	Mean of Uncorrected Stored Sample Residue	[2]Mean Corrected Stored Sample Residue	[3]Mean Corrected Stored Sample Recovery
	Months	mg/kg	%	mg/kg	mg/kg	mg/kg	(% of nominal)
Canola Seed	0	0.2	74	0.142	0.147	0.199	99
				0.152			
	3	0.2	89	0.163	0.174	0.195	97
				0.177			
				0.202			
				0.152			
	6	0.2	80	0.181	0.172	0.215	108
				0.189			
				0.160			
				0.158			
	9	0.2	101	0.183	0.187	0.185	92
				0.162			
				0.200			
				0.202			
Canola Meal	0	0.2	99	0.189	0.198	0.199	100
				0.206			
	3	0.2	107	0.204	0.212	0.198	99
				0.221			
				0.193			

Commodity	Storage Interval	Nominal Fortification Level (Procedural Recovery Samples)	[1]Average Recovery for Aged Samples	Uncorrected Stored Sample Residue	Mean of Uncorrected Stored Sample Residue	[2]Mean Corrected Stored Sample Residue	[3]Mean Corrected Stored Sample Recovery
				0.231			
	6	0.2	97	0.213	0.200	0.206	103
				0.200			
				0.220			
				0.168			
	9	0.2	78	0.209	0.172	0.220	110
				0.166			
				0.148			
				0.164			
Canola Oil	0	0.1	102	0.109	0.102	0.100	100
				0.0947			
	3	0.1	100	0.0857	0.098	0.098	98
				0.107			
				0.106			
				0.0929			
	6	0.1	106	0.0902	0.101	0.095	95
				0.101			
				0.113			
				0.0984			
	9	0.1	105	0.107	0.105	0.100	100
				0.102			
				0.109			
				0.101			

[1] [Mean Procedural Recovery Sample Residue (mg/kg) / Nominal Fortification Level (mg/kg)] x 100
[2] [Mean Uncorrected Stored Sample Residue (mg/kg) x 100] / Mean Procedural Recovery (%)
[3] Based on nominal fortification level = [Mean Corrected Stored Sample Residue (mg/kg) / Nominal Fortification Level (mg/kg)] x 100

III. CONCLUSIONS

Freezer storage stability studies were performed for Canola seed, meal and oil. These are representative of the commodity categories required to support current OECD 506 – Stability of Pesticide Residues in Stored Commodities requirements (crops containing high levels of oil).

It can be concluded that residues of cyprodinil are stable in canola seed, meal and oil when stored at less than or equal to -20ºC for at least 9 months.

Sagan, K. (2009)

Report:	K-CA 6.1/04; Mazlo J. (2010) Cyprodinil – Magnitude of the Residues in or on Almond and Pecan as Representative Commodities of Tree Nuts, Group 14 and Storage Stability of Almonds (Hulls and Nutmeat). Report No. T003062-07 Syngenta File No. CGA219417_50093 (Storage Stability Analytical Phase report in Appendix 3)

Guidelines

U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances (OPPTS). 1995. Residue Chemistry Test Guidelines, OPPTS 860.1380, Storage Stability Data.

GLP

The study is fully compliant with the principles of Good Laboratory Practice standards.

Executive Summary

The storage stability of cyprodinil was determined in almond hulls and nutmeat under freezer conditions of approximately -20ºC over a storage period of 10 months.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

A cyprodinil standard was used to fortify storage stability samples, concurrent recovery samples and to prepare calibration standard solutions. Information pertaining to the cyprodinil standard is given below.

Test Material	CGA219417
Lot No.	410442
Purity	99.5%

A2. Test Commodities

The test commodities were generated by compositing several untreated samples from previous magnitude of residue studies. Tree nuts is a representative of the high oil content commodity category (OECD 506 – Stability of Pesticide Residues in Stored Commodities).

A3. Test Facility

The study was conducted at Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300 USA.

B. STUDY DESIGN

B1.Test Procedures

The almond hull and nutmeat samples were fortified with cyprodinil standard at 1.0 ppm concentration level and were stored frozen under conditions identical to those used to store residue samples prior to analysis. Freezer storage temperatures were monitored daily and were typically less than or equal to -20°C.

The stored samples were analysed at storage intervals of approximately 0, 7, and 10 months. Samples were removed from the freezer to warm up prior to extraction in 80:20 (v:v) methanol:water by shaking for 1 hour at room temperature. All samples were analysed within 1 day of extraction.

B2. Analysis

Residues of cyprodinil were analysed using method AG-631B.

Stock standard solutions were prepared in methanol. Calibration standards for LC-MS/MS were prepared by dilution of the stock standard solution in 0.1% ammonium acetate in water instead of 70:30 (v:v) methanol:water as outlined in the method.

A small amount of concentrated hydrochloric acid was added to the extracts and shaken for an additional 5 minutes prior to centrifugation and filtering. An aliquot of the supernatant was diluted to final volume with 0.1% ammonium acetate in water prior to cyprodinil residues analysis using HPLC with LC-MS/MS. The limit of quantitation (LOQ) was 0.01 ppm.

II. RESULTS AND DISCUSSION

The table below summarises the storage stability for cyprodinil in almond commodities.

Table 6.1-8: Stability of cyprodinil residues in almond commodities following storage at -20ºC

Summary of Storage Stability from Almonds with Cyprodinil			
Matrix	**Mean Storage Stability Results (% of 0 Day) at the Nominal Storage**		
	0-day	**7 Months**	**10 Months**
Almond, Nutmeat	100	92	107
[1]Almond, Hulls	100	97	103

Mean storage stability results (% of 0day) = (interval mean concentration/0 day mean concentration) x 100.
1The mean concentrations were corrected for control background and procedural recoveries <100%.

The table below summarises the individual results for each storage period and expresses these as a corrected percentage of the nominal. The results generated demonstrate no significant differences in the recoveries of cyprodinil in freezer storage samples versus the freshly fortified procedural recovery samples or the designated 0 day analyses which are to serve as a benchmark for the study results. The results show that residues of cyprodinil are stable for up to 328 days (or at least 10 months) in almond nutmeat and hulls under freezer conditions of -20°C.

Table 6.1-7: Cyprodinil sample recovery results in almond following storage at -20ºC

Commodity	**Storage Interval**	**Nominal Fortification Level (Procedural Recovery Samples)**	**Procedural Recovery Residue**	**[1]Mean Procedural Recovery Residue**	**Uncorrected Stored Sample Residue**	**Mean Uncorrected Stored Sample Residue**	**[2]Mean Corrected Stored Sample Residue**	**[3]Mean Corrected Stored Sample Recovery**
	Days	**mg/kg**	**%**	**%**	**mg/kg**	**mg/kg**	**mg/kg**	**(% of nominal)**
Almond Nutmeat	0	1.0	113	116	0.971	0.859	0.74	74
			119		0.747			
	208	1.0	117	111	0.861	0.787	0.71	71
			105		0.713			
	328	1.0	127	115	0.956	0.916	0.80	80
			102		0.876			
Almond Hulls	0	1.0	77	76	0.702	0.7045	0.93	93
			74		0.707			
	208	1.0	74	76	0.652	0.677	0.90	90
			77		0.702			
	328	1.0	80	80	0.76	0.7615	0.96	96
			79		0.763			

[1] [Mean Procedural Recovery Sample Residue (mg/kg) / Nominal Fortification Level (mg/kg)] x 100
[2] [Mean Uncorrected Stored Sample Residue (mg/kg) x 100] / Mean Procedural Recovery (%)
[3] Based on nominal fortification level = [Mean Corrected Stored Sample Residue (mg/kg) / Nominal Fortification Level (mg/kg)] x 100

III. CONCLUSIONS

Freezer storage stability studies are available for almond hulls and nutmeat. These are representative of the commodity categories required to support current EPA Residue Chemistry Test Guidelines, Storage Stability Data, OPPTS 860.1380 requirements (crops containing high levels of oil).

It can be concluded that residues of Cyprodinil can be assumed stable in almond hulls and nutmeat (high oil) when stored at less than or equal to -20^{0}C for at least 10 months.

Mazlo, J. (2010)

The storage stability of cyprodinil (CGA219417) has been investigated in commodities with high water, high acid, high oil and high starch content, and in cereal straw. The storage stability of cyprodinil (CGA219417) and free and conjugated CGA304075 has been demonstrated in animal commodities. Therefore sufficient stability has been demonstrated to support the residue data presented in this document.

CA 6.2 Metabolism, Distribution and Expression of Residues

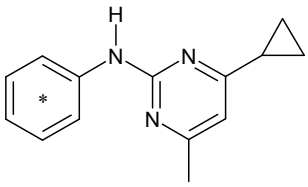
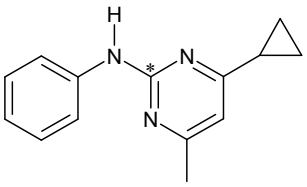
CA 6.2.1 Metabolism, distribution and expression of residues in plants

EU documents: EFSA, 2013, France, 2005

The metabolism of cyprodinil has been studied and the metabolic pathway has been well characterised; consequently no new plant metabolism data are presented.

The metabolism of cyprodinil has been studied in five different crops representative of three crop groups, i.e. root crops (potato), fruit (apple, peach, tomato) and cereal/grass crops (wheat) using ^{14}C-cyprodinil separately labelled in the phenyl and pyrimidine rings except in the apple study where only the pyrimidine ring label was evaluated.

Figure 6.2.1-1: Structure of cyprodinil showing the positions of the radiolabel.

[Phenyl-(U)-^{14}C] cyprodinil	[Pyrimidine-2-^{14}C] cyprodinil
	

* indicates position of radiolabel

The studies were evaluated under Council Directive 91/414/EEC and are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.1, November 2003**).

An overview of the studies in which the metabolism and distribution of cyprodinil has been investigated in plants for inclusion in Annex I of Council Directive 91/414/EEC is summarised in Table 6.2.1-2. An executive summary of the studies submitted for Annex I listing is presented below.

Table 6.2.1-2: Overview of plant metabolism studies evaluated for inclusion of cyprodinil in Annex I of EU Directive 91/414/EEC

Crop Group[2] /Crop Category[3]	Crop	^{14}C-Radiolabel	Growth Conditions	Application	Sampling	Report Reference[1]
Fruits and fruiting vegetables/ Fruit[3]	Apple	pyrimidine-2-^{14}C	Field	Foliar; 3 applications equivalent to 0.05 kg a.s./hL per application. 5-8 weeks between applications	Foliage after each application; fruits and foliage at harvest (PHI = 61days)	4/93
	Peach	phenyl-U-^{14}C or pyrimidine-2-^{14}C	Field	Foliar; 4 applications equivalent to 1.1 kg a.s./ha and 10.9 kg a.s./ha per application. 7 days between applications	Fruit and foliage (PHI = 1 day)	ABR-97002
	Tomato	phenyl-U-^{14}C or pyrimidine-2-^{14}C	Greenhouse	Foliar; 2 applications equivalent to 0.75 kg a.s./ha per application. 28 days between applications	Fruit and foliage after each application; Fruit and foliage at harvest (PHI = 14 days)	20/92 MR 21/92
Root and tuber vegetables/ Root crops[3]	Potato	phenyl-U-^{14}C or pyrimidine-2-^{14}C	Greenhouse	Foliar; 3 applications equivalent to 0.56 kg a.s./ha per application. 19-20 days between applications	Foliage after 1st application; foliage and tuber after 3rd application; Foliage and tubers at harvest (PHI = 14 days)	PMR 03/96 PMR 05/96
Cereals/ Cereal/Grass Crops[3]	Wheat	phenyl-U-^{14}C	Greenhouse	Foliar; 1 application equivalent to 0.75 kg a.s./ha per application.	Whole plant autoradiography; Samples taken at 0 – 35 days	18/92
	Wheat	phenyl-U-^{14}C or pyrimidine-2-^{14}C	Field	Foliar; 2 applications equivalent to 0.5 – 0.75 kg a.s./ha per application. 22 days between applications	Whole plant after each application; Whole plant 41 days after 1st application; Straw, husk and grain at harvest (PHI = 41 days)	18/92 19/92 7/94

1 France, 2005
2 Crop groups for metabolism under Annex I of EU Directive 91/414/EEC
3 Category listed in Annex 1 of OECD 501

Overall Summary of metabolism in plants

The metabolism of cyprodinil has been investigated in potato, tomato, apple, peach and wheat. These crops are representative of root vegetables, fruits and cereals. Full details of the plant metabolism studies are available in the original DAR (France, 2005). The findings are summarised below.

The metabolism of cyprodinil is essentially similar in all crops. Up to 60 days after application cyprodinil remains as the dominant residue in all commodities except in potato tubers where the metabolic pattern results from the translocation of soil metabolites and their subsequent degradation products through the plant. The metabolism in crops where there is a direct contact of cyprodinil with the edible part demonstrates that cyprodinil represents the largest part of the residue (18-90% TRR). In these crops, metabolism proceeds mainly via hydroxylation of the phenyl and pyrimidine rings to form metabolites CGA232449, CGA304076, CGA304075 and CGA275535 followed by sugar conjugation. Of these metabolites, CGA232449 was most prevalent in the tomato metabolism where it was found at 0.63 mg/kg

in the fruit (12.6% TRR) and at a much lower amount than the corresponding level of parent cyprodinil in the fruit (63.2% TRR, 3.2 mg/kg). Lower levels of the other hydroxylated metabolites were found (up to 2.8% TRR). Of these, CGA232449, CGA304076, and CGA304075 are found in the rat and are covered by the toxicological profile of cyprodinil.

Cleavage of the amine bridge between the two ring systems represents a minor degradation route. Incorporation of ultimate degradation products in natural plant components has been demonstrated.

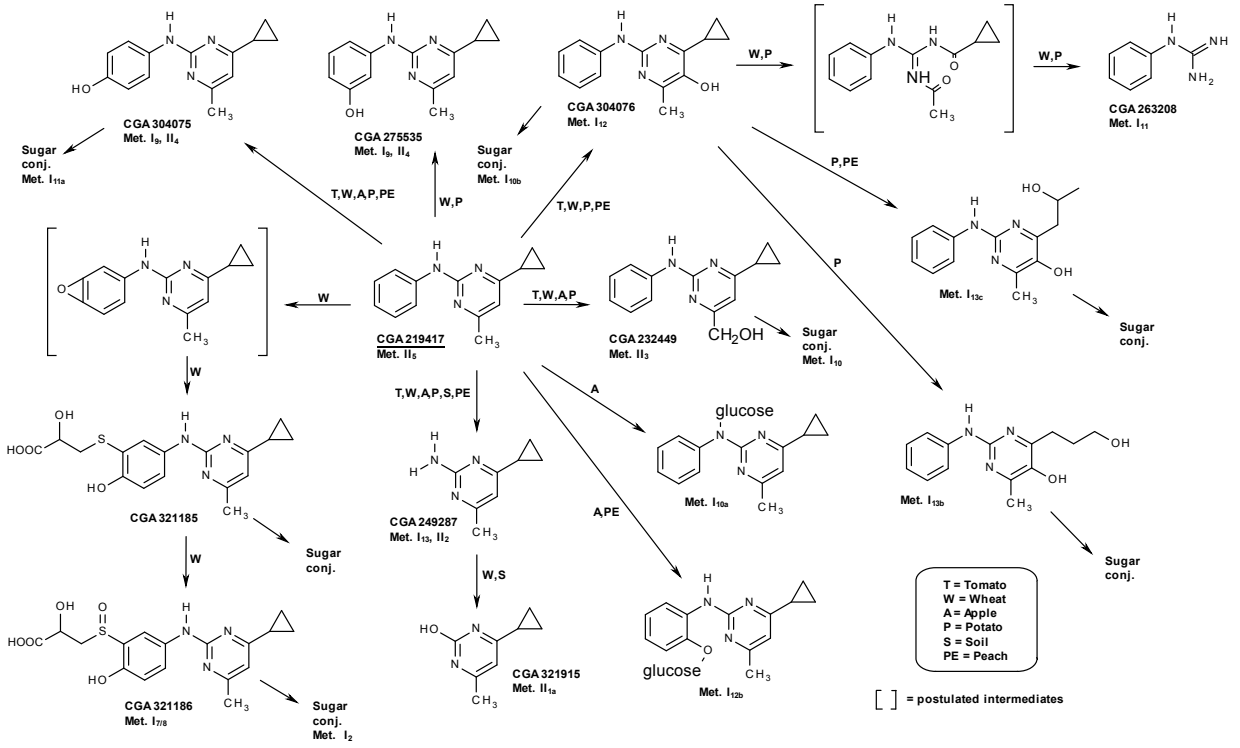
In potato tubers where the edible part of the crop is not directly exposed to the fungicide spray, the residues were low with the TRR in potatoes at <0.1 mg/kg for both labels. Metabolite CGA263208 resulting from cleavage of the pyrimidine ring represented 6.7% TRR in mature whole tuber; four other metabolites were identified as the free and sugar conjugated forms of N-phenyl-4-(2-hydroxypropyl)-5-hydroxy-6-methyl-2-pyrimidinamine (at up to 13.7% TRR) and N-phenyl-4-(3'-hydroxypropyl)-5-hydroxy-6-methyl-2-pyrimidinamine (at up to 15.9% TRR) with no cyprodinil identified; non-identified extractable fractions were present at very low levels and most of the non-extractable radioactivity was incorporated in natural cell constituents. These potato metabolites were not found in the rat metabolism, but due to the low absolute levels at which they were found in the potato metabolism study, they are not of toxicological relevance. In potato leaves/foliage at mature harvest parent cyprodinil was the major component accounting 46-48% of the TRR.

Based on the findings in metabolism studies with cereals and fruit (wheat and tomatoes respectively) it is reasonable to conclude that the metabolic pathway in leafy crops proceeds in a similar pattern. In these studies the results on leaves were comparable with the results across the other fruit and cereal metabolism studies. Since the metabolism was comparable across five different crops in three crop groups the available metabolism data are also applicable to crops in the pulses and oilseeds crop group.

In the original EU evaluation of cyprodinil it was concluded that metabolism was similar in all crops and the residue definition for both risk assessment and monitoring should be established as cyprodinil (parent compound) only.

The metabolic pathway in plants is presented in Figure 6.2.1-1.

Figure 6.2.1-1: Metabolic pathway of cyprodinil in plants



EU documents: France, 2005

These studies were reviewed within the framework of Directive 91/414/EEC and were considered to be acceptable; Syngenta considers that no further metabolism studies in plants are required to support the representative uses on apple and barley presented for cyprodinil in this dossier.

CA 6.2.2 Poultry

EU documents: EFSA, 2013, France, 2010, France, 2005

According to the dietary burden calculations presented in Section CA 6.4, the use of cyprodinil on barley and apple as described in this document may lead to a dietary intake of residues in barley straw and grain, brewer's grain, distiller's grain, and apple pomace of >0.004 mg/kg bw/day for poultry livestock. The nature of cyprodinil residues in commodities of animal origin was investigated in the framework of Directive 91/414/EEC and is summarised below.

The distribution and metabolism of [phenyl-(U)-^{14}C]-cyprodinil and [pyrimidine-2-^{14}C]-cyprodinil was investigated in poultry and the studies are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.2.2, November 2003**).

An overview of the studies in which the metabolism and distribution of cyprodinil has been investigated in poultry for inclusion in Annex I of Council Directive 91/414/EEC, is summarised in Table 6.2.2-1. An executive summary of the studies submitted for Annex I listing is presented below.

Table 6.2.2-1: Overview of poultry metabolism studies evaluated for inclusion of cyprodinil in Annex I of EU Directive 91/414/EEC

Group	Species	^{14}C-Radiolabel	No of animals	Application details		Sample details		Report Reference
				Rate (mg/kg bw/day)	Duration (days)	Commodity	Time	
EU Reviewed Data (France, 2005)								
Laying hens	Hen	phenyl-U-^{14}C	2 4	0.4 18.9	4	Eggs	Daily	6/94 9055
						Excreta	Daily	
						Tissues	After sacrifice	
	Hen	pyrimidine-2-^{14}C	2 4	0.4 19.2	4	Eggs	Daily	
						Excreta	Daily	
						Tissues	After sacrifice	

Cyprodinil was extensively metabolised and eliminated following oral administration to laying hens, resulting in low retention of radioactive residues in tissues and eggs. Residue levels were <0.01 mg/kg in eggs and tissues at the lower dose rate with the exception of liver (0.12 mg/kg) and kidney (0.04 mg/kg).

The metabolism of cyprodinil in the hen proceeds predominantly via oxidation and conjugation reactions:

- Oxidative hydroxylation of the phenyl ring, at the 4 position, to form CGA304075 found in its free form in the excreta.
- Oxidative hydroxylation of the phenyl ring, at the 4 position, followed by conjugation to form the sulphate or glucuronide conjugates, found in eggs, liver and kidney.
- A minor route involving cleavage of the amino bridge between the two rings to give CGA249287.

The studies were reviewed within the framework of Directive 91/414/EEC and were considered to be acceptable; Syngenta considers that no further metabolism study in poultry is required to support the renewal of cyprodinil.

CA 6.2.3 Lactating ruminants

EU documents: EFSA, 2013, France, 2010, France, 2005

According to the dietary burden calculations presented in Section CA 6.4 the use of cyprodinil on barley and apple as described in this document may lead to a dietary intake of residues in barley straw and grain, brewer's grain, distiller's grain, and apple pomace of >0.004 mg/kg bw/day for lactating ruminants. The nature of cyprodinil residues in commodities of animal origin was investigated in the framework of Directive 91/414/EEC and is summarised below.

The distribution and metabolism of [phenyl-(U)-^{14}C]-cyprodinil and [pyrimidine-2-^{14}C]-cyprodinil was investigated in goats. The studies were evaluated under Council Directive 91/414/EEC and are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.2.1, November 2003**).

An overview of the studies in which the metabolism and distribution of cyprodinil has been investigated in poultry for inclusion in Annex I of Council Directive 91/414/EEC is summarised in Table 6.2.3-1.

An additional study was conducted in which [pyrimidine-2-^{14}C] cyprodinil was dosed to a goat to generate radio-labelled incurred residues of cyprodinil and CGA304075 for use in method development

and validation work. This study has not previously been submitted in the EU, so, because of its similarity to a metabolism study, a full summary is also included in this section.

Table 6.2.3-1: Overview of ruminant metabolism studies evaluated for inclusion of cyprodinil in Annex I of EU Directive 91/414/EEC

Group	Species	^{14}C-Radiolabel	No of animals	Application details		Sample details		Report Reference
				Rate (mg/kg bw/day)	Duration (days)	Commodity	Time	
EU Reviewed Data (France, 2005)								
Lactating ruminants	Goat study 1 and 2	phenyl-U-^{14}C	1 1	0.2 9.94	4	Milk	Twice daily	5/94 9050
						Urine and faeces	Daily	
						Tissues	After sacrifice	
		pyrimidine-2-^{14}C	1 1	0.2 9.8	4	Milk	Twice daily	
						Urine and faeces	Daily	
						Tissues	After sacrifice	
	Goat study 3	phenyl-U-^{14}C	1	4.11	4	Milk	Twice daily	17/96
						Urine and faeces	Daily	
						Tissues	After sacrifice	
New Data								
Lactating Ruminant	Goat Study	pyrimidine-2-^{14}C	1		4	Milk	Twice daily	T019338-04
						Urine and faeces	Daily	
						Blood	Prior to sacrifice	
						Tissues	After sacrifice	

An executive overall summary of the studies submitted for Annex I listing is presented after the summary of the new study.

Report:	K-CA 6.2.3/01. Anderson W (2006). [^{14}C] Pyrimidinyl-Cyprodinil (CGA219417): Method development for analysis of CGA-304075 (metabolite of cyprodinil) and related metabolites from a lactating goat. Syngenta Crop Protection Inc., 410 Swing Road, Greensboro NC 27419, USA. Study Dates: December2004 - February 2006. Syngenta Unpublished Report No: T019338-04; Syngenta File No: CGA219417/1497.

Guidelines

Residue Chemistry Test Guidelines, OPPTS 860.1300. Nature of the Residue - Plants, Livestock. United States Environmental Protection Agency, August 1996.

GLP

The study is fully compliant with the principles of Good Laboratory Practice.

Executive Summary

A study was conducted during 2004-2005 in which radio-labelled cyprodinil was dosed to a goat to generate milk and tissue samples containing incurred residues of cyprodinil and its animal metabolites for use in method development work.

^{14}C-Cyprodinil, labelled in the 2-position of the pyrimidinyl ring, was dosed in gelatin capsules and administered to a single goat. Four doses were given, on consecutive days, each containing approximately 150 mg of test substance, equivalent to 100 mg/kg in the diet (~ 4 mg/kg bw/day). The goat was sacrificed 6 hours after the fourth dose and selected tissue samples taken for use in the method validation.

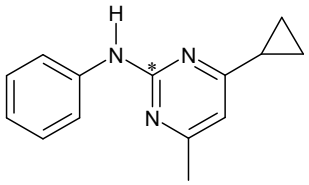
Total radioactive residues in the tissues were determined by combustion analysis, before characterisation of the radioactive residues in these tissues was performed. The results were broadly similar to those of the full metabolism studies summarised above, but rather lower levels of CGA304075 (free and conjugated) were found.

It was demonstrated that, to provide a reliable analytical method for residues of CGA304075 in animal tissues, extraction by reflux in hydrochloric acid (0.5 M) is required. This work formed the basis of method GRM010.01A and is also summarised in Section CA 4.1.2 of this submission.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Structure/Label	Pyrimidinyl-2-^{14}C Cyprodinil
	 (* = ^{14}C position)
Batch Number	CL-LVII-16
Radiochemical Purity	99.3%

A2. Test Organism

A goat (*Capra hircus*), of variety Alpine was used.

A3. Test Facilities

The biological phase and analytical phase 1 (TRR determination and profiling of extracts) of this work were performed at Syngenta Crop Protection Inc., 7145 - 58th Avenue, Vero Beach, FL 32967, USA.

Analytical phase 2 (identification and quantification of metabolites) was performed at Syngenta Crop Protection Inc., 410 Swing Road, Greensboro, NC 27419, USA.

B. STUDY DESIGN AND METHODS

B1. Experimental Conditions

The goat was housed in a metabolism cage designed for the separate collection of urine and faeces. Treatment room lights were on a 12 hour on/off cycle each 24 hour period. During the 5 day acclimation and 4 day dosing period, room temperatures ranged from 24-31°C and humidity from 28-96%. The health of the goat was checked by a veterinarian; overall, the test animal remained in good health throughout the acclimation and dosing period.

Twice a day the goat was offered a measured ration of grain and hay. The daily diet was given in two equal portions of 400 g grain and 500 g hay in the morning and in the afternoon. Commercial bottled drinking water was provided *ad libitum*.

Four gelatin capsules, each containing approximately 150 mg of [pyrimidinyl-2-^{14}C] cyprodinil, were prepared and one capsule per day was administered with a balling gun. The animal was dosed over a period of 4 consecutive days in the morning, after feeding and collection of milk, urine and faeces.

B2. Sampling

Urine and faeces were collected from the test animal at 24-hour intervals in the morning before dosing. Milk was collected twice a day in the morning and afternoon. A whole blood sample was collected from the test animal just prior to sacrifice.

Approximately 6 hours following the last dose, the test animal was stunned with a captive bolt shot and immediately exsanguinated by severing the major neck vessels. Veterinary examination indicated that the animal was healthy at the time of sacrifice; there were no abnormal findings.

After sacrifice, samples were collected in the following order: leg muscle, omental fat, perirenal fat, kidney, liver, bile, gastrointestinal tract and tenderloin. The two muscle samples were combined, as were the two fat samples.

B3. Extraction and Fractionation of Residues

Analytical Phase 1

The total radioactive residues (TRR) in each tissue (including milk) sample were initially determined by direct combustion/LSC.

Solid and semi-solid samples were homogenized by milling with dry ice. Liquid samples were mixed by hand. Triplicate aliquots (solid samples) were combusted and the released CO_2 trapped in Carbon 14 Cocktail. Combustion values were corrected for oxidizer efficiency. Radioassays were obtained by scintillation counting. Weighed aliquots of fat samples were warmed prior to radioassay. Volumetric aliquots of liquid samples were transferred directly to scintillation vials for radioassay. All samples were counted for a 5 minute interval or until a 2-sigma error of <0.5 was achieved. Background values were determined using a scintillation cocktail blank.

Analytical Phase 2

Liver, kidney and milk were extracted by neutral solvent extraction using acetonitrile (milk) or acetonitrile/water (80:20 v/v) for liver and kidney. These extracts were examined by HPLC co-chromatography against standards.

The urine was used to develop hydrolytic conditions for the cleavage of CGA304075 conjugates. Differing concentrations of HCl were investigated under reflux conditions. High concentrations of HCl (> 1N) caused degradation of metabolites to polar compounds. 0.5N HCl was selected because it gave maximum extraction efficiency without degradation of the sample components. This hydrolytic extraction procedure also gave greater extraction efficiency than the neutral solvent.

II. RESULTS AND DISCUSSION

A. TOTAL RADIOACTIVE RESIDUES (TRRs)

Total radioactive residues in the kidney (3.197 mg/kg), liver (3.802 mg/kg) and milk (from afternoon of day 4) (0.425 mg/kg) were comparable to those found in previous studies, as shown in Table 6.2.3-2.

Table 6.2.3-2: Comparison of extraction efficiencies of CGA304075 from animal tissues

Study (Nominal Dose rate)	Tissue	Total radioactive Residue		Extractable Residue (%)	CGA304075 (%)	Gluc-CGA304075* (%)
		(mg/kg)	(% of dose)			
5/94 (5 mg/kg)	Liver	0.277		80.5	2.7	nd
	Kidney	0.216		88.1	17.7	nd
	Milk	0.048		83.5	nd	27.3
17/96 (100 mg/kg)	Liver	2.488	0.3	67.9	27.6	2.7
	Kidney	2.895	0.1	95.5	39.1	4.6
	Milk	0.708	0.5	96.1	nd	55.2
T019338-04 (100 mg/kg)	Liver	3.802	0.5	73.0	3.4	
	Kidney	3.197	0.1	95.3	<0.1	
	Milk	0.425	<0.1	90.3	<0.1	

* - Glucuronide conjugate of CGA304075
nd - not detected

The TRR values determined from the summation of the radioactivity present in the extracts and the debris after initial extraction were in good agreement with those derived from earlier studies.

B. EXTRACTION OF RESIDUES

The urine contained much higher radioactive residues than the tissues and milk, 3.8 - 11.6 of the applied dose and was used to develop hydrolysis conditions to cleave conjugates of CGA304075. Different concentrations of HCl under reflux conditions were investigated. Results are in Table 6.2.3-3, below.

Table 6.2.3-3: Comparison of hydrolysis efficiencies of CGA304075 from goat urine

Extraction Conditions	CGA304075 Extracted (% TRR)
Day 4 urine (Neutral extraction)	0.2
Day 4 urine (Acid reflux, 6N HCl, 1 hr)	<0.1
Day 4 urine (Acid reflux, 3N HCl, 1 hr)	<0.1
Day 4 urine (Acid reflux, 1N HCl, 1 hr)	0.3
Day 4 urine (Acid reflux, 0.5N HCl, 1 hr)	0.3
Day 4 urine (Acid reflux, 0.25N HCl, 1 hr)	0.3

High concentrations of HCl (6N, 3N and 1N) degraded many of the metabolites to polar compounds. Reflux of urine samples with 0.25N HCl and 0.5N HCl followed by HPLC analysis gave highest recovery

of free CGA304075 and the use of 0.5N HCl was selected as giving efficient hydrolysis and recovery without degradation of other components in the sample matrix. The chosen 0.5N HCL reflux extraction also produced higher extraction efficiency than neutral solvent (acetonitrile/water, 80:20, v/v) as shown in Table 6.2.3-4, below.

Table 6.2.3-4: Comparison of extraction efficiencies of CGA304075 from goat tissues

Matrix	Solvent Extraction		Acid Reflux (0.5N HCl)	
	% Extractable	CGA304075 (mg/kg)	% Extractable	CGA304075 (mg/kg)
Liver	73.0	0.129	93.2	0.373
Milk	90.3	Not detected	97.7	0.059

C. CHARACTERISATION AND IDENTIFICATION OF RESIDUES

Free CGA304075 was highest in the liver, 3.4% TRR (0.129 mg/kg), with less than 0.1% detected in the kidney and milk (Table 1). In previous metabolism studies (MR 5/94 and 17/96) the glucuronic acid conjugate of CGA304075 was seen in the liver, kidney and milk. In the current study, in the liver, kidney and milk, a number of polar compounds were detected in the region of the CGA304075 glucuronic acid conjugate, which made quantification of the glucuronic acid conjugate difficult. The analysis results are shown in Table 6.2.3-5. CGA304075 increased in the liver from 3.4% TRR (0.129 mg/kg) by neutral extraction to 9.8% TRR (0.373 mg/kg). CGA304075 in milk increased from <0.1% TRR (<0.001 mg/kg) by neutral extraction to 14% TRR (0.059 mg/kg).

Table 6.2.3-5: Distribution of CGA304075 in liver and milk (extraction by acid reflux)

Matrix	TRR (mg/kg)	TRR (% of Dose)	Extractable (%)	CGA304075
Liver	3.802	0.5	93.2% (3.545 mg/kg)	9.8% (0.373 mg/kg)
Milk	0.425	<0.1	97.7% (0.415 mg/kg)	14.0% (0.059 mg/kg)

III. CONCLUSIONS

This study, intended only to produce tissue samples containing incurred radioactive residues of CGA304075 for method-development purposes, gave tissue concentrations of CGA304075 and its conjugates lower than the metabolism studies in lactating goats.

Despite this quantitative difference, the overall distribution of residues was sufficiently consistent with the metabolism studies, and tissues for method development were successfully generated.

Extraction of tissues and milk by acid reflux gives greater extraction efficiency than extraction with solvents. Reflux using 0.5N HCl was selected to give efficient hydrolysis and recovery of residues of free and conjugated CGA304075 without degradation of other components in the sample matrix.

Overall summary of metabolism in ruminants

The distribution and metabolism of cyprodinil was investigated in lactating goats at nominal dosing rates of 5, 100 and 250 mg/kg in the daily diet. Cyprodinil labelled in either the [phenyl-(U)-^{14}C] - or [2-^{14}C-pyrimidine]- position was administered daily for 4 consecutive days to one goat at a dose level of 0.2 mg/kg body weight (equivalent to 8 mg/kg in the diet) and to one goat at a dose level of 10 mg/kg body weight (equivalent to 267 mg/kg in the diet). In a third study**,** [phenyl-(U)-^{14}C] cyprodinil was administered to two goats for four consecutive days at a rate equivalent to 4.11 mg/kg body weight (100 mg/kg in the diet).

Urine and faeces were collected daily from day 2 to day 4, and cage washes were carried out at 24 hour intervals. Milk was sampled twice daily and blood samples were taken daily. The goats were sacrificed 6 hours after administration of the final dose. After sacrifice, samples of tenderloin, hindquarter and forequarter muscles, omental, renal, and subcutaneous fats, liver and kidneys were taken for analysis. The bile and rumen contents were also sampled.

In the first two studies, 58.01 – 77.42 % of the administered dose was excreted in the urine, faeces and milk. Excretion in the urine was (26.74 - 38.92%) and faeces (19.12 - 29%) from goats dosed at a nominal 5 mg/kg whilst at the higher dose rate of 250 mg/kg in the diet excretion in the urine was 27.4-29% and 39.7-46.6% in faeces. Biliary excretion was also investigated and considered low (0.02 - 0.14%). A further 9.29 - 16.75% remained in the rumen at slaughter. The total recovery of the administered dose was in the range 74.07 - 87.83%. The incomplete recovery was attributed to a portion of the test substance remaining unabsorbed in the gastro-intestinal tract.

Transfer of radioactivity into milk was low for both dosing levels accounting for <0.53% of the total administered dose. Following dosing with [phenyl-(U)-^{14}C] cyprodinil, total radioactive residues in the milk reached a maximum residue of 0.02 and 3.22 mg/kg for the 5 and 250 mg/kg dose rates, respectively. For the pyrimidine label, total TRR in milk reached 0.07 and 1.47 mg/kg for the 5 and 250 mg/kg dose rates, respectively.

TRR were similar for both radiolabels. At the 5 mg/kg dosing rate TRRs were 0.006 mg/kg in muscle, 0.007 mg/kg in fat, 0.172 mg/kg in liver and 0.216 mg/kg in kidney for the phenyl label and 0.007 mg/kg in muscle, 0.010 mg/kg in fat, 0.277 mg/kg in liver and 0.234 mg/kg in kidney for the for the pyrimidine label. At the 250 mg/kg dosing rate TRRs were, 0.109 and 0.169 mg/kg in muscle, 0.048 and 0.257 mg/kg in fat, 9.62 and 12.73 mg/kg in liver and 5.21 and 9.21 mg/kg in kidney, for the phenyl and pyrimidine labels, respectively.

The extractability of radioactive residues from tissues and milk was similar for both radiolabelled forms of cyprodinil. Precipitation of protein and extraction of the milk with acetonitrile resulted in 73.1 and 83.5% TRR being solubilised in the organic phase for the phenyl and pyrimidine labels, respectively. Sequential extraction of tissues resulted in the solubilisation of 70.5 and 80.5% TRR in liver, 87.0 and 88.1% TRR in kidney, 84.2 and 85.4% TRR in muscle for the phenyl and pyrimidine labels, respectively.

The metabolic profile was similar for both radiolabels. Parent cyprodinil was only observed in the liver, representing 1.5% TRR (0.003 mg/kg) and 5.7% TRR (0.016 mg/kg) for phenyl and pyrimidine labels, respectively. The major metabolites excreted in urine were CGA304075, which accounted for 17.7% and 22.2% TRR and its sulphate conjugate at levels of 8.1% TRR and 28.1% TRR, for the phenyl and pyrimidine labels, respectively. An additional sulphate conjugate of CGA304076 represented 6.0% TRR and 9.1% TRR, for the phenyl and pyrimidine labels, respectively.

CGA304075 was also observed as the major metabolite in the kidney representing 18.3 and 17.7% TRR (0.041 and 0.038 mg/kg), for the phenyl and pyrimidine label, respectively, whilst its glucuronic acid conjugate, was present in milk at 15.2 and 27.3% TRR (0.002 and 0.013 mg/kg). The sulphate conjugate of CGA304075 was present in milk at 2.1 and 3.0% TRR (<0.001and 0.001 mg/kg), in liver at 2.0 and 2.0% TRR (0.006 mg/kg), and in kidney at 1.2 and 6.9% TRR (0.003 and 0.015 mg/kg), for the phenyl and pyrimidine labels, respectively.

The sulphate conjugate of CGA304076, was found in milk at 11.7 and 19.1% TRR (0.003-0.006 mg/kg), in liver at 2.4 and 2.8% TRR (0.004 and 0.008 mg/kg) and in kidney at 5.6 and 8.0% TRR (0.013 and 0.017 mg/kg), for the phenyl and pyrimidine labels, respectively.

The pyrimidine label specific metabolite CGA249287, resulting from the cleavage of the amino bridge between the phenyl and pyrimidine rings, was observed in milk at 2.1% TRR (0.001 mg/kg), in liver at 4.2% TRR (0.012 mg/kg) and kidney at 5.8% TRR (0.013 mg/kg).

In the third study (100 mg/kg dose level, phenyl label only), the results were similar to those described for the 5 and 250 mg/kg dose levels, with a mean of 72.2% of the administered dose being excreted in the urine (31.8%) and faeces (39.9%). A mean of 21.5% of the administered dose was found in the gastro-intestinal tract (GIT) at slaughter. The total recovery of the administered dose was 96.4%.

TRR were 0.79 mg/kg for milk, 0.052 mg/kg in muscle, 0.075 mg/kg in fat, 2.49 mg/kg in liver and 2.90 mg/kg in kidney. The extractability of the radioactive residues from faeces was high (81.4% TRR). Extraction of milk, fat and kidney released 96.1, 75.7, and 95.5% TRR, respectively. For muscle and liver, 65.3 and 67.9% TRR, respectively, were extracted. Using microwave-assisted extraction realised a further 7.6 and 30.4% TRR in muscle and liver.

In faeces, CGA304075 was the major component representing 51% TRR. Parent cyprodinil was also found but was present in much smaller amounts (<10% TRR). In urine, the major metabolite was also CGA304075 and its glucuronic acid conjugate. CGA304076 was found in both urine and faeces representing 7.9% and 8.4% TRR, respectively. The sulphate and glucuronide conjugates of CGA304076 accounted for 3.9 and 3.3% TRR, respectively. Several other metabolites (<10%) resulting from single and multiple oxidations at other sites in the molecule were also present, although cyprodinil was not identified.

Parent cyprodinil was the major residue in fat, representing 67.9% TRR (0.05 mg/kg). Cyprodinil accounted for 2.4 and 9.4% TRR in muscle and liver respectively. It was not detected in milk and kidney.

In milk, CGA304075, present as the glucuronide conjugate was the major metabolite, accounting for 55.2% TRR (0.390 mg/kg). The sulphate conjugate of CGA304075 was present as a minor metabolite representing 2.1% TRR (0.015 mg/kg), whilst the non-conjugated form of CGA304075 was not found.

In tissues, CGA304075 was the major component in liver (30.0%), kidneys (39.1%) and muscle (14.5%), and to a smaller extent in fat (2.5%). The sulphate and glucuronide conjugates of CGA304075, were minor components of tissues residues, each accounting for <5.7% TRR.

CGA304076, mainly as the sulphate or glucuronide conjugates was present in all tissues and milk. The sulphate conjugate represented 4.4% in muscle, 6.5% in liver, 10.3% in kidney, and 15.6% in milk whilst the glucuronide conjugate represented 1.8% muscle, 5.8% liver, 10.8% kidney, and 4.1% in milk.

CGA232449, and/or its glucuronide conjugate were present at levels up to 3.5% TRR in muscle, 9.4% TRR in liver, and 12.1% TRR in kidneys.

3,4 Hydroxylated phenyl metabolites, present as the 3-glucuronide and the 3-sulphate conjugates, were found in the liver up to 1.6% TRR and in milk up to 3.8% TRR. Other di- and tri-hydroxylated products were also identified in tissues and milk. Hydroxylated N-phenyl guanidine, resulting from cleavage of the pyrimidine ring was found only in liver, 5.7% TRR; 0.014 mg/kg.

A study primarily designed to generate radiolabelled animal tissues for method development purposes gave tissue concentrations of CGA304075 and its conjugates lower than the metabolism studies in lactating goats. Despite this quantitative difference, the overall distribution of residues was sufficiently consistent with the metabolism studies.

Cyprodinil was extensively metabolised and eliminated following oral administration to lactating goats. The metabolism was similar for both labels and results from hydroxylation of the phenyl ring and formation of monohydroxy derivatives such as CGA304075 and CGA304076, followed by conjugation

with sulphate or glucuronic acid. A minor pathway resulting from the cleavage of the amino bridge between the phenyl and pyrimidine rings has also been observed in milk, liver and kidney resulting in the formation of the metabolite CGA249287.

Syngenta considers that these studies are acceptable and no further metabolism study in ruminants is required to support the renewal of cyprodinil.

CA 6.2.4 Pigs

A metabolism study in pigs is not required as the metabolism in the ruminant, poultry and rat are similar.

CA 6.2.5 Fish

No fish metabolism studies have been conducted for cyprodinil.

Taking account of the document SANCO/10181/2013 Rev. 2.1, 13 May 2013 which states: "*In some cases, agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as no test methods or guidance documents are published in the form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02.*"

It is also recorded in the Summary Report of the Standing Committee meeting on Plants, Animal, Food and Feed (Section Phytopharmaceuticals - Pesticides Residues), held in Brussels on 24-25 November 2014, under item A.24, that " ... *the Commission working document on the nature of residues in fish was discussed in 2013 and it was concluded that it is not yet finalised and ready to be noted as a guidance document."* Additionally the report states under item A.24 *the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived* [as per document SANCO/10181/2013 Rev 2.1]."

In the Summary Report of the SCoPAFF meeting (Section Phytopharmaceuticals - Plant Protection Products - Legislation), held in Brussels on 26-27 January 2015, it is reiterated, under item A.26, "... *some RMS are requesting studies on data requirements for which currently there is no agreed methodology and they consider a dossier incomplete if these data are not provided. The Commission explained that this is not consistent with the Guidance Document SANCO/10181/2013, which was taken note of by Member States.*" The following statements were also made by the Commission: "*In particular cases, ad-hoc studies could be requested, as it is always the case in justified situations. ... However, the Commission referred to the general policy of reducing animal testing and asked Member States to consider this when asking for additional studies on vertebrates.*"

We believe that it is essential that guidance is suitably discussed and peer reviewed, considering both benefits to the assessment of consumer safety and the minimisation of vertebrate testing, before being applied.

In addition there are currently no definitive triggers in Regulation (EC) No. 283/2013 on which to base a decision as to whether a "fish metabolism" study is required or not.

In order to properly assess the potential transfer of pesticide residues from plant-protection-product treated feed items into the consumable tissues of farmed fish we believe that the following need to be in place:

- **A robust and representative dietary burden calculation method** (including the underlying feeding-practice data);

- **An agreed and practicable method for studying the nature of residues in fish;** and (depending on the potential for residues to transfer into fish tissues)
- **An agreed and practicable method for quantitatively studying the transfer of residues of concern into fish tissues.**

~~There is no guidance yet finalised for fish metabolism/fish feeding studies. It is also noted that the summary arising from the SCoPAFF meeting on 24 – 25 November 2014, Section A.24 states that "*the Commission working document is not yet finalised and ready to be noted as a guidance document*." Additionally, "*the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived*."~~

Summary of metabolism, distribution and expression of residues in livestock

The distribution and metabolism of cyprodinil were investigated in hens at nominal dosing rates of 5 and 250 mg/kg in the daily diet. Cyprodinil was extensively metabolised and eliminated, resulting in low retention of radioactive residues in tissues and eggs. The metabolism of cyprodinil in the hen proceeds predominantly via oxidation and conjugation reactions to form CGA304075 and its sulphate or glucuronic conjugates.

The metabolism of cyprodinil in lactating ruminants dosed at nominal concentrations of 5 mg/kg, 100 mg/kg and 250 mg/kg in the diet was investigated. Cyprodinil was extensively metabolised resulting in low retention of radioactive residues in milk and tissues. The metabolism was similar for both labels and results from hydroxylation of the phenyl ring to the monohydroxy derivatives (CGA304075 and CGA304076) followed by conjugation with sulphate or glucuronic acid. A minor pathway resulting from the cleavage of the amino bridge between the phenyl and pyrimidine rings was also observed in milk, liver and kidney resulting in the formation of the metabolite CGA249287.

The metabolism studies in both ruminants and poultry show that cyprodinil is extensively metabolised and proceeds predominantly via hydroxylation of the phenyl and pyrimidine rings and conjugation with sulphate or glucuronic acid. The majority of the radioactivity was eliminated in the urine and faeces. CGA304075 is a major metabolite in in products of animal origin in both its free and conjugated form. In the goat metabolism whilst the CGA304075 was the main metabolite in liver and kidney, the glucuronide conjugated form was the main metabolite found in milk. Other metabolites found at significant levels include CGA304076, CGA232449, and CGA249287. All these metabolites were found in the rat metabolism study.

In the Article 12 review of Regulation (EC) No 396/2005 (EFSA Journal 2013; 11(10):3406), EFSA reconsidered the metabolism data and considered whether the conjugate of CGA304075 needed to be included in the residue definition. It was noted that whilst conjugation does occur in hens, no significant residues in poultry are expected. Significant residues in poultry are also not expected following the representative uses on apple and barley supported in this dossier. Ruminant metabolism studies indicate that residues in animal tissues would consist of cyprodinil and CGA304075; however any cyprodinil residues present in milk at significant levels are likely to be present as conjugated CGA304075.

Therefore, the proposed residue definitions for enforcement and risk assessment in all commodities of animal origin (except milk) are:

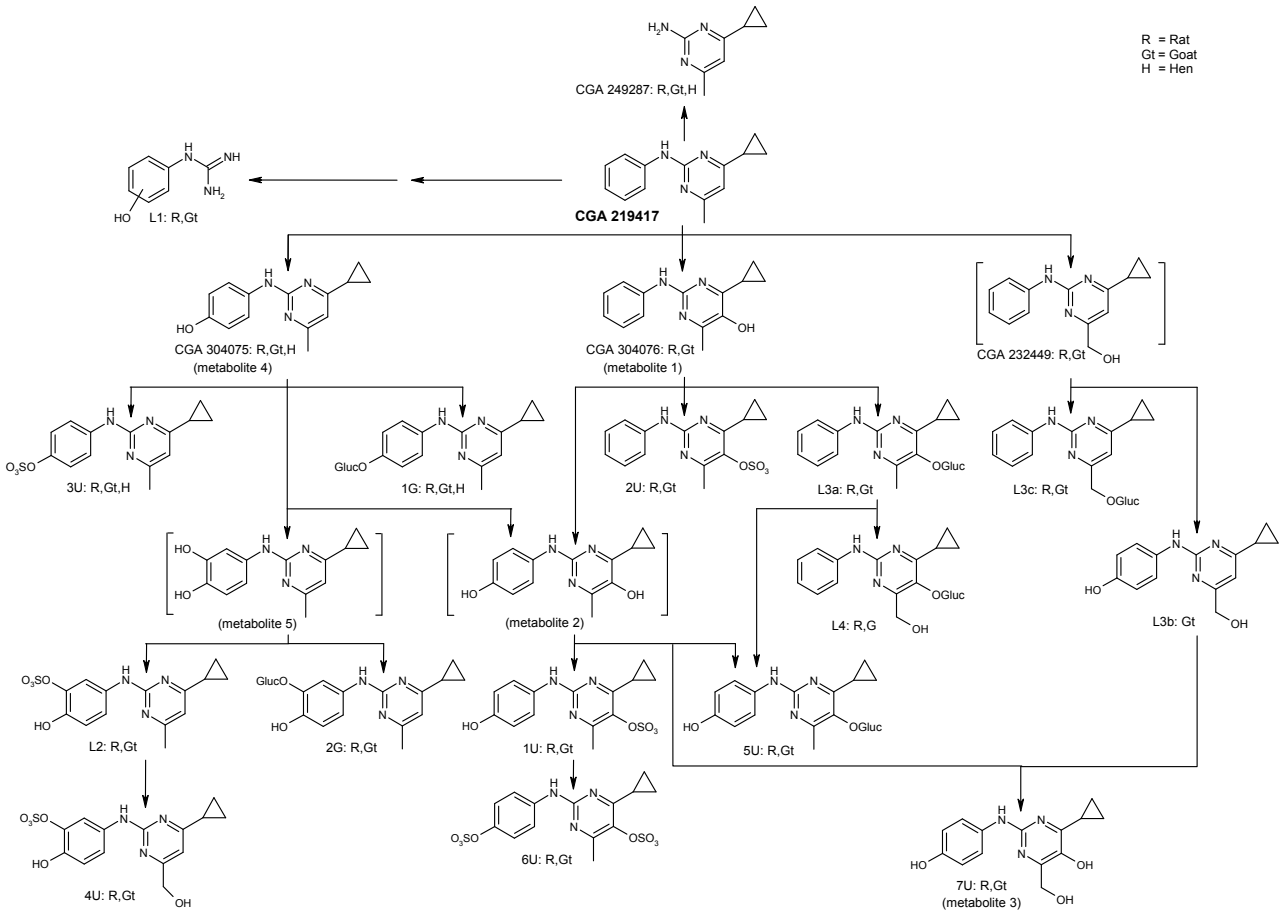
The sum of cyprodinil and CGA304075 expressed as cyprodinil.

The proposed residue definitions for enforcement and risk assessment in milk are:

The sum of cyprodinil and CGA304075 (free and conjugated) expressed as cyprodinil.

The proposed metabolic pathway in animals is presented in Figure 6.2.6-1.

Figure 6.2.6-1: Proposed metabolic pathway of cyprodinil in animals



EU documents: France, 2005

The nature of residues of Cyprodinil (CGA219417) has been adequately investigated in commodities of animal origin. No further studies are required.

CA 6.3 Magnitude of Residues Trials in Plants

The use pattern for evaluation for renewal of approval of cyprodinil is provided in **Document D1** and is summarised below in Table 6.3-1.

Table 6.3-1: Cyprodinil representative use patterns

Crop	Outdoor/ Protected	Growth Stage	Max. No. of Applications	Minimum Application Interval (days)	Max. Application		Minimum PHI (days)
					Rate (kg a.s./ha)	Water (L/ha)	
Apple	Outdoor (NEU)	BBCH 10-71	2-3	21	0.375	450 - 1500	21
	Outdoor (SEU)	BBCH 10-71	2-3	21	0.375	450 - 1500	21
Barley	Outdoor (NEU)	BBCH 30-61	1-2	14	0.450	150 - 400	45[(a)]
	Outdoor (SEU)	BBCH 30-61	1-2	14	0.450	150 - 400	45[(a)]

(a) It is more appropriate for cereal crops to indicate the application timing using growth stage rather than a pre-harvest interval; however a representative PHI has been given.

The representative crops included in the original EU review of cyprodinil included apple; the use pattern was at a more critical GAP than the one being proposed in this document (four applications at similar timings but at a lower application rate). New trials are therefore available to support the new proposed GAP. The representative crops included in the original EU review of cyprodinil did not include barley. New trials are therefore available to support the proposed GAP for barley.

Residue trials in apple and barley conducted in the EU to support the proposed EU GAPs are presented in Sections CA 6.3.1 and CA 6.3.2, respectively, below.

CA 6.3.1 Apple

Cyprodinil is proposed for use on apple (as formulation A8637C, a WG formulation containing 500 g cyprodinil/kg) according to the following EU proposed GAP, detailed in Table 6.3.1-1.

Table 6.3.1–1: Proposed EU GAPs for cyprodinil in A8637C on apple

Region	Outdoor/ Protected	Growth Stage	Max. No. of Applications	Minimum Application Interval (days)	Maximum		Minimum PHI (days)
					Rate (g a.s./ha)	Water (L/ha)	
Northern EU	Outdoor	BBCH 10-71	2-3	21	225 - 375	450-1500	21
Southern EU	Outdoor	BBCH 10-71	2-3	21	225 - 375	450-1500	21

Maximum rate is 225 g a.s./ha applied in 450 L/ha (50 g a.s./hL) and 375 g a.s./ha applied in 1500 L/ha (25 g a.s./hL).

The residue reports supporting the proposed EU GAP for cyprodinil on apple are referenced in Table 6.3.1-2 and the data are presented in Table 6.3.1-5.

Table 6.3.1-2: Report references for trials supporting the proposed EU GAP for cyprodinil on apple

Annex Pt.	Number.	Author/s	Issue Year	Report Title
K-CA 6.3.1/01	(1 of 19)	C Solé	2003	Residue study with fludioxonil (CGA173506) and cyprodinil (CGA219417) in or on apples in France (north) Syngenta File No. CGA173506/5767, Syngenta Report No. 02-2081
K-CA 6.3.1/02	(2 of 19)	C Solé	2003a	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in France (north) Syngenta File No. CGA173506/5768, Syngenta Report No. 02-2082

Annex Pt.	Number.	Author/s	Issue Year	Report Title
K-CA 6.3.1/03	(3 of 19)	C Solé	2003b	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in France (north) Syngenta File No. CGA173506/5625, Syngenta Report No. 02-2123
K-CA 6.3.1/04	(4 of 19)	C Solé	2003c	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in Switzerland Syngenta File No. CGA173506/5641, Syngenta Report No. 02-2154
K-CA 6.3.1/05	(5 of 19)	C Solé	2003d	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on pears in France (north) Syngenta File No. CGA173506/5689, Syngenta Report No. 02-2119
K-CA 6.3.1/06	(6 of 19)	C Solé	2003e	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on pears in France (north) Syngenta File No. CGA173506/5690, Syngenta Report No. 02-2120
K-CA 6.3.1/07	(7 of 19)	C Solé	2003f	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on pears in France (north) Syngenta File No. CGA173506/5691, Syngenta Report No. 02-2121
K-CA 6.3.1/08	(8 of 19)	M Walser	1997	Magnitude of residues in pears after application of cyprodinil (CGA219417) and fludioxonil (CGA173506) as formulation WG 62.5 (A-9219 B) Syngenta File No. CGA173506/0973, Syngenta Report No. 2025/96
K-CA 6.3.1/09	(9 of 19)	C Sole	2003g	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in France (south) Syngenta File No. CGA173506/5626, Syngenta Report No. 02-2126
K-CA 6.3.1/10	(10 of 19)	C Sole	2003h	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in France (South) Syngenta File No. CGA173506/5628, Syngenta Report No. 02-2127
K-CA 6.3.1/11	(11 of 19)	C Sole	2003i	Residue study with fludioxonil (CGA173506) and cyprodinil (CGA219417) in or on apples in Spain Syngenta File No. CGA173506/5623, Syngenta Report No. 02-2124
K-CA 6.3.1/12	(12 of 19)	C Sole	2003j	Residue study with fludioxonil (CGA173506) and cyprodinil (cga219417) in or on apples in Spain Syngenta File No. CGA173506/5624, Syngenta Report No. 02-2125
K-CA 6.3.1/13	(13 of 19)	M Walser	1997a	Magnitude of residues in pears after application of cyprodinil (CGA219417) and fludioxonil (CGA173506) as formulation WG 62.5 (A-9219 B) Syngenta File No. CGA173506/0975, Syngenta Report No. 2063/96
K-CA 6.3.1/14	(14 of 19)	M Walser	1997b	Magnitude of residues in pears after application of cyprodinil (CGA219417) and fludioxonil (CGA173506) as formulation WG 62.5 (A-9219 B) Syngenta File No. CGA173506/0976, Syngenta Report No. 2064/96
K-CA 6.3.1/15	(15 of 19)	M Walser	1998	Residue study with cyprodinil (CGA219417) and fludioxonil (CGA173506) in or on pears in Italy Syngenta File No. CGA173506/1117, Syngenta Report No. 2072/97
K-CA 6.3.1/16	(16 of 19)	M Walser	1998a	Residue study with cyprodinil (CGA219417) and fludioxonil (CGA173506) in or on pears in Spain Syngenta File No. CGA173506/1119, Syngenta Report No. 2055/97
K-CA 6.3.1/17	(17 of 19)	M Walser	1998b	Residue study with cyprodinil (CGA219417) and fludioxonil (CGA173506) in or on pears in France (South) Syngenta File No. CGA173506/1120, Syngenta Report No. 2161/97
K-CA 6.3.1/18	(18 of 19)	C Ertus F Jonchère	2012	Cyprodinil and dithianon - residue study on apples in northern France, Germany and Poland in 2011 Syngenta File No. A17447B_10001, Syngenta Report No. R B1042
K-CA 6.3.1/19	(19 of 19)	C Ertus F Jonchère	2012a	Cyprodinil and dithianon - residue study on apples in southern and Spain in 2011 Syngenta File No. A17447B_10000, Syngenta Report No. R B1043

Annex Pt.	Number.	Author/s	Issue Year	Report Title

Guidelines

The studies meet the requirements of the Commission of the European Communities: General Recommendations for the Design, Preparation and Realization of Residue Trials (**7029/V1/95 rev. 5, 22/7/1997**), and are designed to comply with **Regulation (EC) 1107/2009**.

GLP

All trials (field and analytical phases) were carried out in compliance with the principles of Good Laboratory Practice.

Materials and Methods

Twenty five supervised residue trials were conducted on apple and pear in 1996, 1997, 2002 and 2011 in northern or southern Europe. A summary of the trials conducted is presented in Table 6.3.1-3.

Table 6.3.1-3: Summary of cyprodinil residue trials on pome fruit

Country	1996	1997	2002	2011
Northern Europe				
France (north)	--	--	6 Decline (3 apple, 3 pear)	2 Harvest (apple)
Switzerland	1 Decline (pear)	--	1 Decline (apple)	--
Germany	--	--	--	1 Harvest (apple)
Poland	--	--	--	1 Harvest (apple)
Southern Europe				
France (south)	--	1 Decline (pear)	2 Decline (apple)	2 Harvest (apple)
Spain	--	1 Decline (pear)	2 Decline (apple)	2 Harvest (apple)
Italy	2 Decline (pear)	1 Decline (pear)	--	--

Decline trials are those with three or more sampling times.

Apple is a major crop in northern and southern Europe and therefore generally requires eight trials in each residue region.

Treatments with cyprodinil were conducted as foliar (BBCH 71-87) spray applications utilising the formulations as detailed in Table 6.3.1-4 at a nominal application rate of 375 g a.s./ha (actual rates 292-413 g a.s./ha) with an interval of 6-14 days between applications with the exception of the 2002 trials where the interval between applications 1 and 2 was 44-95 days. In one trial (02-2123), the first of the three applications was applied at 655 g a.s./ha; this first application of cyprodinil at a higher rate than recommended is considered to have had little effect on the final residue as the residue levels in the sample taken immediately prior to the last application (denoted as 0* in table 6.3.1-5) is consistent with the other trials. The longer interval between applications 1 and 2 in some trials is also considered to have had little effect on the final residue. The water volumes during application ranged from 625 to 1915 L/ha.

Table 6.3.1-4: Summary of cyprodinil formulations used in the presented trials

Product code	Formulation Type	Composition
A9219B	WG	375 g/kg cyprodinil 250 g/kg fludioxonil
A17447B	WG	225 g/kg cyprodinil 350 g/kg dithianon

Samples of whole fruits were taken and analysed for residues of cyprodinil by EU reviewed analytical method REM 141.01 with a LOQ of 0.02 mg/kg or REM 141.10 with a LOQ of 0.01 mg/kg. Method REM 141.01 has been fully validated on apple (see MCA Section 4.1.2) and is presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B5.2.2, 2005**). The method is therefore suitable for analysis of residues of cyprodinil in all pome fruit (OECD (2007) Guidance Document on Pesticide Residue Analytical Methods. Environment, Health and Safety Publications, Series on Testing and Assessment No.72 and Series on Pesticides No. 39). Full method description and validation data for REM 141.10 are presented in document M-CA Section 4, CA 4.1.2. Apples are considered a high water crop and acceptable procedural recovery data is provided in the report on lettuce and orange (high water/high acid crops) for method REM 144.10. Additional recovery data on apple is provided in the residue study reports. SANCO/3029/99 rev.4 Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III (part A, Section 5) of Directive 91/414 states that "*it is not a requirement that the whole data set is generated every time a method is used*" and "*reduced validation data for sample matrices within the same crop group (as defined in SANCO/825/00) are acceptable*". Procedural recovery data are presented with the results of the residues trials in Table 6.3.1-5. The method REM 141.10 is appropriately validated and is considered fit-for-purpose for the analysis of apples.

Allowing for a 25% deviation from the proposed maximum application rate, the rates and application timings in all trials cover the proposed EU GAP. The proposed PHI is 21 days and samples from the trials were taken at a latest PHI of 14 (17 trials conducted between 1996 and 2002) or 21 days (eight trials conducted in 2011). On the basis of the available decline data it can be seen that residues of cyprodinil decrease over time therefore residues at a PHI of 21 days can be estimated based on extrapolation from the values measured at 0, 3, 7, 10 and 14 days. An example calculation is given in Appendix 1.

Samples were stored up to a maximum of 8 months from sampling to extraction. Residues of cyprodinil are stable for at least 24 months (see section CA 6.1) and therefore no degradation will have occurred between sampling and analysis.

The available trials are sufficient to support the EU proposed GAP for apple. Twelve acceptable trials are available for northern Europe (8 apple, 4 pear) and 13 acceptable trials are available for southern Europe (8 apple, 5 pear). Since the last application is made after the consumable part of the crop has formed, and a minimum of eight trials (including at least four trials on apple) are available in each region, the data can be extrapolated to the whole pome fruit group with the same GAP, consistent with the recommendations of the Commission of the European Communities (**SANCO 7525/VI/95 rev. 9 March 2011**). Therefore, all trials support the proposed use on apple.

Residues found in the trials from northern and southern Europe are comparable, leading to similar STMR and HR values. The data sets can therefore be combined and give sufficient data to calculate MRLs and to conduct the consumer risk assessment.

The results of the residue trials for cyprodinil are presented in Table 6.3.1-5.

Table 6.3.1-5: Summary of residue data supporting the EU proposed GAP for cyprodinil on apple

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Northern Europe								
Report: 02-2081 Study: 02-2081 Trial: 02-2081 - Study to GLP - Study carried out in 2002	Apple (Jona Gold)	FRANCE (Europe North)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha A9219B	BBCH 83 BBCH 83 BBCH 87	0*	Fruit (BBCH 87)	0.16	Cyprodinil Fruit: mean = 91% RSD = NA (n = 2 in 0.02 and 0.20 mg/kg spiking)
					0	Fruit (BBCH 87)	0.69	
					3	Fruit (BBCH 87)	0.34	
					7	Fruit (BBCH 87)	0.35	
					7	Fruit (BBCH 87)	0.40	
					10	Fruit (BBCH 87)	0.28	
					14	Fruit (BBCH 87)	0.27	
					21♦	Fruit	0.16♦	
Report: 02-2082 Study: 02-2082 Trial: 02-2082 - Study to GLP - Study carried out in 2002	Apple (Akane)	FRANCE (Europe North)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha A9219B	BBCH 72 BBCH 75 - 78 BBCH 83	0*	Fruit (BBCH 83)	0.16	Cyprodinil Fruit: mean = 90% RSD = NA (n = 2 in 0.02 and 0.20 mg/kg spiking)
					0	Fruit (BBCH 83)	0.23	
					3	Fruit (BBCH 83)	0.27	
					7	Fruit (BBCH 85)	0.21	
					7	Fruit (BBCH 85)	0.21	
					10	Fruit	0.13	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						(BBCH 85-87)		
					14	Fruit (BBCH 87)	0.08	
					21♦	Fruit	0.05♦	
Report: 02-2123 Study: 02-2123 Trial: 02-2123 - Study to GLP - Study carried out in 2002	Apple (Jonagored)	FRANCE (Europe North)	655 g a.s./ha 389 g a.s./ha 360 g a.s./ha A9219B	BBCH 74 BBCH 78 BBCH 85	0*	Fruit (BBCH 85)	0.20	Cyprodinil Fruit: mean = 99% RSD = NA (n = 2 in 0.02 and 1.00 mg/kg spiking)
					0	Fruit (BBCH 85)	0.50	
					3	Fruit (BBCH 87)	0.24	
					7	Fruit (BBCH 87)	0.14	
					10	Fruit (BBCH 87)	0.21	
					14	Fruit (BBCH 87)	0.32	
					21♦	Fruit	0.17♦	
Report: 02-2154 Study: 02-2154 Trial: 02-2154 - Study to GLP - Study carried out in 2002	Apple (Golden Delicious)	SWITZERLAND (Europe North)	393 g a.s./ha 380 g a.s./ha 371 g a.s./ha A9219B	BBCH 73 BBCH 85 BBCH 86	0*	Fruit (BBCH 86)	0.32	Cyprodinil Fruit: mean = 94% RSD = NA (n = 2 in 0.02 and 2.00 mg/kg spiking)
					0	Fruit (BBCH 86)	0.56	
					3	Fruit (BBCH 86)	0.56	
					7	Fruit (BBCH 86)	0.52	
					10	Fruit (BBCH 87)	0.38	
					14	Fruit	0.35	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						(BBCH 88)		
					21♦	Fruit	0.27♦	
Report: 02-2119 Study: 02-2119 Trial: 02-2119 - Study to GLP - Study carried out in 2002	Pear (Doyenne du Comice)	FRANCE (Europe North)	365 g a.s./ha 392 g a.s./ha 361 g a.s./ha A9219B	BBCH 72 BBCH 81 BBCH 85	0*	Fruit (BBCH 85)	0.04	Cyprodinil Fruit: mean = 97% RSD = 7% (n = 3 in 0.02 –1.00 mg/kg spiking range)
					0	Fruit (BBCH 85)	0.35	
					3	Fruit (BBCH 85)	0.25	
					7	Fruit (BBCH 87)	0.18	
					10	Fruit (BBCH 87)	0.15	
					14	Fruit (BBCH 87)	0.08	
					21♦	Fruit	0.04♦	
Report: 02-2120 Study: 02-2120 Trial: 02-2120 - Study to GLP - Study carried out in 2002	Pear (William)	FRANCE (Europe North)	381 g a.s./ha 407 g a.s./ha 374 g a.s./ha A9219B	BBCH 71 BBCH 79 BBCH 85	0*	Fruit (BBCH 85)	0.15	Cyprodinil Fruit: mean = 106% RSD = NA (n = 2 in 0.02 and 1.00 mg/kg spiking)
					0	Fruit (BBCH 85)	0.53	
					3	Fruit (BBCH 85)	0.28	
					7	Fruit (BBCH 87)	0.16	
					10	Fruit (BBCH 87)	0.10	
					14	Fruit (BBCH 89)	0.10	
					21♦	Fruit	0.03♦	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Report: 02-2121 Study: 02-2121 Trial: 02-2121 - Study to GLP - Study carried out in 2002	Pear (Conference)	FRANCE (Europe North)	381 g a.s./ha 387 g a.s./ha 413 g a.s./ha A9219B	BBCH 72 - 73 BBCH 81 BBCH 85	0*	Fruit (BBCH 85)	0.15	Cyprodinil Fruit: mean = 94% RSD = 9% (n = 3 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit (BBCH 85)	0.27	
					3	Fruit (BBCH 85-87)	0.17	
					7	Fruit (BBCH 87)	0.12	
					10	Fruit (BBCH 87)	0.09	
					14	Fruit (BBCH 89)	0.09	
					21♦	Fruit	0.04♦	
Report: 2025/96 Study: 2025/96 Trial: 2025/96 - Study to GLP - Study carried out in 1996	Pear (Williams)	SWITZERLAND (Europe North)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha A9219B	BBCH 75 BBCH 76 BBCH 81	0*	Fruit (BBCH 81)	0.07	Cyprodinil Fruit: mean = 102% RSD = 4% (n = 3 in 0.02 – 2.00 mg/kg spiking range)
					0	Fruit (BBCH 81)	0.30	
					7	Fruit (BBCH 82)	0.02	
					14	Fruit (BBCH 87)	0.04	
					21	Fruit (BBCH 88)	0.02	
Report: R B1042 Study: B1042 Trial: B1042 AN1 - Study to GLP - Study carried out in 2011	Apple (Opal)	FRANCE (Europe North)	308 g a.s./ha 308 g a.s./ha 308 g a.s./ha A17447B	BBCH 81 BBCH 81-83 BBCH 85	20	Fruit (BBCH 87-89)	0.28	Cyprodinil Fruit: mean = 95% RSD = NA (n = 2 in 0.01 – 1.10 mg/kg spiking range)
Report: R B1042 Study: B1042	Apple	FRANCE	321 g a.s./ha 305 g a.s./ha	BBCH 81 BBCH 81	21	Fruit	0.18	Cyprodinil

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Trial: B1042 BM1 - Study to GLP - Study carried out in 2011	(Goldrush)	(Europe North)	317 g a.s./ha A17447B	BBCH 85		(BBCH 87)		Fruit: mean = 95% RSD = NA (n = 2 in 0.01 – 1.10 mg/kg spiking range)
Report: R B1042 Study: B1042 Trial: B1042 GE1 - Study to GLP - Study carried out in 2011	Apple (Granny Smith)	Germany (Europe North)	293 g a.s./ha 306 g a.s./ha 301 g a.s./ha A17447B	BBCH 77-78 BBCH 77-78 BBCH 78	21	Fruit (BBCH 87-89)	0.41	Cyprodinil Fruit: mean = 95% RSD = NA (n = 2 in 0.01 – 1.10 mg/kg spiking range)
Report: R B1042 Study: B1042 Trial: B1042 PL1 - Study to GLP - Study carried out in 2011	Apple (Ariwa)	Poland (Europe North)	284 g a.s./ha 284 g a.s./ha 291 g a.s./ha A17447B	BBCH 77-81 BBCH 78-81 BBCH 79-85	20	Fruit (BBCH 87)	0.79	Cyprodinil Fruit: mean = 95% RSD = NA (n = 2 in 0.01 – 1.10 mg/kg spiking range)
Southern Europe								
Report: 02-2126 Study: 02-2126 Trial: 02-2126 - Study to GLP - Study carried out in 2002	Apple (Gala)	FRANCE (Europe South)	371 g a.s./ha 377 g a.s./ha 377 g a.s./ha A9219B	BBCH 72 BBCH 81 BBCH 85	0*	Fruit (BBCH 85)	0.47	Cyprodinil Fruit: mean = 86% RSD = 7% (n = 3 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit (BBCH 85)	0.45	
					3	Fruit (BBCH 85)	0.39	
					7	Fruit (BBCH 87)	0.34	
					10	Fruit (BBCH 87)	0.19	
					14	Fruit (BBCH 89)	0.18	
					21♦	Fruit	0.10♦	
Report: 02-2127 Study: 02-2127 Trial: 02-2127 - Study to GLP - Study carried out in 2002	Apple (Granny)	FRANCE (Europe South)	395 g a.s./ha 359 g a.s./ha 365 g a.s./ha	BBCH 73 - 74 BBCH 85 BBCH 85	0*	Fruit (BBCH 85)	0.12	Cyprodinil Fruit: mean = 96% RSD = 5% (n = 3 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit (BBCH 85)	0.58	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
			A9219B		3	Fruit (BBCH 85)	0.49	
					7	Fruit (BBCH 87)	0.27	
					10	Fruit (BBCH 87)	0.32	
					14	Fruit (BBCH 87)	0.17	
					21♦	Fruit	0.10♦	
Report: 02-2124 Study: 02-2124 Trial: 02-2124 - Study to GLP - Study carried out in 2002	Apple (Reineta)	SPAIN (Europe South)	378 g a.s./ha 381 g a.s./ha 377 g a.s./ha A9219B	BBCH 74 - 75 BBCH 76 BBCH 81	0*	Fruit (BBCH 81)	0.21	Cyprodinil Fruit: mean = 97% RSD = NA (n = 2 in 0.02 and 1.00 mg/kg spiking)
					0	Fruit (BBCH 81)	0.75	
					3	Fruit (BBCH 81-85)	0.74	
					7	Fruit (BBCH 81-85)	0.74	
					10	Fruit (BBCH 85-87)	0.62	
					14	Fruit (BBCH 87-89)	0.27	
					21♦	Fruit	0.23♦	
Report: 02-2125 Study: 02-2125 Trial: 02-2125 - Study to GLP - Study carried out in 2002	Apple (Golden)	SPAIN (Europe South)	379 g a.s./ha 389 g a.s./ha 389 g a.s./ha A9219B	BBCH 74 BBCH 81 BBCH 87	0*	Fruit (BBCH 87)	0.25	Cyprodinil Fruit: mean = 98% RSD = NA (n = 2 in 0.02 and 1.00 mg/kg spiking)
					0	Fruit (BBCH 87)	0.50	
					3	Fruit (BBCH 87-89)	0.40	
					7	Fruit	0.22	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						(BBCH 89)		
					10	Fruit (BBCH 89)	0.28	
					14	Fruit (BBCH 89)	0.22	
					21♦	Fruit	0.14♦	
Report: 2063/96 Study: 2063/96 Trial: 2063/96 - Study to GLP - Study carried out in 1996	Pear (Kaiser A.)	ITALY (Europe South)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha A9219B	BBCH 75 BBCH 75 - 77 BBCH 77	0*	Fruit (BBCH 77)	0.27	Cyprodinil Fruit: mean = 99% RSD = 11% (n = 5 in 0.02 – 2.00 mg/kg spiking range)
					0	Fruit (BBCH 77)	0.59	
					7	Fruit (BBCH 77)	0.46	
					14	Fruit (BBCH 77-79)	0.33	
					21	Fruit (BBCH 79-81)	0.22	
Report: 2064/96 Study: 2064/96 Trial: 2064/96 - Study to GLP - Study carried out in 1996	Pear (Kaiser)	ITALY (Europe South)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha A9219B	BBCH 77 BBCH 77 - 79 BBCH 79	0*	Fruit (BBCH 77)	0.55	Cyprodinil Fruit: mean = 99% RSD = 11% (n = 5 in 0.02 – 2.00 mg/kg spiking range)
					0	Fruit (BBCH 77)	1.05	
					7	Fruit (BBCH 77)	0.70	
					14	Fruit (BBCH 79)	0.56	
					21	Fruit (BBCH 87)	0.61	
Report: 2072/97 Study: 2072/97 Trial: 2072/97 - Study to GLP	Pear (Abate Fetel)	ITALY (Europe South)	375 g a.s./ha 375 g a.s./ha 375 g a.s./ha	BBCH 77 BBCH 77 - 79 BBCH 79	0*	Fruit (BBCH 79)	0.11	Cyprodinil Fruit: mean = 102% RSD = 8% (n = 3 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit	0.26	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
- Study carried out in 1997			A9219B			(BBCH 79)		
					7	Fruit (BBCH 79-81)	0.26	
					14	Fruit (BBCH 81)	0.13	
					21	Fruit (BBCH 85)	0.10	
Report: 2055/97 Study: 2055/97 Trial: 2055/97 - Study to GLP - Study carried out in 1997	Pear (Conference)	SPAIN (Europe South)	373 g a.s./ha 373 g a.s./ha 373 g a.s./ha A9219B	BBCH 75 BBCH 77 BBCH 78	0*	Fruit (BBCH 78)	0.09	Cyprodinil Fruit: mean = 97% RSD = 10% (n = 5 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit (BBCH 78)	0.75	
					3	Fruit (BBCH 78)	0.50	
					7	Fruit (BBCH 79)	0.36	
					14	Fruit (BBCH 85)	0.19	
					21	Fruit (BBCH 85-86)	0.12	
Report: 2161/97 Study: 2161/97 Trial: 2161/97 - Study to GLP - Study carried out in 1997	Pear (Williams)	FRANCE (Europe South)	371 g a.s./ha 371 g a.s./ha 379 g a.s./ha A9219B	BBCH 75 BBCH 77 BBCH 77	0*	Fruit (BBCH 77)	0.07	Cyprodinil Fruit: mean = 102% RSD = 8% (n = 3 in 0.02 – 1.00 mg/kg spiking range)
					0	Fruit (BBCH 77)	0.54	
					3	Fruit (BBCH 81)	0.14	
					7	Fruit (BBCH 83)	0.11	
					14	Fruit (BBCH 87)	0.05	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
					21	Fruit (BBCH 89)	0.04	
Report: R B1043 Study: B1043 Trial: B1043 DR1 - Study to GLP - Study carried out in 2011	Apple (Goldrush)	FRANCE (Europe South)	292 g a.s./ha 298 g a.s./ha 304 g a.s./ha A17447B	BBCH 81 BBCH 81 BBCH 87	20	Fruit (BBCH 89)	0.07	Cyprodinil Fruit: mean = 93% RSD = 5% (n = 3 in 0.01 – 1.00 mg/kg spiking range)
Report: R B1043 Study: B1043 Trial: B1043 ES1 - Study to GLP - Study carried out in 2011	Apple (Golden Reinders)	SPAIN (Europe South)	313 g a.s./ha 310 g a.s./ha 294 g a.s./ha A17447B	BBCH 79-81 BBCH 79-81 BBCH 81	20	Fruit (BBCH 85-87)	0.22	Cyprodinil Fruit: mean = 93% RSD = 5% (n = 3 in 0.01 – 1.00 mg/kg spiking range)
Report: R B1043 Study: B1043 Trial: B1043 ES2 - Study to GLP - Study carried out in 2011	Apple (Golden Reinders)	SPAIN (Europe South)	316 g a.s./ha 300 g a.s./ha 297 g a.s./ha A17447B	BBCH 78-79 BBCH 79-81 BBCH 79-81	21	Fruit (BBCH 87-89)	0.24	Cyprodinil Fruit: mean = 93% RSD = 5% (n = 3 in 0.01 – 1.00 mg/kg spiking range)
Report: R B1043 Study: B1043 Trial: B1043 TL1 - Study to GLP - Study carried out in 2011	Apple (Gala)	FRANCE (Europe South)	308 g a.s./ha 304 g a.s./ha 310 g a.s./ha A17447B	BBCH 77 BBCH 81 BBCH 85	20	Fruit (BBCH 89)	0.25	Cyprodinil Fruit: mean = 93% RSD = 5% (n = 3 in 0.01 – 1.00 mg/kg spiking range)

Notes:
* - sample taken prior to last application
♦ - extrapolated data from 0, 4, 7, 10 and 14 day PHI residues. An example calculation is given in Appendix 1.
NA = not applicable.
No residues were found above the LOQ in untreated samples except at trial 2055/97 where a residue of 0.10 mg/kg was found in one of the three untreated samples.

Response to a query from the RMS : Apple, pear : Please precise the storage time of extracts before analysis for the following studies: K-CA6.3.1/01 toK-CA6.3.1 and K-CA6.3.1/09 to K-CA6.3.1-17. In these studies, if analysis of extracts is performed more than 24 hours after the extraction, the stability of extracted samples should be demonstrated for more than 24 hours in conditions used in the studies, according OECD guideline 506.

Although the residue trials in question do not state the length of time that the extraction solutions were stored prior to analysis, procedural recovery samples stored under the same conditions demonstrate the data is acceptable and validate the series.

For MRL setting and risk assessment, the definition of the residue for cyprodinil is parent cyprodinil only. Calculations are presented below.

Cyprodinil residue calculations for MRL setting

In one trial in northern Europe and five trials in southern Europe, samples of apples and pears were taken at the required PHI of 21 days. In the remaining trials, samples of apples and pears were taken at several time points up to 14 days after the final application of cyprodinil. Estimated residue values at PHI 21 days are calculated from the available data at 0, 3, 7, 10 and 14 days after application by plotting a graph of the natural logarithm of the residue against time, assuming degradation according to first order kinetics. An example calculation is presented in Appendix 1 of this document. These data provide a significant understanding of the behaviour of the chemical with time and provide data, which allow the residue to be extrapolated to the proposed GAP as permitted in **SANCO 7039/VI/95 EN 22/7/1997**.

MRLs values for pome fruit have been calculated for northern and southern Europe for cyprodinil according to the OECD calculator (**OECD Series on pesticides No. 56, ENV/JM/MONO (2011)2, 1 March 2011**). In these calculations a single data point from each trial supporting the EU proposed GAP has been considered. The cyprodinil residue values used in the MRL calculations are underlined in Table 6.3.1-5. The calculated outputs are presented in Table 6.3.1-6.

Table 6.3.1-6: MRL, STMR and HR calculations for cyprodinil on pome fruit – proposed EU GAPs

Region	Outdoor / Protected	Residue Data (mg/kg)	MRL OECD Method (mg/kg)	MRL OECD Rounded (mg/kg)	STMR (mg/kg)	HR (mg/kg)
Northern EU	Outdoor	0.16, 0.05, 0.17, 0.27, 0.04, 0.03, 0.04, 0.02, 0.28, 0.18, 0.41, 0.79	1.091	1.5	0.17	0.79
Southern EU	Outdoor	0.10, 0.10, 0.23, 0.14, 0.22, 0.61, 0.10, 0.12, 0.04, 0.07, 0.22, 0.24, 0.25	0.770	0.8	0.14	0.61
Combined EU	Outdoor	0.16, 0.05, 0.17, 0.27, 0.04, 0.03, 0.04, 0.02, 0.10, 0.10, 0.23, 0.14, 0.22, 0.61, 0.10, 0.12, 0.04, 0.28, 0.18, 0.41, 0.79, 0.07, 0.22, 0.24, 0.25	0.924	1	0.16	0.79

There is an existing EU MRL of 1.5 mg/kg (**Commission Regulation (EU) 400/2015**) for cyprodinil on pome fruit. The data presented in Table 6.3.1-6 from trials supporting the proposed EU GAP indicate that all residues will be within the existing EU MRL of 1.5 mg/kg.

Cyprodinil residue calculations risk assessment

STMR and HR values for pome fruit have been calculated for northern and southern Europe for cyprodinil. The STMR is the median residue and the HR is the highest residue value found. In these calculations a single data point from each trial supporting the proposed EU GAP has been considered.

The residue values used in the MRL and STMR calculations are underlined in Table 6.3.1-5. A summary of the calculated outputs are presented in Table 6.3.1-7.

Table 6.3.1-7: STMR and HR calculations for cyprodinil on apple – proposed EU GAP

Commodity (code)	Calculated MRL (mg/kg)	Existing EU MRL (mg/kg)	STMR (mg/kg)	HR (mg/kg)
Apple (0130010)	1.0	1.5	0.16	0.79

Conclusions

The use of cyprodinil at the representative GAP leads to a calculated MRL of 1.0 mg/kg for apple and therefore does not exceed the existing EU MRL of 1.5 m/kg (**Commission Regulation (EU) 400/2015**).

The representative use of product A8637C on apples is supported by sufficient residue data.

CA 6.3.2 Barley

Cyprodinil is proposed for use on barley (as formulation A14325E, an EC formulation containing 300 g cyprodinil/L) according to the following EU GAP, detailed in Table 6.3.2-1.

Table 6.3.2–1: Proposed EU GAPs for cyprodinil in formulation A14325E on barley

Region	Outdoor/ Protected	Growth Stage	Max. No. of Applications	Minimum Application Interval (days)	Maximum		Minimum PHI (days)
					Rate (g a.s./ha)	Water (L/ha)	
Northern EU	Outdoor	BBCH 30-61	1-2	14	450	150-400	45[(a)]
Southern EU	Outdoor	BBCH 30-61	1-2	14	450	150-400	45[(a)]

(a) It is more appropriate for cereal crops to indicate the application timing using growth stage rather than a pre-harvest interval; however a representative PHI has been given.

The residue reports supporting the proposed EU proposed GAP for cyprodinil on barley are referenced in Table 6.3.2-2 and the data are presented in Table 6.3.2-5.

Table 6.3.2-2: Report references for trials supporting the proposed EU GAP for cyprodinil on barley

Annex Pt.	Number.	Author/s	Issue Year	Report Title
K-CA 6.3.2/01	(1 of 54)	M Meyer	2015	Cyprodinil - residue study on barley in the United Kingdom, Germany and northern France in 2013 Syngenta File No. A14325E_10078, Syngenta Report No. IF-13/02563482
K-CA 6.3.2/02	(2 of 54)	C Mahlo J Bodsch	2015	Cyprodinil - residue study on barley in Denmark, Germany the United Kingdom and Hungary in 2014 Syngenta File No. A14325E_10084, Syngenta Report No. TK0223253
K-CA 6.3.2/03	(3 of 54)	M Meyer	2015a	Cyprodinil – residue study on barley in Southern France, Spain and Greece in 2013 Syngenta File No. A14325E_10083, Syngenta Report No. TK0178712-REG
K-CA 6.3.2/04	(4 of 54)	C Mahlo J Bodsch T Link	2015	Cyprodinil - residue study on barley in Spain and Italy in 2014 Syngenta File No. A14325E_10085, Syngenta Report No. TK0223256-REG

Annex Pt.	Number.	Author/s	Issue Year	Report Title
K-CA 6.3.2/05-	(5 of 5)-	C-Ertus	2016	~~Study ongoing to replace 2 lost SEU (Spain) trials conducted in 2014. Final reports expected in 2016.~~ Cyprodinil – Residue Study on Winter Barley under Field Conditions in Southern France and Italy in 2015, Syngenta File No. A14325E_10094, Report Number R B5092

Guidelines

The studies meet the requirements of the Commission of the European Communities: General Recommendations for the Design, Preparation and Realization of Residue Trials (**7029/V1/95 rev. 5, 22/7/1997**), and are designed to comply with **Regulation (EC) 1107/2009**.

GLP

All trials (field and analytical phases) were carried out in compliance with the principles of Good Laboratory Practice.

Materials and Methods

Fourteen supervised residue trials were conducted on barley in 2013 and 2014 in northern or southern Europe. A summary of the trials conducted is presented in Table 6.3.2-3.

Table 6.3.2-3: Summary of cyprodinil residue trials on barley

Country	2013	2014	2015
Northern Europe			
France (north)	1 Decline	--	--
United Kingdom	1 Decline	1 Decline	--
Germany	2 Harvest	1 Harvest	--
Denmark	--	1 Harvest	--
Hungary	--	1 Decline	--
Southern Europe			
France (south)	1 Decline	--	1
Spain	1 Harvest, 1 Decline	1 Decline	--
Italy	1 Harvest	--	1
Greece	--	1 Decline	

Decline trials are those with three or more sampling times.

Barley is a major crop in northern and southern Europe and therefore generally requires eight trials in each residue region. Two trials in southern Europe (Spain) in 2014 were lost; the first application was carried out at BBCH 30 in trials 14-00689-02 and -04 but due to the hot weather the plants did not start booting or heading. The trials are being repeated in 2015 and the results are expected in 2016.

Treatments with cyprodinil were conducted as foliar spray applications at BBCH 24-31 (BBCH 30 in most trials) and BBCH 61-75 (BBCH 65 in most trials) utilising the formulation as detailed in Table 6.3.2-4 at a nominal application rate of 450 g a.s./ha (actual rates 430-473 g a.s./ha) with an interval of 21-50 days between applications. The longer interval between applications is considered to have had little effect on the final residue. The water volumes during application ranged from 197 to 404 L/ha.

Table 6.3.2-4: Summary of cyprodinil formulations used in the presented trials

Product code	Formulation Type	Composition
A14325E	EC	300 g/L cyprodinil

Samples of whole plants, grain and straw were taken and analysed for residues of cyprodinil by analytical method REM 141.10 with a LOQ of 0.01 mg/kg. Method REM 141.10 has been fully validated on barley grain, and full method description and validation data are presented in document M-CA Section 4, CA 4.1.2 for REM 141.10. Procedural recovery data are presented with the results of the residues trials in Table 6.3.2-5

Allowing for a 25% deviation from the proposed maximum application rate, the rates in all trials cover the proposed EU GAP. The latest application timings were equal to or later than the latest recommended timing according to the proposed GAP and so the trials represent a worst-case.

Samples were stored up to a maximum of 12 months from sampling to extraction. Residues of cyprodinil are stable in wheat ears and stalks for at least 24 months (see section CA 6.1) and therefore no degradation will have occurred between sampling and analysis.

The available trials are sufficient to support the EU GAP for barley. Eight acceptable trials are available for northern Europe and six acceptable trials are currently available for southern Europe; two further trials are currently in progress.

Residues of cyprodinil found in the trials from southern Europe were somewhat higher than those from northern Europe, leading to higher STMR and HR values.

The results of the residue trials for cyprodinil are presented in Table 6.3.2-5.

Table 6.3.2-5: Summary of residue data supporting the EU proposed GAP for cyprodinil on barley

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Northern Europe								
Report:TK0178711 Study:IF-13/02563-482 Trial: 13-00252-01 - Study to GLP - Study carried out in 2013	Barley (Flagon)	UNITED KINGDOM (Europe North)	453 g a.s./ha 430 g a.s./ha A14325E	BBCH 30-31 BBCH 65-69	0	Whole plant (BBCH 65-69)	9.0	Cyprodinil Whole plant: mean = 99% RSD = NA (n = 2 in 0.01 and 3.03 mg/kg spiking) Grain: mean = 96% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 91% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					10	Whole plant (BBCH 69)	1.3	
					21	Whole plant (BBCH 73-77)	0.44	
					30	Whole plant (BBCH 75-83)	0.34	
					39	Whole plant (BBCH 85-87)	0.33	
					46	Grain (BBCH 89)	0.26	
					46	Straw (BBCH 89)	0.55	
Report:TK0178711 Study:IF-13/02563-482 Trial: 13-00252-02 - Study to GLP - Study carried out in 2013	Barley (Highlight)	GERMANY (Europe North)	449 g a.s./ha 464 g a.s./ha A14325E	BBCH 29-30 BBCH 61-65	45	Grain (BBCH 89)	0.61	Cyprodinil Whole plant: mean = 99% RSD = NA (n = 2 in 0.01 and 3.03 mg/kg spiking) Grain: mean = 96% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 91% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					45	Straw (BBCH 89)	1.5	
Report:TK0178711 Study:IF-13/02563-482 Trial: 13-00252-03 - Study to GLP - Study carried out in 2013	Barley (Shandy)	FRANCE (Europe North)	465 g a.s./ha 456 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	9.8	Cyprodinil Whole plant: mean = 99% RSD = NA (n = 2 in 0.01 and 3.03 mg/kg spiking) Grain: mean = 96% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 91% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					9	Whole plant (BBCH 75)	2.2	
					20	Whole plant (BBCH 85)	0.79	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
					30	Whole plant (BBCH 87)	1.2	
					41	Whole plant (BBCH 89)	0.93	
					44	Grain (BBCH 89)	0.92	
					44	Straw (BBCH 89)	0.96	
Report:TK0178711 Study:IF-13/02563-482 Trial: 13-00252-04 - Study to GLP - Study carried out in 2013	Barley (KWS Thessa)	GERMANY (Europe North)	442 g a.s./ha 453 g a.s./ha A14325E	BBCH 24-30 BBCH 65-67	45	Grain (BBCH 89)	0.43	Cyprodinil Whole plant: mean = 99% RSD = NA (n = 2 in 0.01 and 3.03 mg/kg spiking) Grain: mean = 96% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 91% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					45	Straw (BBCH 89)	0.16	
Report:TK0223253-REG Study:IF-14/02973045 Trial: 14-00701-01 - Study to GLP - Study carried out in 2014	Barley (Evergreen)	DENMARK (Europe North)	458 g a.s./ha 433 g a.s./ha A14325E	BBCH 30 BBCH 75	36	Grain (BBCH 90)	0.30	Cyprodinil Whole plant: mean = 92% RSD = 6.1% (n = 3 in 0.01 to 14 mg/kg spiking) Grain: mean = 93% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 95% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					36	Straw (BBCH 90)	0.33	
Report:TK0223253-REG Study:IF-14/02973045 Trial: 14-00701-02 - Study to GLP - Study carried out in 2014	Barley (Salome)	GERMANY (Europe North)	460 g a.s./ha 465 g a.s./ha A14325E	BBCH 30 BBCH 65	37	Grain (BBCH 89)	0.79	Cyprodinil Whole plant: mean = 92% RSD = 6.1% (n = 3 in 0.01 to 14 mg/kg spiking) Grain: mean = 93% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 95% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					37	Straw (BBCH 89)	0.17	
Report:TK0223253-REG Study:IF-14/02973045 Trial: 14-00701-03 - Study to GLP - Study carried out in 2014	Barley (Concerto)	UNITED KINGDOM (Europe North)	469 g a.s./ha 440 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	8.0	Cyprodinil Whole plant: mean = 92% RSD = 6.1% (n = 3 in 0.01 to 14 mg/kg spiking) Grain: mean = 93% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					19	Whole plant (BBCH 83)	1.0	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
					42	Whole plant (BBCH 89)	0.88	Straw: mean = 95% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					47	Grain (BBCH 89)	0.72	
					47	Straw (BBCH 89)	0.50	
					49	Grain (BBCH 89)	0.88	
					49	Straw (BBCH 89)	0.58	
					56	Grain (BBCH 89)	0.83	
					56	Straw (BBCH 89)	0.61	
Report:TK0223253-REG Study:IF-14/02973045 Trial: 14-00701-04 - Study to GLP - Study carried out in 2014	Barley (Scarlett)	HUNGARY (Europe North)	468 g a.s./ha 452 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	9.7	Cyprodinil Whole plant: mean = 92% RSD = 6.1% (n = 3 in 0.01 to 14 mg/kg spiking) Grain: mean = 93% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking) Straw: mean = 95% RSD = NA (n = 2 in 0.01 and 2.00 mg/kg spiking)
					20	Whole plant (BBCH 85)	3.2	
					42	Whole plant (BBCH 88)	0.90	
					44	Grain (BBCH 89)	0.28	
					44	Straw (BBCH 89)	1.3	
					48	Grain (BBCH 89)	0.29	
					48	Straw (BBCH 89)	1.3	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
					53	Grain (BBCH 89)	0.29	
					53	Straw (BBCH 89)	1.0	
Southern Europe								
Report:TK0178712-REG Study:IF-13/02561770 Trial: 13-00247-01 - Study to GLP - Study carried out in 2013	Barley (Olympic)	FRANCE (Europe South)	446 g a.s./ha 461 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	12	Cyprodinil Whole plant: mean = 94% RSD = 13% (n = 3 in 0.01 to 17 mg/kg spiking) Grain: mean = 96% RSD = 12% (n = 4 in 0.01 to 4 mg/kg spiking) Straw: mean = 100% RSD = NA (n = 2 in 0.01 and 2 mg/kg spiking)
					10	Whole plant (BBCH 73)	2.4	
					19	Whole plant (BBCH 83)	2.3	
					29	Whole plant (BBCH 85)	1.2	
					39	Whole plant (BBCH 89)	0.81	
					47	Grain (BBCH 89)	0.74	
					47	Straw (BBCH 89)	0.45	
Report:TK0178712-REG Study:IF-13/02561770 Trial: 13-00247-02 - Study to GLP - Study carried out in 2013	Barley (Pewter)	SPAIN (Europe South)	439 g a.s./ha 459 g a.s./ha A14325E	BBCH 30 BBCH 65	45	Grain (BBCH 89)	1.1	Cyprodinil Whole plant: mean = 94% RSD = 13% (n = 3 in 0.01 to 17 mg/kg spiking) Grain: mean = 96% RSD = 12% (n = 4 in 0.01 to 4 mg/kg spiking) Straw: mean = 100% RSD = NA (n = 2 in 0.01 and 2 mg/kg spiking)
					45	Straw (BBCH 89)	2.6	
Report:TK0178712-REG Study:IF-13/02561770 Trial: 13-00247-03 - Study to GLP - Study carried out in 2013	Barley (Pewter)	SPAIN (Europe South)	458 g a.s./ha 473 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	15	Cyprodinil Whole plant: mean = 94% RSD = 13% (n = 3 in 0.01 to 17 mg/kg spiking) Grain: mean = 96% RSD = 12% (n = 4 in 0.01 to 4 mg/kg spiking)
					9	Whole plant (BBCH 73)	1.9	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
					20	Whole plant (BBCH 83)	1.4	Straw: mean = 100% RSD = NA (n = 2 in 0.01 and 2 mg/kg spiking)
					29	Whole plant (BBCH 85)	1.6	
					40	Whole plant (BBCH 87)	1.4	
					47	Grain (BBCH 89)	1.1	
					47	Straw (BBCH 89)	1.8	
Report:TK0178712-REG Study:IF-13/02561770 Trial: 13-00247-04 - Study to GLP - Study carried out in 2013	Barley (Moutso)	GREECE (Europe South)	450 g a.s./ha 449 g a.s./ha A14325E	BBCH 30 BBCH 65	44	Grain (BBCH 89)	0.38	Cyprodinil Whole plant: mean = 94% RSD = 13% (n = 3 in 0.01 to 17 mg/kg spiking) Grain: mean = 96% RSD = 12% (n = 4 in 0.01 to 4 mg/kg spiking) Straw: mean = 100% RSD = NA (n = 2 in 0.01 and 2 mg/kg spiking)
					44	Straw (BBCH 89)	0.61	
Report:TK0223256-REG Study:IF-14/02973058 Trial: 14-00689-01 - Study to GLP - Study carried out in 2014	Barley (Arturio)	SPAIN (Europe South)	470 g a.s./ha 461 g a.s./ha A14325E	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	9.3	Cyprodinil Whole plant: mean = 98% RSD = 7.7% (n = 5 in 0.01 to 15 mg/kg spiking) Grain: mean = 86% RSD = NA (n = 2 in 0.01 and 1.90 mg/kg spiking) Straw: mean = 91% RSD = 11% (n = 4 in 0.01 to 3.90 mg/kg spiking)
					20	Whole plant (BBCH 85)	3.1	
					42	Whole plant (BBCH 89)	2.4	
					46	Grain (BBCH 89)	2.2	
					46	Straw (BBCH 89)	2.7	
Report:TK0223256-REG Study:IF-14/02973058 Trial: 14-00689-03 - Study to GLP	Barley (Reni)	ITALY (Europe South)	437 g a.s./ha 453 g a.s./ha	BBCH 30 BBCH 65	0	Whole plant (BBCH 65)	12	Cyprodinil Whole plant: mean = 98% RSD = 7.7% (n = 5 in 0.01 to 14 mg/kg spiking) Grain: mean = 89% RSD = 10% (n = 3 in
					20	Whole plant	1.1	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
- Study carried out in 2014			A14325E			(BBCH 85)		0.01 to 5 mg/kg spiking) Straw: mean = 92% RSD = 8.6% (n = 3 in 0.01 to 5 mg/kg spiking)
					25	Grain (BBCH 89)	<0.01	
					25	Straw (BBCH 89)	0.56	
Report: R B5092 Study:B5029 Trial: B5092 IT1	Barley (Touareg)	ITALY (Europe South)	437 g a.s./ha 443 g a.s./ha A14325E	BBCH 31 BBCH 59	0	Whole plant (BBCH 59)	5.72	Cyprodinil Whole plant: mean = 86% RSD = 11% (n = 5 in 0.01 to 6.1 mg/kg spiking) Grain: mean = 92% RSD = 11% (n = 3 in 0.01 to 1.5 mg/kg spiking) Straw: mean = 93% RSD = 6% (n = 3 in 0.01 to 1.5 mg/kg spiking)
					20	Whole plant (BBCH 73-75)	1.18	
					42	Whole plant (BBCH 87-89)	0.94	
					45 (NCH)	Grain (BBCH 89)	0.87	
					45 (NCH)	Straw (BBCH 89)	1.34	
					48	Grain (BBCH 89)	0.70	
					48	Straw (BBCH 89)	1.12	
					55	Grain (BBCH 89)	1.00	
					55	Straw (BBCH 89)	0.90	
Report: R B5092 Study:B5029 Trial: B5092 TL1	Barley (Cassia)	FRANCE (Europe South)	464 g a.s./ha 468 g a.s./ha A14325E	BBCH 49 BBCH 77	0	Whole plant (BBCH 49)	5.54	Cyprodinil Whole plant: mean = 86% RSD = 11% (n = 5 in 0.01 to 6.1 mg/kg spiking) Grain: mean = 92% RSD = 11% (n = 3 in 0.01 to 1.5 mg/kg spiking) Straw: mean = 93% RSD = 6% (n = 3 in
					20	Whole plant (BBCH 83)	0.83	
					42	Whole plant	1.02	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate Product Code	Growth Stage at Application	PHI (days)	Crop Part (Growth stage at sampling)	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						(BBCH 89)		0.01 to 1.5 mg/kg spiking)
					45 (NCH)	Grain (BBCH 89)	1.36	
					45 (NCH)	Straw (BBCH 89)	0.84	
					48	Grain (BBCH 89)	0.86	
					48	Straw (BBCH 89)	0.76	
					55	Grain (BBCH 89)	0.88	
					55	Straw (BBCH 89)	0.98	
Notes: NA = not applicable. No residues were found above the LOQ in untreated samples except at trial 13-00252-01 where a residue of 0.01 mg/kg was found in the untreated straw sample.								

For MRL setting and risk assessment, the definition of the residue for cyprodinil is parent cyprodinil only. Calculations are presented below.

Cyprodinil residue calculations for MRL setting

MRLs for barley grain have been calculated for northern and southern Europe according to the OECD calculator (**OECD Series on pesticides No. 56, ENV/JM/MONO (2011)2, 1 March 2011**) for parent cyprodinil only. In these calculations a single data point from each trial supporting the EU proposed GAP has been considered. The cyprodinil residue values used in the MRL calculations are underlined in Table 6.3.2-5. The calculated outputs are presented in Table 6.3.2-6.

Table 6.3.2-6: MRL, STMR and HR calculations for cyprodinil on barley grain – proposed EU GAPs

Region	Outdoor / Protected	Residue Data (mg/kg)	MRL OECD Method (mg/kg)	MRL OECD Rounded (mg/kg)	STMR (mg/kg)	HR (mg/kg)
Northern EU	Outdoor	0.26, 0.61, 0.92, 0.43, 0.30, 0.79, 0.88, 0.29	1.680	2	0.52	0.92
Southern EU	Outdoor	0.74, 1.1, 1.1, 0.38, 2.2, <0.01, 1.0, 1.36	~~3.944~~ 3.614	4	~~0.92~~ 1.05	2.2

There is an existing EU MRL of 4.0 mg/kg (**Commission Regulation (EU) 400/2015**) for cyprodinil on barley. The data presented in Table 6.3.2-6 from trials supporting the proposed EU GAP indicate that all residues will be within the existing EU MRL of 4.0 mg/kg.

Cyprodinil residue calculations for risk assessment

STMR and HR values for barley grain have been calculated for northern and southern Europe for cyprodinil. The STMR is the median residue and the HR is the highest residue value found. In these calculations a single data point from each trial supporting the proposed EU GAP has been considered. The cyprodinil residue values used in the MRL and STMR calculations are underlined in Table 6.3.2-5. The calculated outputs are presented in Table 6.3.2-6.

STMR and HR values for barley straw as potential livestock feed items have also been calculated for northern and southern Europe. It is understood that the vast majority of cereal grain production in the EU is for grain production - hence a negligible amount of barley crops are harvested green for forage, hay and silage production and the GAP is different when grown for these uses. (Reference - ***the Minutes of the 1st meeting on the MRLs procedures (of the Network on Pesticides Steering Committee), held on 19.06 – 20.06.2014, EFSA Parma***). It was minuted that by default uses on cereals should be understood as "on cereal for grain production" and only residues in grain and straw should be considered for the animal burden calculation. Therefore the conversion factors for cyprodinil in barley hay, forage and silage have not been calculated.

The residue values for straw used in the HR and STMR calculations are underlined in Table 6.3.2-5. The calculated outputs are presented in Table 6.3.2-7.

Table 6.3.2-7: STMR and HR calculations for cyprodinil on barley straw – proposed EU GAP

Region	Outdoor / Protected	Residue Data (mg/kg)	STMR (mg/kg)	HR (mg/kg)
Northern EU	Outdoor	0.55, 1.5, 0.96, 0.16, 0.33, 0.17~~6~~, 0.61, 1.3	0.58	1.5
Southern EU	Outdoor	0.45, 2.6, 1.8, 0.61, 2.7, 0.56, 1.34, 0.98	~~1.2~~ 1.16	2.7

Conclusions

The proposed EU MRL for cyprodinil together with the corresponding STMR and HR for risk assessment for barley are presented in Table 6.3.2-8. For use in dietary burden estimations, STMR and HR values for barley straw are also presented in Table 6.3.2-8.

Table 6.3.2-8: Proposed EU MRL, STMR and HR for cyprodinil on barley

Commodity (code)	Calculated MRL (mg/kg)	Proposed EU MRL (mg/kg)	STMR (mg/kg)	HR (mg/kg)
Barley (0500010)	4.0	4.0	0.92	2.2
Barley straw (no code)	-	-	~~1.2~~ 1.16	2.7

The use of cyprodinil at the representative GAP leads to a calculated MRL of 4.0 mg/kg for barley grain and therefore does not exceed the existing EU MRL of 4.0 mg/kg (**Commission Regulation (EU) 400/2015**).

The representative use of product A14325E on barley is supported by sufficient residue data.

CA 6.4 Feeding Studies

Dietary burden calculations

It is an EU data requirement (**Commission Regulation (EU) No 283/2013, 1 March 2013**) and guideline requirement (**OECD 505, Residues in Livestock**) to estimate the dietary intakes for poultry, dairy cattle, beef cattle and pigs if residues are likely in crops or part of crops fed to animals.

The potential dietary exposure to cyprodinil residues in the supported representative crops of apple and barley or their processed products has been calculated using the EU methodologies described. According to available OECD guidance, for the crops considered in this document, products from apple and barley may form a part of global livestock diets and on the basis of the OECD feeding tables the following commodities form part of the dietary burden for livestock species in the EU:

Barley straw and grain, brewer's grain, distiller's grain, apple pomace.

Barley forage, hay and silage are not considered relevant crops as the proposed use for cyprodinil is on barley for grain production only.

The dietary inputs for the calculation are summarised in Table 6.4-1. The highest residues in supervised trials (HR) are used to calculate the maximum potential dietary intake except for feed commodities that are bulked, where the STMR is used, or processed, where the STMR-P is used, as detailed in Table 6.4-1. The STMR values in supervised trials have been used to calculate the median potential dietary intake.

Table 6.4-1: Cyprodinil residue values used for calculation of livestock dietary burdens

Commodity	Commodity Category[1]	STMR (mg/kg)	Processing Factor	STMR-P (mg/kg)	HR (mg/kg)	Origin
Barley straw	Forages	~~1.2~~ 1.16	--	--	2.7	Residue data in CA 6.3.2
Barley grain	Cereal grains/ Crops seeds	0.92	--	--	--	Residue data in CA 6.3.2
Apple pomace	By-products	0.16	3.9	0.62	--	Residue data in CA 6.3.1 Mean processing factor for apple pomace used. (CA 6.7.1)
Distillers grain[2]		0.92	1.0	0.92	--	Residue data in CA 6.3.2 Mean processing factor for spent grain used.
Brewers grain		0.92	1.0	0.92	--	Residue data in CA 6.3.2 Mean processing factor for spent grain used.

[1] - As defined in ENV/JM/MONO(2009)31.
[2] - As defined in US EPA Residue Chemistry Test Guidelines, OPPTS 860.1520, Processed Food/Feed, 1996.
For the purposes of calculation values stated to be "<"are assumed to be at that value e.g. <0.01mg/kg is assumed to be 0.01.

A summary presents a summary of the dietary burden calculations calculated for cyprodinil in each livestock species is presented in Table 6.4-2.

Table 6.4-2: Maximum and median dietary intakes of residues of cyprodinil in livestock species

Livestock Species	Maximum Residue Intake		Median Residue Intake	
	(mg a.s./kg bw/day)	(mg/kg DM in feed)	(mg a.s./kg bw/day)	(mg/kg DM in feed)
Beef cattle	0.042	1.75	~~0.030~~ 0.029	~~1.24~~ 1.22
Dairy cattle	0.057	1.48	~~0.038~~ 0.037	~~0.98~~ 0.97
Rams/Ewes	0.075	2.24	~~0.041~~ 0.040	~~1.23~~ 1.20
Lambs	0.097	2.29	~~0.054~~ 0.053	~~1.28~~ 1.25
Breeding Swine	0.024	1.04	0.024	1.04
Finishing Swine	0.031	1.04	0.031	1.04
Broiler hens	0.059	0.83	0.059	0.83
Laying hens	0.078	~~1.15~~ 1.14	~~0.073~~ 0.072	1.06
Turkey	~~0.044~~ 0.045	0.62	0.044	0.62

CA 6.4.1 Poultry

Taking into account the supported crop uses in this submission, the calculated maximum and median dietary burdens of cyprodinil in poultry are summarised in Table 6.4.1-1.

Table 6.4.1-1: Intakes of cyprodinil residues in poultry

	Maximum Residue Intake		Median Residue Intake	
	(mg a.s./kg bw/day)	(mg/kg DM in feed)	(mg a.s./kg bw/day)	(mg/kg DM in feed)
Broiler	0.059	0.83	0.059	0.83
Laying hen	0.078	~~1.15~~ 1.14	~~0.073~~ 0.072	1.06
Turkey	~~0.044~~ 0.045	0.62	0.044	0.62

No feeding studies were submitted for Annex I listing of cyprodinil and no new studies are available.

Hen metabolism data have been summarised in section CA 6.2.2.

In metabolism studies, cyprodinil labelled in either the [phenyl-(U)-^{14}C]- or [2-^{14}C-pyrimidine]- position was administered daily for four consecutive days to two hens at a dose level of 0.4 mg/kg body weight (equivalent to 4.7 mg/kg in the diet) and to four hens at a dose level of 19 mg/kg body weight (equivalent to 220 mg/kg in the diet). ~~These doses represent 5-9 times and 244-432 times, respectively, the estimated maximum dietary burdens of cyprodinil in poultry.~~ These doses represent 5.1-8.9 times and 242-429 times, respectively, the estimated maximum dietary burdens of cyprodinil in poultry.

Total radioactive residue levels measured in the metabolism study were <0.01 mg/kg in eggs and tissues at the lower dose rate with the exception of liver (0.12 mg/kg) and kidney (0.04 mg/kg). ~~At the estimated maximum intake, maximum residues in liver and kidney are not expected to exceed 0.02 mg/kg (i.e. 0.012 ÷ 5) and <0.01 mg/kg (i.e. 0.04 ÷ 5).~~ At the estimated maximum intake, maximum residues in liver and kidney are not expected to exceed 0.02 mg/kg (i.e. 0.12 ÷ 5.1) and <0.01 mg/kg (i.e. 0.04 ÷ 5.1).

It can be concluded that residues of cyprodinil (cyprodinil + CGA304075) will not occur in poultry products at levels above the combined LOQs of cyprodinil and CGA304075 (0.02 mg/kg) on the basis of livestock intakes of cyprodinil. Although no plateau was reached in egg during the hen metabolism studies, cyprodinil is shown to be extensively metabolised with the majority of the radioactivity being eliminated in the urine and faeces. Metabolism data in hens were sufficient to confirm an expectation of insignificant residues in poultry. Residue levels in poultry commodities are expected to remain below the enforcement LOQ of 0.01 mg/kg in poultry products, including muscle, fat, eggs, liver and kidney. Hence, no livestock feeding study for poultry is needed; MRLs, STMR and HR values and risk assessment values for the relevant commodities in poultry can be established at the LOQ level (see Section CA 6.4.5 below).

CA 6.4.2 Ruminants

Taking into account the supported crop uses in this submission, the calculated maximum and median dietary burdens of cyprodinil in ruminants are summarised in Table 6.4.2-1.

Table 6.4.2-1: Intakes of cyprodinil residues in ruminants

	Maximum Residue Intake		Median Residue Intake	
	(mg a.s./kg bw/day)	(mg/kg DM in feed)	(mg a.s./kg bw/day)	(mg/kg DM in feed)
Beef cattle	0.042	1.75	~~0.030~~ 0.029	~~1.24~~ 1.22
Dairy cattle	0.057	1.48	~~0.038~~ 0.037	~~0.98~~ 0.97
Rams/Ewes	0.075	2.24	~~0.041~~ 0.040	~~1.23~~ 1.20
Lambs	0.097	2.29	~~0.054~~ 0.053	~~1.28~~ 1.25

Feeding studies with cyprodinil and metabolite CGA304075 in lactating ruminants were evaluated under Council Directive 91/414/EEC and are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.7, November 2003**) and addendum (**Addendum to Volume 3 – Annex B.7 and B.9 (post annex 1 inclusion), Section B.7.8, March 2010**).

Commodity	Author/s	Issue Year	Report Number
Cow	Van Geluwe K	1995	ABR-95088
Cow	Joseph AT, Hamilton LS	2006	T001784-05

It is not clear whether the second feeding study (T001784-05) in cattle has been peer-reviewed in the EU following review during the approval process (France, 2010), so a full summary of the study is presented below. A summary of the feeding studies is presented following the summary of feeding study T001784-05.

Report:	K-CA 6.4.2/01 Joseph T, Hamilton L (2006). Cyprodinil: Cyprodinil - magnitude of the residues, including CGA304075, in meat and milk resulting from the feeding of three levels to dairy cattle. Syngenta Crop Protection Inc., USA. Report Number T001784-05. Study Dates: May 2005 - June 2006. (Syngenta Regulatory Document CGA219417/1528).

Guidelines

Residue Chemistry Test Guidelines, OPPTS 860.1480 (Meat/Milk/Poultry/Eggs), **EU guideline Document 7031/VI/95 rev. 4**.

GLP

The study is fully compliant with the principles of Good Laboratory Practice standards.

EXECUTIVE SUMMARY

The purpose of this study was to generate residue data for cyprodinil and its metabolite, CGA304075 in or on dairy livestock commodities.

Eleven healthy Holstein cows were pre-acclimatised for two days and then divided into three treatment groups comprising of three animals each. One animal was assigned as the control and one assigned as a back-up. Lactating cows in the three treatment groups were dosed daily for 29 – 30 days. The selected 1X dose rate of cyprodinil for the biological phase of the study was 2 mg/kg (dry weight basis) and the exaggerated rates were 15 mg/kg (7.5X) and 50 mg/kg (25X). The animals were sacrificed over a two-day period at the end of the dosing period to allow for the collection of tissue samples.

Samples were collected in duplicate for each matrix; milk, liver, kidney, fat (omental, perirenal, and subcutaneous), and muscle (diaphragm, round, and tenderloin). Milk samples were collected at days 0, 2, 5, 8, 12, 15, 19, 22, 26, and 28. Samples collected in this study were analysed for residues of cyprodinil and CGA304075 using analytical method GRM010.01A (see CA 4.1.2).

The maximum residues of cyprodinil and CGA304075 obtained from the analyses of 25X treated samples are shown below:

Table 6.4.2-2: Maximum residues of cyprodinil and CGA304075 from analysis of animal tissues from Holstein cows dosed with cyprodinil at 50 mg/kg in the diet

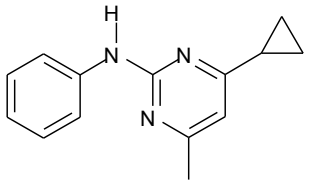
Matrix	Maximum Residue (mg/kg)	
	Cyprodinil	CGA304075
Milk	<0.01	<0.01
Liver	0.02	0.07
Kidney	<0.01	0.12
Fat	<0.01	<0.01
Muscle	<0.01	<0.01

Fat and muscle treated at the 7.5X rate were analysed for cyprodinil and CGA304075 however no detectable residues (<0.01 mg/kg) were found. Liver and kidney treated at the 7.5X rate and the 1X rate were analysed. Residues in liver and kidney declined according to decreasing rate and no detectable residues of cyprodinil or CGA304075 (<0.01 mg/kg) were found at the 1X rate. Milk was only analysed at the 25X rate since no detectable residues of cyprodinil or CGA304075 were found in any milk sample at this level.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Structure	Cyprodinil
	
Batch Number	FL 940578 GLP
Purity	99.2%

A2. Test Organism

Cows of variety Holstein were used.

A3. Test Facilities

The biological phase of this work were performed at Syngenta Crop Protection Inc., 7145 - 58th Avenue, Vero Beach, FL 32967, USA.

The analytical phase was performed at Syngenta Crop Protection Inc., 410 Swing Road, Greensboro, NC 27419, USA.

B. STUDY DESIGN AND METHODS

B1. Treatment

Eleven healthy lactating Holstein cows were pre-acclimatised for two days and then assigned to four test groups. One group consisted of a control and a back-up animal; the remaining three groups consisted of

three cows each. After assignment to groups, the treatment groups were housed in individual pastures and the cows were acclimatised for seven further days before dosing commenced.

Cows were dosed daily with cyprodinil for 29-30 days at rates equivalent to 0, 2, 15, and 50 mg/kg in the feed. The appropriate daily dose of the test substance, cyprodinil, was administered to the cows in gelatin capsules. The treatments were as follows:

Table 6.4.2–3: Cyprodinil dosing rates

Dose Group	Cyprodinil Concentration in Diet (mg/kg)*	Individual Dose (Cyprodinil)
0X	0 (Control)	Empty gelatin capsule
1X	2	40 mg per capsule
7.5X	15	300 mg per capsule
25X	50	1000 mg per capsule

* - based on an expected average feed consumption of approximately 20 kg per day (hay and dairy concentrate based on typical average historical daily intake of dairy cattle).

The 1X rate was chosen based on reviews from regulatory agencies stating that 2 mg/kg is the expected maximum dietary burden for cattle based on residue studies.

B2. Sampling

All samples were collected in duplicate (Replicates A and B) for milk, liver, kidney, fat (omental, perirenal, and subcutaneous), and muscle (diaphragm, round, and tenderloin). Two samples of each tissue were collected, with a maximum sample size of 2 kilogram each of perirenal fat, omental fat, subcutaneous fat, round muscle, tenderloin muscle, diaphragm muscle, and liver from each animal at sacrifice. The tissue samples were stored frozen in plastic bags.

Milk samples were collected on day 0 (pre-dose), and on the following days after dose administration: 2, 5, 8, 12, 15, 19, 22, 26, and 28. Two one-quart milk samples (Reps A and B) were collected from each animal on each sampling date. The milk samples were stored frozen in Nalgene or glass bottles allowing adequate head space for sample expansion.

B3. Analytical Procedures

Except for the periods during which the samples were prepared and during the removal of aliquots for analysis, the samples were stored frozen. Samples were ground in a Hobart food cutter, using dry ice as necessary to keep the samples frozen. The samples were then maintained frozen until analysed for residues of cyprodinil and CGA304075 using method number GRM010.01A. Samples (10 g) were refluxed for 1 hour in aqueous hydrochloric acid (HCl, 0.5M, 200 mL) to convert conjugated residues of CGA304075 to CGA304075. The solutions were cooled and vacuum filtered through Whatman No 5 filter paper. Aliquots (5 mL) of the filtered extracts were applied directly to pre-rinsed (5 mL methanol, then 5 mL 0.5M HCL) Bond-Elut SCX cartridges. The cartridges were washed with methanol/water (1:1 v/v, 12 mL) and then the analytes eluted with methanol/ammonium hydroxide (95:5 v/v, 8mL). The eluates were evaporated to near-dryness and reconstituted in mobile phase for determination by high-performance liquid chromatography with single-quadrupole mass-spectrometric detection.

This method includes a hydrolysis step to release conjugated residues of CGA304075; the efficiency of the extraction in releasing conjugated CGA304075 has been validated (see MCA Section 4).

The LOQ for both analytes in all substrates was 0.01 mg/kg.

II. RESULTS AND DISCUSSION

Storage Stability

From sampling to extraction, samples in this study were stored frozen for a maximum of 3 months. The storage intervals are shown in Table 6.4.2-4.

Table 6.4.2–4: Summary of storage intervals

Matrix	Storage Temp. (°C)	Maximum Storage Interval (Months)	Demonstrated Storage Stability (Months)	
			Cyprodinil	CGA304075
Milk	-20	3	18	3
Liver	- 20	3	18	6
Muscle	- 20	3	2*	3

* - Residues in the storage stability study declined to 70% of the nominal value after two months of freezer storage then remained constant for the duration of the study (18 months).

Based on these results, residues of cyprodinil and CGA304075 were not adversely affected by freezer storage and are an accurate representation of actual residues.

Residue Analysis

The performance of the method was demonstrated by analysing procedural recovery samples alongside each analytical sample set. Recovery values were corrected for control residues if present. The overall mean recovery of cyprodinil was 83% (s.d. = 10, n = 49). The overall mean recovery of CGA304075 was 86% (s.d. = 12, n = 47).

Results for the analysis of cyprodinil and CGA304075 in dairy livestock commodities are presented in Tables 6.4.2-5 and 6.4.2-6. The residue results were not corrected for procedural recovery values.

Table 6.4.2–5: Cyprodinil residues in tissues and milk from ruminant feeding study

Matrix	Feeding Rate (mg/kg)	Cyprodinil Found (mg/kg)					
		n	Min.	Max.	Median (STMR)	Mean	S.D.
Milk	50	30	<0.01	<0.01	<0.01	na	na
Liver	50	3	0.01	0.02	0.01	0.01	0.005
	15	3	<0.01	<0.01	<0.01	na	na
	2	3	<0.01	<0.01	<0.01	na	na
Kidney	50	3	<0.01	<0.01	<0.01	na	na
	15	3	<0.01	<0.01	<0.01	na	na
	2	3	<0.01	<0.01	<0.01	na	na
Fat	50	9	<0.01	<0.01	<0.01	na	na
	15	9	<0.01	<0.01	<0.01	na	na
Muscle	50	9	<0.01	<0.01	<0.01	na	na
	15	9	<0.01	<0.01	<0.01	na	na

S.D. - Standard Deviation.
na - Not applicable.

Table 6.4.2–6: CGA304075 residues in tissues and milk from ruminant feeding study

Matrix	Feeding Rate (mg/kg)	CGA304075 Found (mg/kg)					
		n	Min.	Max.	Median (STMR)	Mean	S.D.
Milk	50	30	<0.01	<0.01	<0.01	na	na
Liver	50	3	0.07	0.07	0.07	0.07	0.004
	15	3	0.02	0.02	0.02	0.02	na
	2	3	<0.01	<0.01	<0.01	na	na
Kidney	50	3	0.11	0.12	0.12	0.12	0.006
	15	3	0.02	0.03	0.03	0.03	0.005
	2	3	<0.01	<0.01	<0.01	na	na
Fat	50	9	<0.01	<0.01	<0.01	na	na
	15	9	<0.01	<0.01	<0.01	na	na
Muscle	50	9	<0.01	<0.01	<0.01	na	na
	15	9	<0.01	<0.01	<0.01	na	na

S.D. - Standard Deviation.
na - Not applicable.

Transfer factors for the two analytes in cow tissues and milk may be calculated and are presented below (these calculations are not included in the Study Report). The transfer factor is calculated from the ratio of the residue of cyprodinil or CGA304075 found in the tissues to the concentration of cyprodinil in the feed. The results appear in Tables 6.4.2-7 and 6.4.2-8.

Table 6.4.2–7: Cyprodinil transfer factors in lactating cows

Tissue	Cyprodinil Dose (mg/kg)	Mean Cyprodinil Residue (mg/kg)	Transfer Factor
Milk	50	<0.01	<0.0002
Liver	50	0.01	0.0002
Kidney	50	<0.01	<0.0002
Fat	50	<0.01	<0.0002
Muscle	50	<0.01	<0.0002

Table 6.4.2–8: CGA304075 transfer factors in lactating cows

Tissue	Cyprodinil Dose (mg/kg)	Mean CGA304075 Residue (mg/kg)	Transfer Factor
Milk	50	<0.01	<0.0002
Liver	50	0.07	0.0014
	15	0.02	0.0013
Kidney	50	0.12	0.0024
	15	0.03	0.0020
Fat	50	<0.01	<0.0002
Muscle	50	<0.01	<0.0002

III. CONCLUSIONS

The objective of this study was to generate residue data for cyprodinil and CGA304075 in or on representative dairy livestock commodities after feeding with parent cyprodinil. The selected 1X dose rate

of cyprodinil was 2 mg/kg (dry weight basis) and the exaggerated rates were 15 mg/kg (7.5X) and 50 mg/kg (25X).

Cows were dosed daily for 29 – 30 days with regular collection of milk; tissues were sampled at the end of the dosing period.

The maximum residue of cyprodinil in this study was 0.02 mg/kg found in liver from the 25X dose group. No residues of cyprodinil were found in any other sample from this group, or in any samples from the 7.5X group.

Residues of CGA304075 were found in samples of kidney and liver from the 25X group (maximum 0.12 mg/kg and 0.07 mg/kg respectively). Residues of CGA304075 were also found in samples of kidney and liver from the 7.5X dose group (maximum 0.03 mg/kg and 0.02 mg/kg respectively). No residues of CGA304075 were found in the other matrices (milk, fat, or muscle) from the 25X or 7.5X dose groups, or in any samples from the 1X group.

The transfer factor for cyprodinil in liver, calculated from the 50 mg/kg dose level, was 0.0002 (mean cyprodinil residue in liver relative to dose rate). Since no residues were found, transfer factors in all other tissues (including milk) cannot be calculated but must be less than 0.0002 in each case.

The transfer factor for CGA304075 in liver, calculated from the 50 mg/kg dose level, was 0.0014 (mean CGA304075 residue in liver relative to dose rate of cyprodinil). The transfer factor for CGA304075 in kidney, also calculated from the 50 mg/kg dose level, was 0.0024. These transfer factors are slightly higher (worse case) than those calculated from the 7.5X group, which were very similar. Since no residues were found, transfer factors in other tissues (including milk) cannot be calculated but must be less than 0.0002 in each case.

Overall summary of ruminant feeding studies

In the first study (ABR-95088), cows were fed at dosing levels equivalent to 5, 15 or 50 mg/kg cyprodinil in the diet for a period of 28-30 days. No residues of cyprodinil were found at or above the LOQ (<0.01 mg/kg) in any of the milk or tissue samples from the highest dose rate (50 mg/kg diet) except in liver, where two of the three samples contained cyprodinil residues at 0.011 and 0.013 mg/kg. The EU DAR concluded that no cyprodinil was expected in animal products. The study was considered inadequate to conclude on the metabolites, since they were not analysed.

In the second study (T001784-05), lactating cows were dosed daily for 29-30 days at 2, 15 and 50 mg/kg (dry weight basis). Samples underwent an acid reflux which was demonstrated to convert residues of conjugated CGA304075 to CGA304075 (see method GRM010.01A in Section 4.1.2).

No residues of cyprodinil or CGA304075 above the LOQ (<0.01 mg/kg) were found in milk following the 50 mg/kg feeding rate. Milk from the lower rates was therefore not analysed.

In tissues, no residues of cyprodinil and CGA304075 above the LOQ (<0.01 mg/kg) were found in fat or muscle treated at the 15 mg/kg and 50 mg/kg rates. Samples from the lowest rate were therefore not analysed.

Residues in liver and kidney declined according to decreasing dose rate. In liver, maximum residues of cyprodinil were 0.02 mg/kg following the 50 mg/kg rate and <0.01 mg/kg following rates of 15 and 2 mg/kg. Maximum residues of CGA304075 in liver were 0.07, 0.02 and <0.01 mg/kg following rates of 50, 15 and 2 mg/kg, respectively. In kidney, maximum residues of cyprodinil were <0.01 mg/kg following rates of 50, 15 and 2 mg/kg. Maximum residues of CGA304075 in kidney were 0.12, 0.03 and <0.01 mg/kg following dose rates of 50, 15 and 2 mg/kg, respectively.

The highest estimated livestock intake of cyprodinil residues is 0.098 mg/kg bw/day for lambs, 0.075 mg/kg bw/day for rams/ewes, 0.057 mg/kg for dairy cattle and 0.042 mg/kg bw/day for beef cattle (1.49 – 2.30 mg/kg DM feed). These intakes are comparable to the lowest dose rate applied in the second feeding study (2 mg/kg).

The median estimated livestock intake of cyprodinil residues is 0.055 mg/kg bw/day for lambs, 0.041 mg/kg bw/day for rams/ewes, 0.038 mg/kg bw/day for dairy cattle and 0.030 mg/kg bw/day for beef cattle (0.99-1.29 mg/kg DM feed). These intakes are also comparable to the lowest dose rate applied in the second feeding study 2 mg/kg).

In the Article 12 review (EFSA Journal 2013;11(10):3406), EFSA noted that the frozen stability data showed conflicting information for liver and kidney and that there were limited stability data available for muscle, milk and fat showing instability (see CA 6.1) but considered it unlikely that the validity of the results in the animal feeding studies was compromised. EFSA did not consider that a new feeding study should be generated.

The residue levels in bovine commodities based on the values found in the second feeding study are summarised in Table 6.4.2-9.

Table 6.4.2-9: Residue levels in bovine commodities based on dietary livestock burdens of cyprodinil (from study T001784-05)

Commodity	Dose Level (mg/kg diet)	Cyprodinil Residues (mg/kg)		CGA304075 Residues (mg/kg)	
		Mean	Maximum	Mean	Maximum
Muscle	2	na	na	na	na
	15	<0.01	<0.01	<0.01	<0.01
	50	<0.01	<0.01	<0.01	<0.01
Fat	2	na	na	na	na
	15	na	na	<0.01	<0.01
	50	<0.01	<0.01	<0.01	<0.01
Liver	2	<0.01	<0.01	<0.01	<0.01
	15	<0.01	<0.01	0.02	0.02
	50	0.01	0.02	0.07	0.07
Kidney	2	<0.01	<0.01	<0.01	<0.01
	15	na	na	0.03	0.03
	50	<0.01	<0.01	0.12	0.12
Milk	2	na	na	na	na
	15	<0.01	<0.01	na	na
	50	<0.01	<0.01	<0.01	<0.01

na = not analysed.

On the basis of the results above, MRL, STMR and HR values for ruminant products have been proposed (see Section CA 6.4.5 below).

CA 6.4.3 Pigs

Taking into account the supported crop uses in this submission, the calculated maximum and median dietary burdens of cyprodinil in pigs are summarised in Table 6.4.3-1.

Table 6.4.3-1: Intakes of cyprodinil residues in pigs

	Maximum Residue Intake		Median Residue Intake	
	(mg a.s./kg bw/day)	(mg/kg DM in feed)	(mg a.s./kg bw/day)	(mg/kg DM in feed)
Breeding swine	0.024	1.04	0.024	1.04
Finishing swine	0.031	1.04	0.031	1.04

The metabolism of cyprodinil in ruminants was similar to that seen in the rat. Metabolism and feeding studies in pigs are therefore not required, as data for ruminants can be used to address the potential for residues in pigs.

In the main study (T001784-05), no residues of cyprodinil and CGA304075 above the LOQ (<0.01 mg/kg) were found in fat or muscle treated at the 15 mg/kg and 50 mg/kg rates. The results in milk are not relevant to pigs.

Residues in liver and kidney declined according to decreasing dose rate. In liver, maximum residues of cyprodinil were 0.02 mg/kg following the 50 mg/kg rate and <0.01 mg/kg following rates of 15 and 2 mg/kg. Maximum residues of CGA304075 in liver were 0.07, 0.02 and <0.01 mg/kg following rates of 50, 15 and 2 mg/kg, respectively. In kidney, maximum residues of cyprodinil were <0.01 mg/kg following rates of 50, 15 and 2 mg/kg. Maximum residues of CGA304075 in kidney were 0.12, 0.03 and <0.01 mg/kg following rates of 50, 15 and 2 mg/kg, respectively.

The highest/median estimated livestock intake of cyprodinil residues is 0.024 mg/kg bw/day for breeding swine and 0.031 mg/kg bw/day for finishing swine (1.0 mg/kg DM feed). These intakes are lower than the lowest dose rate applied in the second feeding study (2 mg/kg) and so the lowest dose rate in the feeding study represents a worst-case for swine commodities.

Table 6.4.3-2: Residue levels in swine commodities based on dietary livestock burdens of cyprodinil (from study T001784-05)

Commodity	Dose Level (mg/kg diet)	Cyprodinil Residues (mg/kg)		CGA304075 Residues (mg/kg)	
		Mean	Maximum	Mean	Maximum
Muscle	2	na	na	na	na
	15	<0.01	<0.01	<0.01	<0.01
	50	<0.01	<0.01	<0.01	<0.01
Fat	2	na	na	na	na
	15	na	na	<0.01	<0.01
	50	<0.01	<0.01	<0.01	<0.01
Liver	2	<0.01	<0.01	<0.01	<0.01
	15	<0.01	<0.01	0.02	0.02
	50	0.01	0.02	0.07	0.07
Kidney	2	<0.01	<0.01	<0.01	<0.01
	15	na	na	0.03	0.03
	50	<0.01	<0.01	0.12	0.12

na = not analysed.

On the basis of the results above, MRL, STMR and HR values for swine products have been proposed (see Section CA 6.4.5 below).

CA 6.4.4 Fish

No fish feeding studies have been conducted for cyprodinil.

Based on document SANCO/10181/2013 Rev. 2.1, 13 May 2013 which states: "*In some cases, agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as no test methods or guidance documents are published in the form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02.*"

It is also recorded in the Summary Report of the Standing Committee meeting on Plants, Animal, Food and Feed (Section Phytopharmaceuticals - Pesticides Residues), held in Brussels on 24-25 November 2014, under item A.24, that " *... the Commission working document on the nature of residues in fish was discussed in 2013 and it was concluded that it is not yet finalised and ready to be noted as a guidance document."* Additionally the report states under item A.24 *the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived* [as per document SANCO/10181/2013 Rev 2.1]."

In the Summary Report of the SCoPAFF meeting (Section Phytopharmaceuticals - Plant Protection Products - Legislation), held in Brussels on 26-27 January 2015, it is reiterated, under item A.26, "*... some RMS are requesting studies on data requirements for which currently there is no agreed methodology and they consider a dossier incomplete if these data are not provided. The Commission explained that this is not consistent with the Guidance Document SANCO/10181/2013, which was taken note of by Member States.*" The following statements were also made by the Commission: "*In particular cases, ad-hoc studies could be requested, as it is always the case in justified situations. ... However, the Commission referred to the general policy of reducing animal testing and asked Member States to consider this when asking for additional studies on vertebrates.*"

We believe that it is essential that guidance is suitably discussed and peer reviewed, considering both benefits to the assessment of consumer safety and the minimisation of vertebrate testing, before being applied.

We believe that it is essential that guidance is suitably discussed and peer reviewed, considering both benefits to the assessment of consumer safety and the minimisation of vertebrate testing, before being applied.

In addition there are currently no definitive triggers in Regulation (EC) No. 283/2013 on which to base a decision as to whether a "fish metabolism" study is required or not.

In order to properly assess the potential transfer of pesticide residues from plant-protection-product treated feed items into the consumable tissues of farmed fish we believe that the following need to be in place:

- **A robust and representative dietary burden calculation method** (including the underlying feeding-practice data);
- **An agreed and practicable method for studying the nature of residues in fish;** and (depending on the potential for residues to transfer into fish tissues)

An agreed and practicable method for quantitatively studying the transfer of residues of concern into fish tissues.

~~There is no guidance yet finalised for fish metabolism/fish feeding studies. It is also noted that the summary arising from the SCoPAFF meeting on 24 – 25 November 2014, Section A.24 that "*the*~~

~~*Commission working document is not yet finalised and ready to be noted as a guidance document*.~~" ~~Additionally, "*the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived*.~~"

Conclusions from feeding studies

MRL, STMR and HR values for products of animal origin are proposed based on the results presented in Sections CA 6.4.1, CA 6.4.2 and CA 6.4.3 above. These values have been calculated from the maximum/mean residues measured at the relevant dose levels (cyprodinil + CGA304075) for the estimated maximum or median cyprodinil intake values.

There are existing MRLs for cyprodinil for products of animal origin (residue definition sum of cyprodinil and CGA304075) as published in Annexes to EC Reg 396/2005. EFSA (EFSA Journal 2013;11(10):3406) have also proposed MRLs for products of animal origin. The data presented in Table 6.4.5-1 summarises the current and proposed EU MRLs, including the proposals based on the representative uses in apple and barley supported in this document.

In conclusion, residues of cyprodinil and CGA304075 (both free and conjugated) are not expected above the LOQ in animal tissues based on the representative uses. The MRL, STMR and HR values are therefore equivalent to the sum of the LOQs for cyprodinil and CGA304075.

Table 6.4.5-1: Proposed EU MRL and proposed STMR and HR for residues in products of animal origin

Commodity	Existing EU MRL[1] (mg/kg)	Proposed EU MRL[2] (mg/kg)	Proposed MRL[3] (mg/kg)	Proposed STMR[3] (mg/kg)	Proposed HR[3] (mg/kg)
Meat (swine, bovine, sheep, goat, equine)	0.05*	0.02*	0.02*	0.02	0.02
Fat tissue (swine, bovine, sheep, goat, equine)	0.05*	0.02*	0.02*	0.02	0.02
Liver (bovine, sheep, goat,)	0.05*	0.05	0.02*	0.02	0.02
Liver (swine, equine)	0.05*	0.02*	0.02*	0.02	0.02
Kidney (bovine, sheep, goat,)	0.05*	0.05	0.02*	0.02	0.02
Kidney (swine, equine)	0.05*	0.02*	0.02*	0.02	0.02
Other edible offal (swine, bovine, sheep, goat, equine)	0.05*	0.02*	0.02*	0.02	0.02
Poultry tissues and eggs	0.05*	0.02*	0.02*	0.02	0.02
Milk	0.05*	0.02*	0.02*	0.02	0.02

[1] – MRLs as given in EC Reg. 396/2005

[2] – MRLs recommended in EFSA Journal 2013;11(10):3406.

3 – Values calculated for the representative uses supported in this document.

The magnitude of residues of cyprodinil (CGA219417) and metabolite CGA304075 (both free and conjugated forms) has been adequately investigated in commodities of animal origin. Robust MRLs can be set and no further studies are required.

CA 6.5 Effects of Processing

CA 6.5.1 Nature of the residue

The effect of hydrolysis on the nature of the residue of cyprodinil under conditions typical of those found in industrial and household processes such as pasteurisation, boiling and sterilisation was investigated. The study was evaluated under Council Directive 91/414/EEC and is presented in the cyprodinil draft assessment report (**Vol.3, Annex B, Section B.7.8.1, November 2003**).

Conditions	Identified Compounds (%)	Report Reference	Source
EU Reviewed Data			
Pasteurisation (20 min, 90°C, pH 4)	^{14}C-pyrimidine-labelled cyprodinil (100)	00MO07	France, 2005
Baking, boiling, brewing (60 min, 100°C, pH 5)	^{14}C-pyrimidine-labelled cyprodinil (100)		
Sterilisation (20 min, 120°C, pH 6)	^{14}C-pyrimidine-labelled cyprodinil (100)		

No breakdown or reaction products were formed during hydrolysis of cyprodinil under representative processing conditions. Thus, it was concluded that for processed crop commodities the same residue definition (parent cyprodinil) would be applicable.

CA 6.5.2 Distribution of the residue in inedible peel and pulp

There are no crops in this submission (barley and apple) which have inedible peel. Therefore the distribution of the residues in peel/pulp is not relevant.

CA 6.5.3 Magnitude of residues in processed commodities

Processing studies were not reviewed for Annex I listing of cyprodinil as the TDMI calculated for cyprodinil in a British infant (the worst case) was only 4% of the ADI and no residues exceeding 0.1 mg/kg were found in either barley grain or apples. However, studies in apple which included processing of fruit into juice and wet pomace were reviewed in the magnitude of residues section and summarised in the ***EFSA DAR, June 2005***. These studies are summarised below along with new processing studies in barley and apple not submitted for Annex I listing.

Processed Commodity	Number of Studies	Median PF [(a)]	Report References	Source
EU reviewed Data				
Apples, juice	13	0.25	OF94127/KJ97 OF94127/SJ91 OF94124/SJ90 OF94127/LD84 OF94125/FP05 OF94124/FP07 OF94126/FP08 2051/94 2052/94 2053/94	France, 2005

Processed Commodity	Number of Studies	Median PF [a]	Report References	Source
EU reviewed Data				
			2054/94 2055/94 2056/94 2105/94 2106/94 2107/94 2108/94 2085/95	
Apples, wet pomace	4	1.25	Kissling, M.: 2051/94 (1995b) 2052/94 (1995c) 2053/94 (1995d) Walser, M.: 2085/95 (1996)	France, 2005
New Data				
Apple, washed	1	0.9	Solé C. 03-0801 (2004)	KCA 6.5.3.1/01
Apple, wet pomace	1	3.9		
Apple, dry pomace	4	8.8		
Apple, pasteurised juice	4	0.08		
Apple, sterilised puree	4	0.23		
Barley, Malt (all types)	24	1.2	Maffezzoni M. OF95151/DE93 (1998) 9810301 (1999) 9810302 (1999) 9810401 (1999) 9810402 (1999) 9715402 (1999) 9715801 (1999) 9715401 (1999) 9715802 (1998) 9715001 (1998) 9715002 (1998) 9715702 (1998) OF96142/DE11 (1998) OF95151/KJ30 (1998) Tribolet R. 2023/99 (2001) 2025/99 (2001) 2026/99 (2001) Smith JA. gr 44496 (1998) gr 42298 (1999) gr 44598 (1999) gr 41198 (1999) gr 43498 (1999) Beinhauser K. 971064026 (1999) 971047027 (1999)	KCA 6.5.3.2/01 - /25
Barley, Malt germ	3	0.42		
Barley, Spent grain	3	1.0		
Barley, Flocs	3	0.28		
Barley, Yeast	3	0.29		
Barley, Wort (all types)	21	<0.09		
Beer	19	<0.04		
Barley, Pearling dust	6	1.9		
Pearl barley	6	0.55		

(a) The median processing factor is obtained by calculating the median of the individual processing factors of each processing study.

(b): The median conversion factor for enforcement to risk assessment is obtained by calculating the median of the individual conversion factors of each processing study.

The new processing studies for apple and barley are presented below.

Apple

Report:	K-CA 6.5.3/01. Solé C. (2004), Residue study with cyprodinil (CGA219417) and fludioxonil (CGA173506) in or on apples in Switzerland. Syngenta, Jealott's Hill International Research Centre, Bracknell, United Kingdom. Syngenta Report Number 03-0801. (Syngenta Regulatory Document No: CGA173506/6057).

Guidelines

FAO Guidelines on Producing Pesticide Residues Data from Supervised Trials (Rome, 1990).

Commission of the European Communities. General Recommendations for the Design, Preparation and Realization of Residue Trials (**SANCO 7029/V1/95 rev. 5 22/7/1997**).

Guidelines and Criteria for the Preparation and Presentation of Complete Dossiers and of Summary Dossiers for the Inclusion of Active Substances in Annex I of Directive 91/414/EEC (Article 5.3 and 8.2), 1996.

GLP

The study was carried out according to the principles of Good Laboratory Practice.

Executive Summary

Apples grown in Southern France were treated with A9219B, a WG formulation containing cyprodinil. Trees were sprayed three times with nominal application rates of 370 g cyprodinil/ha. Samples were harvested 7 days after the last application of A9219B and a sub-sample analysed to determine residues of cyprodinil. An additional sample of apple fruit taken at 7 days from the treated plot was used for the production of apple juice and apple puree and samples of various processed commodities were analysed for cyprodinil. A full mass balance study was conducted to determine the accountability of the cyprodinil residue, and three follow-up studies were conducted to determine residue transfer into the processed commodities.

The % residue recovered (mass balance) for apple juice was 82% and for apple puree was 99%. The average processing factors (P*f*) for cyprodinil determined for the various edible process fractions were as follows:

$$Pf = \frac{\text{residue level in processed commodity}}{\text{residue level in the RAC or commodity to be processed}}$$

Unwashed fruit to washed fruit:	0.9
Unwashed fruit to wet pomace	3.9
Unwashed fruit to dry pomace	8.8
Unwashed fruit to pasteurised juice	0.08
Unwashed fruit to sterilised puree	0.23

From these results it can be concluded cyprodinil would tend to concentrate in wet and dry pomace but would not be expected to concentrate in apple juice or apple puree. Low residues of cyprodinil were removed from the fruit through washing.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Test Material	A9219B
Description	Water dispersible granule formulation containing cyprodinil and fludioxonil
Purity	370 g cyprodinil/kg + 253 g fludioxonil/kg
Batch number	WM011288
Stability of test compound	The test substance has been shown to be stable under the storage and test conditions of the study

A2. Test Facilities

The field trial was performed at Syngenta Crop Protection AG, Les Barges, CH-1896, Vouvry, Switzerland

The processing phase was performed at VITI RD, 101 Impasse des Capitelles, F-34400 Villetelle, France

The analytical phase was performed at ADME Bioanalyses, 75 Chemin de Sommières, 30310, Vergèze, France.

B. STUDY DESIGN AND METHODS

B1. Processing phase

Apples were treated three times with a foliar spray of the formulation A9219B, at nominal rates of 370 g cyprodinil/ha. The interval between the applications was 7-8 days.

Apple fruit was harvested 7 days after the last application. The fruit was washed with water from a constant pressure sprayer and used for the production of apple juice and apple puree.

The washed apples were crushed and pressed. Pectolytic enzymes were added to the extracted raw juice which was left to settle for at least 12 hours. The juice was racked, filtered under nitrogen pressure and the pH was corrected to 3.5 using citric acid. The juice was pasteurised by heating to approximately 85°C for one minute. A sample of the wet pomace remaining after juice extraction was dried at approximately 60°C to produce dry pomace.

Apple puree was produced by blanching the washed fruit in boiling water and then crushing and sieving to remove seeds and peels. Sugar was added, the puree was reduced by heating to obtain a Brix degree of 24% and then sterilised (115-120°C for 10 minutes).

B2. Analytical Phase

Samples of the raw agricultural commodity (apple fruit) and various processed fractions were analysed for cyprodinil using EU reviewed method REM 141.01. **ENV/JM/MONO(2007)17** states that "*if the method* [for determination of residues in processed commodities] *is substantially the same for both the raw agricultural commodity (RAC) and the processed commodity, then a limited or reduced validation may suffice."* `Method REM 141.01 has been validated on a wide range of crops and is therefore appropriate for the analysis of cyprodinil in the processed commodities presented here. The LOQ was 0.02 mg/kg in all commodities. A summary of the data previously reviewed is presented in document M-CA Section 4, CA 4.1.2.

The cyprodinil residue accountability for each individual process was calculated from a mass balance study, and transfer factors from the washed fruit into various processed commodities determined from this and three additional follow up studies.

II. RESULTS AND DISCUSSION

A summary of the measured residues from the various fractions for each of the separate processed fractions is given in Table 6.5.3-1.

Table 6.5.3-1: Summary of cyprodinil residues in apple processed commodities

Commodity	Residues (mg/kg or mg/L for washing water and juices)			
	Balance 1	Follow-up 1	Follow-up 2	Follow-up 3
	cyprodinil	cyprodinil	cyprodinil	cyprodinil
Field samples				
Apple fruit residue prior to processing	0.30	0.30	0.30	0.30
Apple juice production				
Washed fruit	0.28	--	--	--
Washing water	0.03	--	--	--
Wet pomace	1.16	--	--	--
Raw juice	0.03	--	--	--
Dry pomace	1.78	2.76	3.61	2.45
Pasteurised juice	0.02	0.02	0.03	0.02
Apple puree production				
Sieved puree	0.05	0.05	0.05	0.05
Waste	0.72	0.69	0.78	1.15
Puree	0.06	0.06	0.08	0.07

--: not analysed in follow up study.

The mean processing factors for cyprodinil for each commodity were calculated and presented in Table 6.5.3-2.

Table 6.5.3-2: Summary of cyprodinil processing factors into processed apple products

Commodity	Processing Factor	Mean Processing Factor
Washed fruit	0.9	0.9
Washing water	0.10	0.10
Wet pomace	3.9	3.9
Dry pomace	5.9, 9.2, 12.0, 8.2	8.8
Apple juice (raw)	0.10	0.10
Apple juice (pasteurised)	0.07, 0.07, 0.10, 0.07	0.08
Sieved puree	0.17, 0.17, 0.17, 0.17	0.17
Waste	2.4, 2.3, 2.6, 3.8	2.8
Apple puree	0.20, 0.20, 0.27, 0.23	0.23

Processing factor = residue in processed commodity/mean residue prior to processing (e.g. for wet pomace 1.16/0.30 = 3.9)

A mass balance study was conducted to determine the accountability of the cyprodinil residue. The results are not reported in detail here, however the % residue recovered (mass balance) for apple juice was 82% and for apple puree was 99%.

III. CONCLUSIONS

Sufficient data is available to allow processing factors to be calculated for cyprodinil residues from raw apple fruit into apple juice and apple puree. It can be concluded that cyprodinil residues would be expected to concentrate in wet and dry pomace, although it would not be expected to concentrate in juice or puree. Low residues of cyprodinil were removed from the fruit through washing.

Barley

New processing studies in barley not previously submitted are available and are summarised below.

The residue reports determining residues of cyprodinil in processed products are referenced in Table 6.5.3-3 and the data are presented below.

Table 6.5.3-3: Report references for trials for barley processed products

Annex Pt.	Number.	Author/s	Issue Year	Report Title
KCA 6.5.3/02	(1 of 25)	M Maffezzoni	1998	Magnitude of Residues After Application of CGA219417 as Formulation A8779A, WG 75 in Malting Barley. Syngenta File No. CGA219417/0861, Syngenta Report No. OF95151/DE93.
KCA 6.5.3/03	(2 of 25)	M Maffezzoni	1999	Residue Study with CGA219417 + Cyproconazole in or on Winter Barley in North of France. Syngenta File No. SAN619/6778, Syngenta Report No. 9810301.
KCA 6.5.3/04	(3 of 25)	M Maffezzoni	1999a	Residue Study with CGA219417 + Cyproconazole in or on Winter Barley in North of France. Syngenta File No. SAN619/6777, Syngenta Report No. 9810302.
KCA 6.5.3/05	(4 of 25)	M Maffezzoni	1999b	Residue Study with CGA219417 + Cyproconazole in or on Spring Barley in North of France. Syngenta File No. SAN619/6801, Syngenta Report No. 9810401.
KCA 6.5.3/06	(5 of 25)	R Tribolet	2001	Residue Study with Cyprodinil (CGA219417) in or on Winter Barley in France (North). Syngenta File No. CGA219417/1011, Syngenta Report No. 2023/99.

Annex Pt.	Number.	Author/s	Issue Year	Report Title
KCA 6.5.3/07	(6 of 25)	R Tribolet	2001a	Residue Study with Cyprodinil (CGA 219417) in or on Spring Barley in France (North). Syngenta File No. CGA219417/1013, Syngenta Report No. 2025/99
KCA 6.5.3/08	(7 of 25)	M Maffezzoni	1999c	Residue Study with CGA 219417 + Cyproconazole in or on Spring Barley in North of France. Syngenta File No. SAN619/6802, Syngenta Report No. 9810402
KCA 6.5.3/09	(8 of 25)	M Maffezzoni	1999d	Residue Study with CGA 219417 in or on spring Barley in North of France. Syngenta File No. CGA219417/0928, Syngenta Report No. 9715402
KCA 6.5.3/10	(9 of 25)	M Maffezzoni	1998a	CGA 114900 + CGA 219417, EC 375, A-9939 A (70552A), Spring barley, France (North). Syngenta File No. CGA114900/0675, Syngenta Report No. 9715801
KCA 6.5.3/11	(10 of 25)	M Maffezzoni	1999e	Residue Study with CGA 219417 in or on spring Barley in North of France. Syngenta File No. CGA219417/0929, Syngenta Report No. 9715401
KCA 6.5.3/12	(11 of 25)	M Maffezzoni	1998b	CGA 114900 + CGA 219417, EC 375, A-9939 A (70552A), Spring barley, France (North). Syngenta File No. CGA114900/0674, Syngenta Report No. 9715802
KCA 6.5.3/13	(12 of 25)	R Tribolet	2001b	Residue Study with Cyprodinil (CGA 219417) in or on Spring Barley in France (North). Syngenta File No. CGA219417/1014, Syngenta Report No. 2026/99
KCA 6.5.3/14	(13 of 25)	M Maffezzoni	1998c	CGA 64250 + CGA 219417, EC 290, A-9532 B, Barley (malting), France (North). Syngenta File No. CGA64250/3369, Syngenta Report No. 9715001
KCA 6.5.3/15	(14 of 25)	M Maffezzoni	1998d	CGA 114900 + CGA 219417, Podium EC 375, A-9939 A, Winter barley, France (North). Syngenta File No. CGA114900/0670, Syngenta Report No. 9715701
KCA 6.5.3/16	(15 of 25)	M Maffezzoni	1998e	CGA 64250 + CGA 219417, EC 290, A-9532 B, Spring barley (malting), France (North). Syngenta File No. CGA64250/3418, Syngenta Report No. 9715002
KCA 6.5.3/17	(16 of 25)	M Maffezzoni	1998f	CGA 114900 + CGA 219417, Podium EC 375, A-9939 A, Winter barley, France (North). Syngenta File No. CGA114900/0671, Syngenta Report No. 9715702
KCA 6.5.3/18	(17 of 25)	M Maffezzoni	1998g	CGA 64250 + CGA 219417, EC 290, A-9532 B, Barley (malting), France (North). Syngenta File No. CGA64250/3370, Syngenta Report No. OF96142/DE11
KCA 6.5.3/19	(18 of 25)	M Maffezzoni	1998h	CGA 219417, WG 75, A-8779 A, Barley (malting), France (North). Syngenta File No. CGA219417/0862, Syngenta Report No. OF95151/KJ30
KCA 6.5.3/20	(19 of 25)	JA Smith	1998	CGA 64250 + CGA 219417, EC 312.5, A-8593 C, Spring barley, processing, Germany. Syngenta File No. CGA64250/3380, Syngenta Report No. gr 44496
KCA 6.5.3/21	(20 of 25)	JA Smith	1999	Determination of Residues of Cyprodinil in Spring Barley and Beer processing products. Syngenta File No. CGA219417/0901, Syngenta Report No. gr 42298
KCA 6.5.3/22	(21 of 25)	K Beinhauer	1999	Residues of Cyprodinil in Winter Barley According to BBA Guideline IV, 3-3 and 3-4 (1990). Syngenta File No. CGA219417/0894, Syngenta Report No. 971064026
KCA 6.5.3/23	(22 of 25)	JA Smith	1999a	Determination of Residues of Cyprodinil in Spring Barley and Beer processing products. Syngenta File No. CGA219417/0903, Syngenta Report No. gr 44598
KCA 6.5.3/24	(23 of 25)	JA Smith	1999b	Determination of Residues of Cyprodinil in Spring Barley and Beer processing products. Syngenta File No. CGA219417/0900, Syngenta Report No. gr 41198

Annex Pt.	Number.	Author/s	Issue Year	Report Title
KCA 6.5.3/25	(24 of 25)	JA Smith	1999c	Determination of Residues of Cyprodinil in Spring Barley and Beer processing products. Syngenta File No. CGA219417/0902, Syngenta Report No. gr 43498
KCA 6.5.3/26	(25 of 25)	K Beinhauer	1999a	CGA 219417, A-8779 A, Winter barley, Germany. Syngenta File No. CGA219417/0895, Syngenta Report No. 971047027

Guidelines

The studies meet the requirements of the Commission of the European Communities, Processing Studies; **7035/V1/95 rev. 5 (rev. 5, working document**).

GLP

All trials (field and analytical phases) were carried out in compliance with the principles of Good Laboratory Practice.

Materials and Methods

Twenty-five supervised residue trials were conducted on barley between 1995 and 1999 in northern Europe.

Treatments were applied as foliar (BBCH 32-73) spray applications using cyprodinil formulated as a WG 75, WG 45.3, EC 375, EC 290 or EC 312.5 applied once or twice at application rates of 364-1000 g a.s./ha.

Samples of grain were taken 43 to 59 days after application and processed. Samples of grain, malt, malt germ, spent grain, flocs, yeast, wort, beer, pearl barley and pearling dust were analysed for residues of cyprodinil by analytical methods REM 141.03 with a LOQ of 0.02 mg/kg (grain and malt) and REM 141.05 (wort) with a LOQ of 0.01 mg/kg, or method REM 141.01 (or AGR/MOA/219417-1 which is based on REM 141.01) with a LOQ of 0.01 mg/kg, 0.02 mg/kg or 0.05 mg/kg (grain and processed products) and in some studies a LOQ of 0.002 mg/L (wort and beer) or 0.005 mg/kg (beer). A summary of EU reviewed method REM 141.01 and validation data are presented in document M-CA Section 4, CA 4.1.2. **ENV/JM/MONO(2007)17** states that "*if the method* [for determination of residues in processed commodities] *is substantially the same for both the raw agricultural commodity (RAC) and the processed commodity, then a limited or reduced validation may suffice."* `Method REM 141.01 has been validated on a wide range of crops and is therefore appropriate for the analysis of cyprodinil in the processed commodities presented here. Procedural recovery data are presented with the results of the residues trials in Table 6.5.3-4.

Samples were stored up to a maximum of 21 months from sampling to extraction. Residues of cyprodinil are stable in wheat grain for at least 24 months (see section CA 6.1) and therefore no degradation will have occurred between sampling and analysis.

Table 6.5.3-4: Summary of cyprodinil residues in barley grain and processed commodities

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Northern Europe								
Report: OF95151 Study: OF95151 Trial: DE93 - Study to GLP - Study carried out in 1995	Barley (Plaisant)	FRANCE (Europe North)	600 g a.s./ha (Plot 3)	BBCH 73	46	Grain	0.58 mg/kg	Cyprodinil Mean = 93% RSD = N/A (n = 2 in 0.04 - 0.50 mg/kg spiking range) Malt Mean = 97% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Mean = 86% RSD = N/A (n = 2 in 0.01 - 0.10 mg/kg spiking range)
						Malt	0.63 mg/kg	
						Wort	<0.01 mg/kg	
			600 g a.s./ha 600 g a.s./ha (Plot 4)	BBCH 33 – 34 BBCH 73	46	Grain	0.75 mg/kg	
						Malt	0.73 mg/kg	
						Wort	<0.01 mg/kg	
Report: 9810301 Study: 9810301 Trial: 9810301 - Study to GLP - Study carried out in 1998	Barley (Plaisant)	FRANCE (Europe North)	578 g a.s./ha 588 g a.s./ha	BBCH 32 BBCH 69	59	Grain	0.86 mg/kg	Cyprodinil Grain Mean = 102% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Mean = 97% RSD = N/A (n = 2 in 0.01 - 0.10 mg/L spiking range) Malt Mean = 104% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Mean = 90% RSD = 12% (n = 4 in 0.01 - 0.10 mg/L spiking range)
						Grain	0.84 mg/kg	
						Beer	<0.01 mg/L	
						Beer	<0.01 mg/L	
						Malt	1.07 mg/kg	
						Malt	0.87 mg/kg	
						Wort	0.01 mg/L	
						Wort	<0.01 mg/L	
Report: 9810302 Study: 9810302 Trial: 9810302 - Study to GLP - Study carried out in 1998	Barley (Plaisant)	FRANCE (Europe North)	574 g a.s./ha 606 g a.s./ha	BBCH 31 – 32 BBCH 61 – 65	43	Grain	0.74 mg/kg	Cyprodinil Grain Mean = 102% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Mean = 97% RSD = N/A. (n = 2 in 0.01 - 0.10 mg/L spiking range) Malt Mean = 104% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Mean = 98% RSD = N/A (n = 2 in 0.01 - 0.10 mg/L spiking range)
						Grain	0.73 mg/kg	
						Beer	<0.01 mg/L	
						Beer	<0.01 mg/L	
						Malt	0.82 mg/kg	
						Malt	0.81 mg/kg	
						Wort	<0.01 mg/L	
						Wort	<0.01 mg/L	
Report: 2023/99 Study: 2023/99 Trial: 2023/99 - Study to GLP	Barley (Esterel)	FRANCE (Europe North)	648 g a.s./ha 611 g a.s./ha	BBCH 31 BBCH 59	53	Grain	1.15 mg/kg	Cyprodinil Grain Mean = 106% RSD = 12% (n = 4 in 0.02 - 0.20 mg/kg spiking range) Beer Mean = 104% RSD = N/A (n = 2 in
						Grain	1.04 mg/kg	
						Beer	<0.002 mg/L <0.002 mg/L	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
- Study carried out in 1999						Malt 1D	1.17 mg/kg	0.00 - 0.02 mg/L spiking range) Malt Mean = 105% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Mean = 102% RSD = 7% (n = 6 in 0.00 - 0.20 mg/L spiking range)
						Malt 2D	1.24 mg/kg	
						Malt 4D	1.19 mg/kg	
						Pre-process	1.12 mg/kg 1.08 mg/kg	
						Unfermented Wort 1K	<0.02 mg/L	
						Unfermented Wort 2K	0.003 mg/L	
						Unfermented Wort 1K	<0.02 mg/L	
						Unfermented Wort 2K	<0.02 mg/L	
						Fermented Wort 1L	0.003 mg/L	
						Fermented Wort 2L	0.002 mg/L	
						Brewing Wort 1G	0.003 mg/L	
						Brewing Wort 2G	<0.02 mg/L	
Report: 9810401 Study: 9810401 Trial: 9810401 - Study to GLP - Study carried out in 1998	Barley (Alexis)	FRANCE (Europe North)	573 g a.s./ha 588 g a.s./ha	BBCH 32 BBCH 71	48	Grain	0.65 mg/kg	Cyprodinil Grain Mean = 102% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.10 mg/L spiking range) Malt Mean = 100% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Mean = 86% RSD = N/A (n = n in 0.01 - 0.10 mg/L spiking range)
						Grain	0.68 mg/kg	
						Beer	<0.01 mg/L	
						Beer	<0.01 mg/L	
						Malt	0.90 mg/kg	
						Malt	0.98 mg/kg	
						Wort	<0.01 mg/L	
						Wort	<0.01 mg/L	
Report: 2025/99 Study: 2025/99 Trial: 1 - 2025/99 - Study to GLP - Study carried out in 1999	Barley (Cork)	FRANCE (Europe North)	611 g a.s./ha 603 g a.s./ha	BBCH 31 BBCH 51	52	RAC Grain	0.15 mg/kg	Cyprodinil Grain Mean = 106% RSD = 12% (n = 4 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 104% RSD = N/A (n = 2 in 0.00 - 0.02 mg/L spiking range) Malt Grain Mean = 105% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Grain Mean = 102% RSD = 7% (n = 6 in 0.00 - 0.20 mg/L spiking range)
						Beer	<0.002 mg/kg	
						Malt 1D	0.17 mg/kg	
						Malt 2D	0.16 mg/kg	
						Unfermented Wort 1K	<0.002 mg/kg	
						Unfermented Wort 2K	<0.002 mg/kg	
						Fermented Wort 1L	<0.02 mg/kg	
						Fermented Wort 2L	<0.02 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						Brewing Wort G	<0.02 mg/kg	
Report: 9810402 Study: 9810402 Trial: 1 - Esbarres - Study to GLP - Study carried out in 1998	Barley (Prisma)	FRANCE (Europe North)	581 g a.s./ha 594 g a.s./ha	BBCH 31 - 32 BBCH 51 - 55	45	RAC Grain	0.26; 0.29 mg/kg	Cyprodinil Grain Mean = 102% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.10 mg/kg spiking range) Malt Grain Mean = 100% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Grain Mean = 86% RSD = N/A (n = 2 in 0.01 - 0.10 mg/kg spiking range)
						Malt	0.44, 0.49 mg/kg	
						Wort	<0.01, <0.01 mg/kg	
						Beer	<0.01, <0.01 mg/kg	
Report: 9715402 Study: 9715402 Trial: 1 - 9715402 - Study to GLP - Study carried out in 1998	Barley (Prisma)	FRANCE (Europe North)	613 g a.s./ha 604 g a.s./ha	BBCH 31 - 32 BBCH 57 - 59	52	RAC Grain	0.39 mg/kg	Cyprodinil Grain Mean = 94% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.05 mg/L spiking range) Malt Grain Mean = 100% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 98% RSD = 2% (n = 4 in 0.02 - 0.10 mg/L spiking range)
						Malt	0.41 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 9715801 Study: 9715801 Trial: 1 - Saint Hilaire le Petit - Study to GLP - Study carried out in 1997	Barley (Spring Alexis)	FRANCE (Europe North)	375 g a.s./ha 375 g a.s./ha	BBCH 32 BBCH 57	52	RAC Grain	0.10 mg/kg	Cyprodinil Grain Mean = 93% RSD = 6% (n = 10 in 0.01 - 0.10 mg/kg spiking range)
						Malt	0.14 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 9715401 Study: 9715401 Trial: 1 - 9715401 - Study to GLP - Study carried out in 1998	Barley (Alexis)	FRANCE (Europe North)	609 g a.s./ha 599 g a.s./ha	BBCH 32 BBCH 57	52	RAC Grain	0.06 mg/kg	Cyprodinil Grain Mean = 93% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 107% RSD = N/A (n = 2 in 0.01 - 0.05 mg/L spiking range) Malt Grain Mean = 105% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 87% RSD = 5% (n = 4 in 0.02 - 0.10 mg/L spiking range)
						Malt	0.10 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 9715802 Study: 9715802	Barley (Prisma)	FRANCE (Europe North)	375 g a.s./ha 375 g a.s./ha	BBCH 32 BBCH 59	45	RAC Grain	0.25 mg/kg	Cyprodinil Grain Mean = 92% RSD = N/A (n = 2 in
						Malt	0.38 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Trial: 1 - Courtenon - Study to GLP - Study carried out in 1997						Unfermented Wort	<0.02 mg/kg	0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 106% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Malt Grain Mean = 91% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 88% RSD = 9% (n = 4 in 0.02 - 0.10 mg/kg spiking range)
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 2026/99 Study: 2026/99 Trial: 1 - 2026/99 - Study to GLP - Study carried out in 1999	Barley (Prisma)	FRANCE (Europe North)	588 g a.s./ha 542 g a.s./ha	BBCH 31 BBCH 51	45	RAC Grain	0.09 mg/kg	Cyprodinil Grain Mean = 106% RSD = 12% (n = 4 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 104% RSD = N/A (n = 2 in 0.00 - 0.02 mg/L spiking range) Malt Grain Mean = 105% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Grain Mean = 102% RSD = 7% (n = 6 in 0.00 - 0.20 mg/L spiking range)
						Beer	<0.002 mg/kg	
						Malt 1D	0.10 mg/kg	
						Malt 2D	0.10 mg/kg	
						Unfermented Wort 1K	<0.002 mg/kg	
						Unfermented Wort 2K	<0.002 mg/kg	
						Fermented Wort 1L	<0.02 mg/kg	
						Fermented Wort 2L	<0.02 mg/kg	
						Brewing Wort G	<0.02 mg/kg	
Report: 9715001 Study: 9715001 Trial: 1 - 9715001 - Study to GLP - Study carried out in 1997	Barley (Alexis)	FRANCE (Europe North)	457 g a.s./ha 472 g a.s./ha	BBCH 32 BBCH 57	52	RAC Grain	0.09; 0.08 mg/kg	Cyprodinil Grain Mean = 94% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 91% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Malt Grain Mean = 94% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 100% RSD = 11% (n = 4 in 0.02 - 0.10 mg/kg spiking range)
						Malt	0.09; 0.11 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 9715701 Study: 9715701 Trial: 1 - Chalons en Champagne - Study to GLP - Study carried out in 1997	Barley (Winter Plaisant)	FRANCE (Europe North)	364 g a.s./ha 364 g a.s./ha	BBCH 32 BBCH 61	45	RAC Grain	0.36 mg/kg	Cyprodinil Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 89% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Malt Grain Mean = 93% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 93% RSD = 8% (n = 4 in 0.02 - 0.10 mg/kg spiking range)
						Malt	0.42 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: 9715002 Study: 9715002	Barley (Spring Prisma)	FRANCE (Europe North)	480 g a.s./ha 480 g a.s./ha	BBCH 31 - 32 BBCH 57 - 59	52	RAC Grain	0.19 mg/kg	Cyprodinil Grain Mean = 93% RSD = N/A (n = 2 in

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
Trial: 1 - Magny les Aubigny - Study to GLP - Study carried out in 1997						Malt	0.29 mg/kg	0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 83% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Malt Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 102% RSD = 13% (n = 4 in 0.02 - 0.10 mg/kg spiking range)
						Unfermented Wort	<0.02; <0.02 mg/kg	
						Fermented Wort	<0.02; <0.02 mg/kg	
						Beer	<0.01; <0.01 mg/kg	
Report: 9715702 Study: 9715702 Trial: 1 - Magny les Aubigny - Study to GLP - Study carried out in 1997	Barley (Winter Plaisant)	FRANCE (Europe North)	370 g a.s./ha 384 g a.s./ha	BBCH 31 - 32 BBCH 65	58	RAC Grain	0.18 mg/kg	Cyprodinil Grain Mean = 106% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Beer Grain Mean = 97% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Malt Grain Mean = 97% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 97% RSD = 4% (n = 4 in 0.02 - 0.10 mg/kg spiking range)
						Malt	0.24 mg/kg	
						Unfermented Wort	<0.02 mg/kg	
						Fermented Wort	<0.02 mg/kg	
						Beer	<0.01 mg/kg	
Report: OF96142/DE11 Study: OF96142 Trial: DE11/Plot3 - Study to GLP - Study carried out in 1996	Barley (Plaisant)	FRANCE (Europe North)	480 g a.s./ha	BBCH 65	49	RAC Grain	0.42; 0.38 mg/kg	Cyprodinil Grain Mean = 86% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Malt Grain Mean = 90% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 106% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range)
						Malt	0.40; 0.49 mg/kg	
						Wort	<0.02 mg/kg	
Report: OF96142/DE11 Study: OF96142 Trial: DE11/Plot4 - Study to GLP - Study carried out in 1996	Barley (Plaisant)	FRANCE (Europe North)	480 g a.s./ha 480 g a.s./ha	BBCH 32 BBCH 65	49	RAC Grain	0.40; 0.40 mg/kg	Cyprodinil Grain Mean = 86% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Malt Grain Mean = 90% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range) Wort Grain Mean = 106% RSD = N/A (n = 2 in 0.02 - 0.10 mg/kg spiking range)
						Malt	0.51; 0.56 mg/kg	
						Wort	<0.02 mg/kg	
Report: OF95151/KJ30 Study: OF95151/KJ30 Trial: 1 - St Peravy-Epreux/ Plot4 - Study to GLP - Study carried out in 1995	Barley (A)	FRANCE (Europe North)	600 g a.s./ha 600 g a.s./ha	BBCH 32 BBCH 51 - 55	45	RAC Grain	0.13 mg/kg	Cyprodinil Grain Mean = 93% RSD = N/A (n = 2 in 0.04 - 0.50 mg/kg spiking range) Malt Grain Mean = 97% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
						Malt	0.11 mg/kg	
						Wort	<0.01 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
								Wort Grain Mean = 88% RSD = N/A (n = 2 in 0.01 - 0.10 mg/kg spiking range)
Report: OF95151/KJ30 Study: OF95151/KJ30 Trial: 1 - St Peravy-Epreux - Study to GLP - Study carried out in 1995	Barley (A)	FRANCE (Europe North)	600 g a.s./ha	BBCH 51 - 55	45	RAC Grain	0.07 mg/kg	Cyprodinil Grain Mean = 93% RSD = N/A (n = 2 in 0.04 - 0.50 mg/kg spiking range) Malt Grain Mean = 97% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Wort Grain Mean = 88% RSD = N/A (n = 2 in 0.01 - 0.10 mg/kg spiking range)
						Malt	0.07 mg/kg	
						Wort	<0.01 mg/kg	
Report: GR 44496 Study: gr 44496 Trial: Wallersdorf - Study to GLP - Study carried out in 1996	Barley (Alexis)	GERMANY (Europe North)	375 g a.s./ha	BBCH 45	58	RAC Grain	0.02 mg/kg	Cyprodinil Grain Mean = 91% RSD = 5% (n = 5 in 0.02 - 0.20 mg/kg spiking range) Aspirated Grain Fraction Grain Mean = 91% RSD = N/A (n = 2 in 0.05 - 5.05 mg/kg spiking range) Beer Grain Mean = 99% RSD = N/A (n = 2 in 0.02 - 2.03 mg/kg spiking range) Germ Grain Mean = 97% RSD = N/A (n = 2 in 0.05 - 5.08 mg/kg spiking range) Malt Grain Mean = 82% RSD = N/A (n = 2 in 0.02 - 2.03 mg/kg spiking range) Pearled Barley Grain Mean = 108% RSD = N/A (n = 2 in 0.02 - 2.02 mg/kg spiking range) Spent Grain Mean = 97% RSD = N/A (n = 2 in 0.05 - 4.97 mg/kg spiking range) True Grain Mean = 69% RSD = N/A (n = 2 in 0.05 - 5.08 mg/kg spiking range) Yeast Grain Mean = 95% RSD = N/A (n = 2 in 0.05 - 5.07 mg/kg spiking range)
						Pearl Barley	0.03 mg/kg	
						Pearling Dust	0.05 mg/kg	
						Malt	<0.02 mg/kg	
						Malt Germ	<0.05 mg/kg	
						Spent Grain	<0.05 mg/kg	
						Flocs	<0.05 mg/kg	
						Yeast	<0.05 mg/kg	
						Beer	<0.02 mg/kg	
Report: gr 42298 Study: gr 42298 Trial: 1 - Ivenrode - Study to GLP - Study carried out in 1998	Barley (Barke)	GERMANY (Europe North)	750 g a.s./ha 750 g a.s./ha	BBCH 32 BBCH 49 - 51	55	RAC Grain	0.03 mg/kg	Cyprodinil Grain Mean = 94% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Dust (Pearling) Grain Mean = 72% RSD =
						Pearl Barley	0.02 mg/kg	
						Pearling Dust	0.07 mg/kg	
						Malt	0.03 mg/kg	
						Malt Germ	0.02 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
						Spent Grain	0.04 mg/kg	N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Flocs Grain Mean = 101% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Germ (Malt) Grain Mean = 99% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Malt Grain Mean = 93% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Pearled Barley Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Spent Grain Mean = 91% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Yeast Grain Mean = 95% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
						Flocs	<0.02 mg/kg	
						Yeast	<0.02 mg/kg	
						Beer	<0.005 mg/kg	
Report: 971064026 Study: 971064026 Trial: FR 26/97/20 - Study to GLP - Study carried out in 1997	Barley (Cita)	GERMANY (Europe North)	750 g a.s./ha 750 g a.s./ha	BBCH 31 - 32 BBCH 63	51	RAC Grain	0.85 mg/kg	Cyprodinil Mean = 94% RSD = 13% (n = 9 in 0.02 - 19.27 mg/kg spiking range) Dust (Pearling) Mean = 81% RSD = N/A (n = 2 in 0.20 - 0.98 mg/kg spiking range) Pearled Barley Mean = 103% RSD = N/A (n = 2 in 0.02 - 0.02 mg/kg spiking range)
						Pearl barley	0.46 mg/kg	
						Pearling dust	1.66 mg/kg	
Report: gr 44598 Study: gr 44598 Trial: 1 - Herxheimweyher - Study to GLP - Study carried out in 1998	Barley (Scarlett)	GERMANY (Europe North)	750 g a.s./ha 750 g a.s./ha	BBCH 30 - 31 BBCH 56	53	RAC Grain	0.34 mg/kg	Cyprodinil Grain Mean = 104% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Dust (Pearling) Grain Mean = 72% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Flocs Grain Mean = 101% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Germ (Malt) Grain Mean = 99% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Malt Grain Mean = 93% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Pearled Barley Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
						Pearl Barley	0.12 mg/kg	
						Pearling Dust	0.52 mg/kg	
						Malt	0.30 mg/kg	
						Malt Germ	0.08 mg/kg	
						Spent Grain	0.31 mg/kg	
						Flocs	0.02 mg/kg	
						Yeast	0.03 mg/kg	
						Beer	<0.005 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected) cyprodinil mg/kg	Recovery Data
								Spent Grain Mean = 91% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Yeast Grain Mean = 95% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
Report: gr 41198 Study: gr 41198 Trial: 1 - Sühlen - Study to GLP - Study carried out in 1998	Barley (Alexis)	GERMANY (Europe North)	750 g a.s./ha 750 g a.s./ha	BBCH 30 - 31 BBCH 49 - 51	49	RAC Grain	0.03 mg/kg	Cyprodinil Grain Mean = 89% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Dust (Pearling) Grain Mean = 72% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Pearled Barley Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
						Pearl Barley	0.03 mg/kg	
						Pearling Dust	0.08 mg/kg	
Report: gr 43498 Study: gr 43498 Trial: gr 43498 - Study to GLP - Study carried out in 1998	Barley (Krona)	GERMANY (Europe North)	750 g a.s./ha 750 g a.s./ha	BBCH 31 BBCH 59	49	RAC Grain	0.17 mg/kg	Cyprodinil Grain Mean = 100% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Beer Grain Mean = 102% RSD = N/A (n = 2 in 0.01 - 0.05 mg/kg spiking range) Dust (Pearling) Grain Mean = 72% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Flocs Grain Mean = 101% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Germ (Malt) Grain Mean = 99% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Malt Grain Mean = 93% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Pearled Barley Grain Mean = 92% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Spent Grain Mean = 91% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range) Yeast Grain Mean = 95% RSD = N/A (n = 2 in 0.02 - 0.20 mg/kg spiking range)
						Pearl Barley	0.07 mg/kg	
						Pearling Dust	0.20 mg/kg	
						Malt	0.16 mg/kg	
						Malt Germ	0.06 mg/kg	
						Spent Grain	0.15 mg/kg	
						Flocs	0.02 mg/kg	
						Yeast	0.02 mg/kg	
						Beer	<0.005	
Report: 971047027 Study: 971047027 Trial: FR 27/97/34 - Study to GLP - Study carried out in 1997	Barley (Grete (winter b.))	GERMANY (Europe North)	1000 g a.s./ha 1000 g a.s./ha	BBCH 32 BBCH 69 - 71	48	RAC Grain	1.13 mg/kg	Cyprodinil Grain Mean = 102% RSD = 14% (n = 3 in 0.02 - 2.06 mg/kg spiking range) Dust (Pearling) Grain Mean = 81% RSD = N/A (n = 2 in 0.20 - 0.98 mg/kg spiking range)
						Pearl barley	0.37 mg/kg	
						Pearling dust	2.30 mg/kg	

GLP and Trial Details	Crop (Variety)	Country (Region)	Application Rate	Growth Stage at Application	PHI (days)	Crop Part	Residue Found (Uncorrected)	Recovery Data
							cyprodinil mg/kg	
								Pearled Barley Grain Mean = 103% RSD = N/A (n = 2 in 0.02 - 0.02 mg/kg spiking range)
Notes: N/A not applicable								

Findings

Residues in the barley grain prior to processing and in the processed commodities together with the individual processing factors for each trial are presented in Table 6.5.3-5. Mean processing factors are presented in Table 6.5.3-6.

Table 6.5.3-5: Cyprodinil residues in barley grain and processed commodities, and processing factors

Trial Site	Crop (Variety)	Commodity	Cyprodinil Residue (mg/kg or mg/L)	Processing Factor[1]
Report: OF95151 Study: OF95151 Trial: DE93/Plot 3	Barley (Plaisant)	RAC Grain	0.58	--
		Malt	0.63	1.09
		Unfermented wort	<0.01	<0.02
Report: OF95151 Study: OF95151 Trial: DE93/Plot 4	Barley (Plaisant)	RAC Grain	0.75	--
		Malt	0.73	0.97
		Unfermented wort	<0.01	<0.01
Report: 9810301 Study: 9810301 Trial: 9810301	Barley (Plaisant)	RAC Grain	0.85*	--
		Malt	0.97*	1.14
		Wort	<0.01*	<0.01
		Beer	<0.01*	<0.01
Report: 9810302 Study: 9810302 Trial: 9810302	Barley (Plaisant)	RAC Grain	0.74*	--
		Malt	0.82*	1.11
		Wort	<0.01*	<0.01
		Beer	<0.01*	<0.01
Report: 2023/99 Study: 2023/99 Trial: 2023/99	Barley (Esterel)	RAC Grain	1.10*	--
		Beer	<0.002	<0.01
		Malt 1D	1.17	1.06
		Malt 2D	1.24	1.13
		Malt 4D	1.19	1.08
				Mean all malt = 1.09
		Unfermented Wort 1K	0.002	0.002
		Unfermented Wort 2K	0.003	0.003
		Unfermented Wort 1K	0.003	0.003
		Unfermented Wort 2K	0.003	0.003
		Fermented Wort 1L	<0.02	<0.02
		Fermented Wort 2L	<0.02	<0.02
		Brewing Wort 1G	<0.02	<0.02
		Brewing Wort 2G	<0.02	<0.02
				Mean all wort = <0.01
Report: 9810401 Study: 9810401 Trial: 9810401	Barley (Alexis)	RAC Grain	0.67*	--
		Malt	0.94*	1.40
		Wort	<0.01*	<0.02
		Beer	<0.01*	<0.02
Report: 2025/99 Study: 2025/99 Trial: 1 - 2025/99	Barley (Cork)	RAC Grain	0.15	--
		Beer	<0.002	<0.01
		Malt 1D	0.17	1.13
		Malt 2D	0.16	1.07
				Mean all malt = 1.10
		Unfermented Wort 1K	<0.002	<0.01

Trial Site	Crop (Variety)	Commodity	Cyprodinil Residue (mg/kg or mg/L)	Processing Factor[1]
		Unfermented Wort 2K	<0.002	<0.01
		Fermented Wort 1L	<0.02	<0.13
		Fermented Wort 2L	<0.02	<0.13
		Brewing Wort G	<0.02	<0.13
				Mean all wort = <0.08
Report: 9810402 Study: 9810402 Trial: 1 - Esbarres	Barley (Prisma)	RAC Grain	0.28*	--
		Malt	0.47*	1.68
		Wort	<0.01*	<0.04
		Beer	<0.01*	<0.04
Report: 9715402 Study: 9715402 Trial: 1 - 9715402	Barley (Prisma)	RAC Grain	0.39	--
		Malt	0.41	1.05
		Unfermented Wort	<0.02	<0.05
		Fermented Wort	<0.02	<0.05
				Mean all wort = <0.05
		Beer	<0.01	<0.03
Report: 9715801 Study: 9715801 Trial: 1 - Saint Hilaire le Petit	Barley (Spring Alexis)	RAC Grain	0.10	--
		Malt	0.14	1.40
		Unfermented Wort	<0.02	<0.20
		Fermented Wort	<0.02	<0.20
				Mean all wort = <0.20
		Beer	<0.01	<0.10
Report: 9715401 Study: 9715401 Trial: 1 - 9715401	Barley (Alexis)	RAC Grain	0.06	--
		Malt	0.10	1.67
		Unfermented Wort	<0.02	<0.33
		Fermented Wort	<0.02	<0.33
				Mean all wort = <0.33
		Beer	<0.01	<0.02
Report: 9715802 Study: 9715802 Trial: 1 – Courtenon	Barley (Prisma)	RAC Grain	0.25	--
		Malt	0.38	1.52
		Unfermented Wort	<0.02	<0.08
		Fermented Wort	<0.02	<0.08
				Mean all wort = <0.08
		Beer	<0.01	<0.04
Report: 2026/99 Study: 2026/99 Trial: 1 - 2026/99	Barley (Prisma)	RAC Grain	0.09	--
		Beer	<0.002	<0.02
		Malt 1D	0.10	1.11
		Malt 2D	0.10	1.11
				Mean all malt = 1.11
		Unfermented Wort 1K	<0.002	<0.02
		Unfermented Wort 2K	<0.002	<0.02
		Fermented Wort 1L	<0.02	<0.22
		Fermented Wort 2L	<0.02	<0.22
		Brewing Wort G	<0.02	<0.22
				Mean all wort = <0.14
Report: 9715001 Study: 9715001	Barley (Alexis)	RAC Grain	0.09*	--
		Malt	0.10*	1.11

Trial Site	Crop (Variety)	Commodity	Cyprodinil Residue (mg/kg or mg/L)	Processing Factor[1]
Trial: 1 - 9715001		Unfermented Wort	<0.02	<0.22
		Fermented Wort	<0.02	<0.22
				Mean all wort = <0.22
		Beer	<0.01	<0.11
Report: 9715701 Study: 9715701 Trial: 1 - Chalons en Champagne	Barley (Winter Plaisant)	RAC Grain	0.36	--
		Malt	0.42	1.17
		Unfermented Wort	<0.02	<0.06
		Fermented Wort	<0.02	<0.06
				Mean all wort = <0.06
		Beer	<0.01	<0.03
Report: 9715002 Study: 9715002 Trial: 1 - Magny les Aubigny	Barley (Spring Prisma)	RAC Grain	0.19	--
		Malt	0.29	1.53
		Unfermented Wort	<0.02*	<0.11
		Fermented Wort	<0.02*	<0.11
				Mean all wort = <0.11
		Beer	<0.01*	<0.05
Report: 9715702 Study: 9715702 Trial: 1 - Magny les Aubigny	Barley (Winter Plaisant)	RAC Grain	0.18	--
		Malt	0.24	1.33
		Unfermented Wort	<0.02	<0.11
		Fermented Wort	<0.02	<0.11
				Mean all wort = <0.11
		Beer	<0.01	<0.06
Report: OF96142/DE11 Study: OF96142 Trial: DE11/Plot3	Barley (Plaisant)	RAC Grain	0.40*	--
		Malt	0.45*	1.13
		Wort	<0.02	<0.05
Report: OF96142/DE11 Study: OF96142 Trial: DE11/Plot4	Barley (Plaisant)	RAC Grain	0.40*	--
		Malt	0.54*	1.35
		Wort	<0.02	<0.05
Report: OF95151/KJ30 Study: OF95151/KJ30 Trial: 1 - St Peravy-Epreux/ Plot4	Barley (A)	RAC Grain	0.13	--
		Malt	0.11	0.85
		Wort	<0.01	<0.08
Report: OF95151/KJ30 Study: OF95151/KJ30 Trial: 1 - St Peravy-Epreux	Barley (A)	RAC Grain	0.07	--
		Malt	0.07	1.00
		Wort	<0.01	<0.14
Report: GR 44496 Study: gr 44496 Trial: Wallersdorf	Barley (Alexis)	RAC Grain	0.02	--
		Pearl Barley	0.03	-- #
		Pearling Dust	0.05	-- #
		Malt	<0.02	-- #
		Malt Germ	<0.05	-- #
		Spent Grain	<0.05	-- #
		Flocs	<0.05	-- #
		Yeast	<0.05	-- #
		Beer	<0.02	-- #
Report: gr 42298 Study: gr 42298	Barley (Barke)	RAC Grain	0.03	--
		Pearl Barley	0.02	0.67

Trial Site	Crop (Variety)	Commodity	Cyprodinil Residue (mg/kg or mg/L)	Processing Factor[1]
Trial: 1 - Ivenrode		Pearling Dust	0.07	2.30
		Malt	0.03	1.00
		Malt Germ	0.02	0.67
		Spent Grain	0.04	1.33
		Flocs	<0.02	<0.67
		Yeast	<0.02	<0.67
		Beer	<0.005	<0.17
Report: 971064026 Study: 971064026 Trial: FR 26/97/20	Barley (Cita)	RAC Grain	0.85	--
		Pearl barley	0.46	0.54
		Pearling dust	1.66	1.95
Report: gr 44598 Study: gr 44598 Trial: 1 - Herxheimweyher	Barley (Scarlett)	RAC Grain	0.34	--
		Pearl Barley	0.12	0.35
		Pearling Dust	0.52	1.53
		Malt	0.30	0.88
		Malt Germ	0.08	0.24
		Spent Grain	0.31	0.91
		Flocs	0.02	0.06
		Yeast	0.03	0.09
		Beer	<0.005	<0.01
Report: gr 41198 Study: gr 41198 Trial: 1 - Sühlen	Barley (Alexis)	RAC Grain	0.03	--
		Pearl Barley	0.03	1.00
		Pearling Dust	0.08	2.67
Report: gr 43498 Study: gr 43498 Trial: gr 43498 - Study to GLP	Barley (Krona)	RAC Grain	0.17	--
		Pearl Barley	0.07	0.41
		Pearling Dust	0.20	1.18
		Malt	0.16	0.94
		Malt Germ	0.06	0.35
		Spent Grain	0.15	0.88
		Flocs	0.02	0.12
		Yeast	0.02	0.12
		Beer	<0.005	<0.03
Report: 971047027 Study: 971047027 Trial: FR 27/97/34	Barley (Grete)	RAC Grain	1.13	--
		Pearl barley	0.37	0.33
		Pearling dust	2.30	2.04
		Beer	<0.005	<0.01

1 - Processing Factor = Residue in processed commodity/residue in raw agricultural commodity (grain).

* Mean of two analyses.

Processing factors not calculated as the residue in the grain was at the LOQ.

Table 6.5.3-6: Summary of cyprodinil processing factors into processed barley products

Commodity	Processing Factor	Mean Processing Factor
Malt (all types)	1.09, 0.97, 1.14, 1.11, 1.09*, 1.40, 1.10*, 1.68, 1.05, 1.40, 1.67, 1.52, 1.11*, 1.11, 1.17, 1.53, 1.33, 1.13, 1.35, 0.85, 1.00, 1.00, 0.88, 0.94	1.2
Malt germ	0.67, 0.24, 0.35	0.42
Spent grain	1.33, 0.91, 0.88	1.0
Flocs	<0.67, 0.06, 0.12	0.28
Yeast	<0.67, 0.09, 0.12	0.29
Wort (all types)	<0.02, <0.01, <0.01, <0.01, <0.01*, <0.02, <0.08*, <0.04, <0.05*, <0.20*, <0.33*, <0.08*, <0.14*, <0.22, <0.06*, <0.11*, <0.11*, <0.05, <0.05, <0.08, <0.14	<0.09
Beer	<0.01, <0.01, <0.01, <0.02, <0.01, <0.04, <0.03, <0.10, <0.02, <0.04, <0.02, <0.11, <0.03, <0.05, <0.06, <0.17, <0.01, <0.03, <0.01	<0.04
Pearling dust	2.30, 1.95, 1.53, 2.67, 1.18, 2.04	1.9
Pearl barley	0.67, 0.54, 0.35, 1.00, 0.41, 0.33	0.55

* Mean value from each trial.

Conclusions

Sufficient data is available to allow processing factors to be calculated for cyprodinil residues from barley into brewing products and pearl barley. It is concluded that residues of cyprodinil would not be expected to concentrate in malt germ, spent grain, flocs, yeast wort, beer or pearl barley. Cyprodinil residues concentrated in malt during the production of beer and in pearling dust during the production of pearl barley. In **SANCO 70354/V1/95 rev. 5 22/7/1997**, studies to measure residues in pot barley are suggested. Pot barley and pearl barley are processed from barley grain in the same way and so the results in pearl barley and pot barley are expected to be similar and lower than in the unprocessed grain.

Summary of processing studies in crops

Processing studies have been conducted on apple and barley which cover processed commodities important for the calculation of dietary exposure of humans and animals as recommended in OECD 508 Magnitude of the Pesticide Residues in Processed Commodities. The studies presented have investigated the transfer of cyprodinil residues in processes representative of major industrial procedures for apple (preparation of fruit juice) and barley (preparation of alcoholic beverages and distribution on milling), and for minor industrial procedures and domestic or home procedures; wet and dry pomace, and puree for apple, and pearling for barley.

In apple, cyprodinil residues would be expected to concentrate in wet and dry pomace but not in juice or puree. Low residues of cyprodinil were removed from the fruit through washing.

In barley, residues of cyprodinil did not concentrate in malt germ, spent grain, flocs, yeast wort, beer or pearl barley. Residues of cyprodinil did concentrate in malt and pearling dust.

An overall summary of processing factors for cyprodinil in processed apple and barley commodities is presented in Table 6.5.3-7.

Table 6.5.3-7: Summary of processing factors for cyprodinil from new studies presented

Crop	Processed Commodity	Number of Studies	Mean Processing Factor
Apple	Washed fruit	1	0.9
	Wet pomace	1	3.9
	Dry pomace	4	8.8
	Pasteurised juice	4	0.08
	Sterilised puree	4	0.23
Barley	Malt (all types)	24	1.2
	Malt germ	3	0.42
	Spent grain	3	1.0
	Flocs	3	0.28
	Yeast	3	0.29
	Wort (all types)	21	<0.09
	Beer	19	<0.04
	Pearling dust	6	1.9
	Pearl barley	6	0.55

The nature of residues of cyprodinil (CGA219417) has been adequately investigated in processed apple and barley products to support the representative uses proposed in this dossier. Robust processing factors can be proposed. No further studies are required.

CA 6.6 Residues in Rotational Crops

CA 6.6.1 Metabolism in rotational crops

The metabolism in rotational crops was considered during the EU evaluation of cyprodinil using ^{14}C-cyprodinil labelled in both the phenyl and pyrimidine position. The studies were evaluated under Council Directive 91/414/EEC and are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.9, November 2003**).

Table 6.6.1-1: Summary of metabolism in rotational crops for cyprodinil

Group (OECD Guideline 502)	Crop	Label Position	Application and Sampling Details				Report Reference	Source
			Method, F or G[a]	Rate (kg a.s./ha)	Sowing Interval (DAT)	Harvest Interval (DAT)		
EU Reviewed Data								
Leafy vegetables	Lettuce	U-^{14}C-phenyl	F[b]	0.75 + 0.5	43	Not reported	28-92	France, 2005
Root and tuber vegetables	Sugar beet				272			
Cereals	Wheat Maize				106 302			
Leafy vegetables	Lettuce	U-^{14}C-pyrimidine	F[b]	0.75 + 0.5	43	77 96	28-92 29-92	France, 2005

Group (OECD Guideline 502)	Crop	Label Position	Application and Sampling Details				Report Reference	Source
			Method, F or G[(a)]	Rate (kg a.s./ha)	Sowing Interval (DAT)	Harvest Interval (DAT)		
Root and tuber vegetables	Sugar beet				272	365 398 483		
Cereals	Wheat Maize				106 302	317 365 398 365 398 483		
Pulses and oilseeds	Mustard	U-^{14}C-phenyl and 2-^{14}C-pyrimidine	F[(c)]	3.2 - 3.6	42 130 283 365	Not reported	135-96	France, 2005
Root and tuber vegetables	Radish							
Cereals	Wheat							
Leafy vegetables	Lettuce	2-^{14}C-pyrimidine	F[(c)]	1.25	29 124 365	'maturity'	97DG56	France, 2005
Root and tuber vegetables	Radish				29 124 365	'maturity'		
Cereals	Wheat				29 180 365	'interim samples and maturity'		

(a) Outdoor/field application (F) or glasshouse/protected/indoor application
(b) Application of cyprodinil to a primary crop of spring wheat
(c) Application of cyprodinil to bare soil

An executive summary of the studies submitted for Annex I listing is presented below.

In the first two studies (Reports 28-92, and 29-92), two applications of either [phenyl-(U)-^{14}C] - or [2-^{14}C-pyrimidine] - cyprodinil were made to spring wheat at 0.75 kg a.s./ha (BBCH 16-18) and then at 0.50 kg a.s./ha (BBCH 51). After harvest of the spring wheat, representative rotational crops of lettuce, sugar beet, maize and winter wheat were planted at intervals of 43, 272, 302 and 106 days respectively after the second application.

For the phenyl label, total radioactive residues (TRR) in all crops were below 0.01 mg/kg. For the pyrimidine label TRR were low; 0.036, 0.044 and <0.01 mg/kg, respectively, in mature wheat straw, husks and grain. TRR were 0.016, <0.01 and <0.01 mg/kg, respectively, in mature maize straw, cobs and grain. TRR in sugar beet were <0.01 mg/kg. In immature lettuce plants TRR were 0.017 mg/kg, decreasing to <0.01 mg/kg at maturity.

Samples with TRR > 0.01 mg/kg were extracted; extractability ranged from 20% in mature straw (maize and wheat) to 62% in immature lettuce. Only wheat husks contained sufficient radioactivity for further characterisation, showing 0.01 mg/kg (22.7% TRR) of parent cyprodinil.

In the third study (135-96), [phenyl-(U)-^{14}C] - or [2-^{14}C-pyrimidine] - cyprodinil was applied to bare soil at a nominal application rate of 3.3 kg/ha (corresponding to 4 times the maximum seasonal application

rate applied for in this submission). Representative rotational crops of wheat, mustard and radishes were sown into the plots at nominal intervals of 30, 120, 270 and 365 days after application. Wheat was harvested at 25%, 50% and 100% maturity while mustard and radishes were harvested at maturity only.

Total radioactive residues were significant in all crops for all plant back intervals. The residues observed were higher for the pyrimidine label than for the phenyl label, most likely due to the preferred uptake and metabolism of pyrimidine specific soil metabolites.

For the phenyl label TRR in mature wheat fodder were 0.379, 0.462, 0.071 and 0.102 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature wheat grain were 0.107, 0.174, 0.031 and 0.039 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature mustard leaves were 0.341, 0.259, 0.018 and 0.023 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature radish leaves were 0.428, 0.192, 0.033 and 0.074 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature radish roots were 0.394, 0.384, 0.070 and 0.073 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively.

For the pyrimidine label TRR in mature wheat fodder were 2.842, 11.82, 1.955 and 5.504 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature wheat grain were 0.135, 0.434, 0.099 and 0.151 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature mustard leaves were 2.060, 2.797, 0.088 and 0.269 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature radish leaves were 1.523, 1.682, 0.119 and 1.530 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively. TRR in mature radish roots were 0.834, 1.216, 0.213 and 0.353 mg/kg, for the 30, 120, 270 and 365 plant back intervals, respectively.

Characterisation of the extracts showed extensive metabolism of cyprodinil via soil uptake in plants as numerous metabolite fractions were separated. For each radiolabelled position, the metabolite profiles were similar in all the crops and at each plant-back interval.

Analysis of pre and post cellulose extracts suggest significant conjugation of metabolites with sugars; the profiles of the post cellulose extracts of both wheat grain, leafy and root crop samples showed the presence of phenyl guanidine (CGA263208) and from the pyrimidinyl ring label only of 4-cyclopropyl-6-methyl-pyrimidine-2-ylamine (CGA249287) and 2-amino-6-cyclopropyl-pyrimid-4-yl methanol (NOA422054).

Minor characterised and/or identified metabolites that were present in samples from both labels included cyprodinil, CGA232449, CGA263208, CGA304076, NOA413167 and CGA304075. Cyprodinil and metabolites CGA304075, CGA263208 and CGA232449 were most evident in samples from the shorter plant-back intervals (30 and 120 DAT) and decreased in abundance at later intervals. Minor pyrimidine specific metabolites identified were guanidine, urea and CGA321915. A significant amount of the radioactivity, from both the phenyl and pyrimidine labelled crops samples was incorporated into glucose.

The pyrimidine label specific metabolite NOA422054 was unique to rotational crops and represented up to 46.2% of the total radioactive residue (0.71 mg/kg) and 1.5 mg/kg (12.8% TRR) in respectively, 365 DAT radish leaves and 120 DAT mature wheat straw. This metabolite, not found in soil is believed to be formed via plant uptake of the soil metabolite CGA249287, followed by hydroxylation of the methyl group, or *via* cleavage of the amine bridge of CGA232449. No evidence was observed for any of the corresponding phenyl labelled metabolites suggesting that the phenyl portion of the parent structure was degraded in the soil to single carbon units which were taken up by the plants and incorporated into natural products.

In a fourth study [2-^{14}C-pyrimidine]-cyprodinil was applied to bare soil at a rate of 1.25 kg/ha, corresponding to 1.7 times the maximum seasonal application rate applied for in this submission. Representative crops of lettuce and radish were planted or sown 29, 124 and 365 days after the

application. Spring wheat crops were sown 29 and 365 days after application and winter wheat crops 180 days after application. Plants samples were collected at maturity except for cereals where immature samples were also taken.

TRR ranged from 0.09 to 0.025 mg/kg, 0.066 to 0.025 mg/kg, and 0.034 to 0.011 mg/kg in spring wheat grain, lettuce and radish roots, respectively. In all samples residues decreased with longer plant back intervals.

For lettuce, extractability of residues was high, ranging from 81.2% (29 day PBI) to 98.5% (365 day PBI). For the 29 day PBI lettuce, 27.6% TRR was identified as conjugated NOA422054. Parent cyprodinil accounted for 14.2% TRR. Major components identified in the 124 day lettuce sample were CGA321915 (22.8% TRR), and NOA422054 (12.6% TRR, + 4.8% TRR as its sugar conjugate). Parent cyprodinil accounted for only 1.1% TRR. For the 365-day PBI the major components were NOA422054 as its sugar conjugate (7% TRR) and the N-sugar conjugate of NOA436942 (21.3% TRR). CGA321915 accounted for 20.4% TRR, whilst parent cyprodinil accounted for only 0.9% TRR.

For radishes, extractability of residues was high, ranging from 72.7% (124 day PBI) to 75.4% (365 day PBI) for roots and 89.7% (29 day PBI) to 99.8% TRR (124 day PBI) for tops. For the 29-day PBI, the residue in roots was found to consist mainly as conjugated NOA422054 of (10.8% TRR), cyprodinil (10.0% TRR) and metabolite CGA249287 (11.4% TRR). In radish tops conjugated NOA422054 was the largest component at 39.6% TRR and parent cyprodinil accounted for 0.6% TRR. For the 124-day PBI, the metabolite pattern was very similar to the earlier radish samples, with the major component in roots identified as conjugated NOA422054 (18.3% TRR). CGA321915 accounted for 4.7% TRR and parent cyprodinil accounted for 1.3% TRR. In tops, conjugated NOA422054 was again the largest fraction, accounting for 44.3% TRR, CGA321915 accounted for 10.8% TRR and parent cyprodinil was not detected. For the 365-day PBI, the major component in roots was CGA249287 (29.1% TRR). CGA321915 accounted for 3.5% TRR and parent cyprodinil accounted for 1.1% TRR. In tops, conjugated NOA422054 was again the largest fraction, accounting for 33.2% TRR, CGA321915 accounted for 16.1% TRR and parent cyprodinil was not detected.

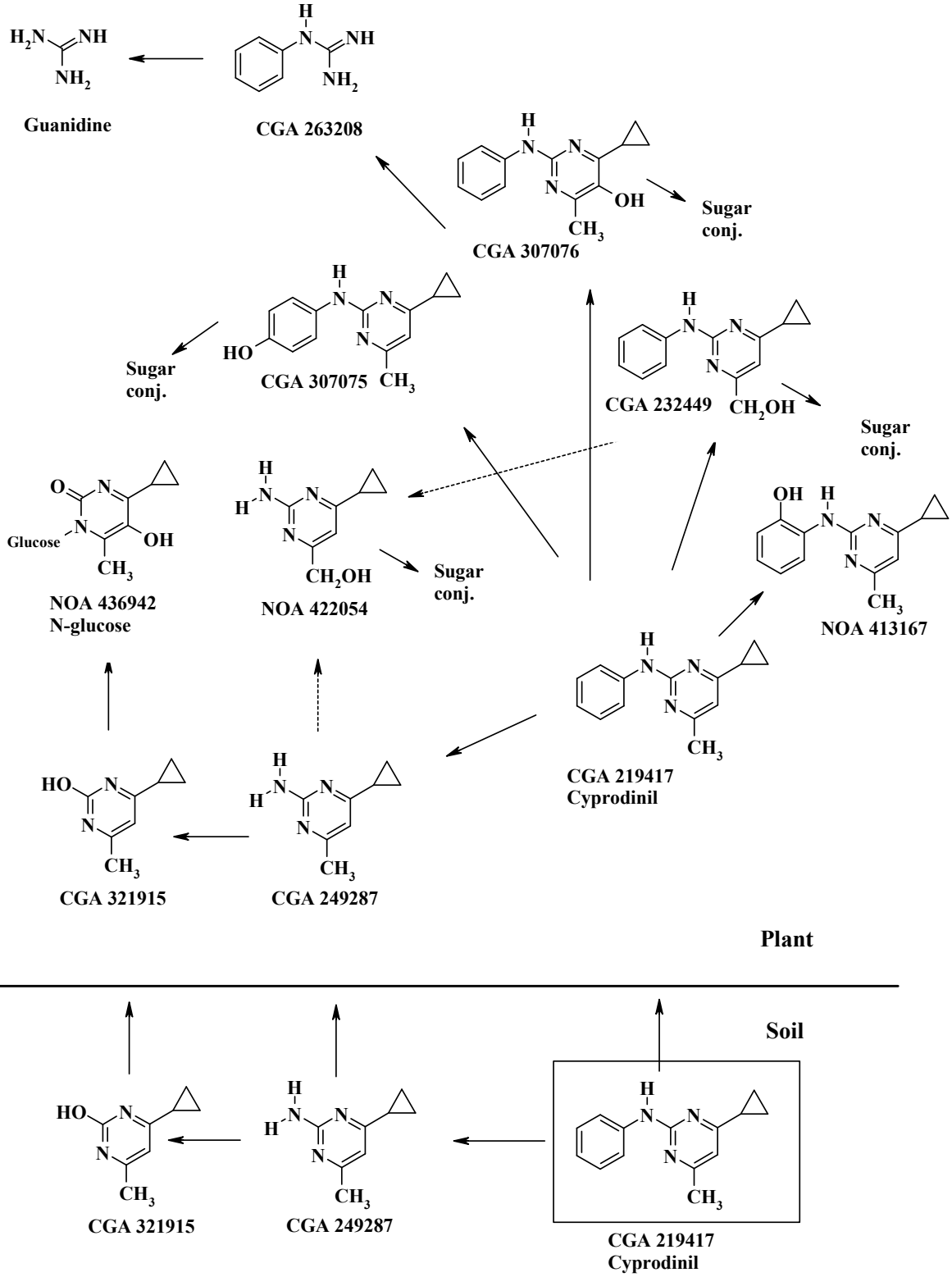
In mature spring wheat, extractability ranged from 70.3% (365 day PBI) to 74.5% (29 day PBI) for grain and 64.3% (29 day PBI) to 76.3% TRR (365 day PBI) for straw. For the 29 day PBI, the major component of the residue in grain was a fraction accounting for 17.8% TRR; within this fraction about 3% TRR was composed of guanidine and the remainder being an O-sugar conjugate of ~~CGA~~NOA422054 or an N-sugar conjugate of NOA436942. A further unknown fraction accounted for 10.9% TRR. Other components were minor and parent cyprodinil was not detected. In straw, the major component of the residue was a fraction composed of guanidine (4% TRR) and conjugated NOA422054 (6.5% TRR). CGA249287 accounted for 8.0% TRR. Other components were minor and parent cyprodinil accounted for 0.9% TRR. Acid and base hydrolysis of the non-extractable residue in straw released a further 23.0 % TRR; this was identified as CGA249287 (0.083 mg/kg, 0.2 % of the TRR) and radioactivity associated with lignin (5.8% TRR). The pectin and cellulase fractions accounted for only 0.1%TRR. For the 365-day PBI, the residue in grain was too low to allow any identification of metabolites. In straw, the major component of the residue was a fraction accounting for 14.8% TRR; about 7% of this fraction (1% TRR) was composed of guanidine and 21% (3.1% TRR) was conjugated NOA422054. CGA249287 made up 12.1% TRR and CGA321915 was 9.2% TRR. Parent cyprodinil accounted for 0.3% TRR.

In mature winter wheat (180-day PBI only), 70.6% TRR and 73.8% TRR was extractable from grain and straw, respectively. In grain, the major component of the residue was CGA249287, but this amounted to only 5.2% TRR. CGA321915 made up 2.8% TRR. A number of other components, including parent cyprodinil, totalled 6.3% TRR. In straw, the major component of the residue was a fraction which amounted to 17.0% TRR; the fraction was composed of guanidine (1.9% TRR) and conjugated NOA422054 (1.2% TRR). CGA321915 made up 12.8% TRR and other components were below 10% TRR. Parent cyprodinil was not detected.

The proposed metabolic pathway in rotational crops is given in Figure 6.6.1-1.

The metabolism of cyprodinil in rotational crops is sufficiently elucidated. When radiolabelled cyprodinil was applied to a primary crop (spring wheat) at an application rate of 1.25 kg a.s./ha, no significant cyprodinil residues (TRR<0.01 mg/kg) were found in any of the edible parts of the succeeding crops tested. When cyprodinil was applied to bare soil, the studies identified four major cyprodinil metabolites in the succeeding crops (wheat, lettuce and radishes) sown at any of the replant intervals: CGA 321915 (up to 0.013, 0.012, and 0.066 mg/kg in 124 DAT head lettuce, 124 DAT radish top and 29 DAT wheat straw, respectively), CGA 249287 (up to 0.001, 0.48 and 0.20 mg/kg in 29 DAT lettuce head, 130 DAT wheat straw and 130 DAT mustard leaves, respectively), NOA 422054 (major metabolite representing up to 12.6% of the TRR (0.007 mg/kg), 46.2% of the TRR (0.71 mg/kg) and 12.8% of the TRR (1.5 mg/kg) in 29 DAT lettuce head, 365 DAT radish leaves and 130 DAT wheat straw, respectively), and CGA263208 (up to 0.38 and 0.064 mg/kg in 130 DAT mustard leaves and 42 DAT wheat straw, respectively). The EU evaluation concluded that as CGA 249287 and NOA 422054 were not found to be of toxicological concern, they do not need to be included in the residue definition for plants **(Vol.3, Annex B, Section B.7.7, November 2003)**. Residues of CGA263208 were seen only after application to bare soil at exaggerated rates and absolute levels are low. The proposed definition of the residue in succeeding crops is therefore parent cyprodinil only, consistent with the definition of the residue in primary crops.

Figure 6.6.1-1: Metabolic pathway for cyprodinil in succeeding crops



CA 6.6.2 Magnitude of residues in rotational crops

Field studies to measure the magnitude of residues in rotational crops were considered during the EU evaluation of cyprodinil. The studies were evaluated under Council Directive 91/414/EEC and are presented in the cyprodinil draft Assessment Report (**Vol.3, Annex B, Section B.7.9, November 2003**).

Table 6.6.2-1: Summary of residues in rotational crops for cyprodinil

Primary crop	Rate (kg a.s./ha) (GS at application or PHI)	Residue levels in rotational crops			Report reference	Source
		Succeeding crop group	Succeeding crop	Sowing intervals (DAT)		
EU Reviewed data						
Bare soil (California, Florida and New York, USA)	2.24 (4 x 0.56)	Leafy vegetables	Lettuce	30 90 150 210	174-97	France, 2005
		Root and tuber vegetables	Turnips			
		Cereals	Wheat grain and straw			
Wheat (UK)	0.75 (BBCH 30)	Leafy vegetables	Lettuce	35-37	209/99 210/99	France, 2005
		Root and tuber vegetables	Radish tops and whole plant	35-37 112-114		
		Cereals	Wheat ears, grain and stalks	35-37 135 314-316		
Wheat (Switzerland and Germany)	0.75 (BBCH 30)	Leafy vegetables	Lettuce	30 120	201/00 gr33800	France, 2005
		Root and tuber vegetables	Radish leaves and whole plant	30 120		
		Cereals	Spring Wheat	30 55 331-370		
New data						
Bare soil (Austria and UK)	1.5	Leafy vegetables	Lettuce	30 56-63 365-383	37SRX09R03	KCA-6.6.2/01
		Root and tuber vegetables	Carrot tops and roots			

Primary crop	Rate (kg a.s./ha) (GS at application or PHI)	Residue levels in rotational crops			Report reference	Source
		Succeeding crop group	Succeeding crop	Sowing intervals (DAT)		
		Cereals	Wheat grain and straw	30 56-63 212-216 365-383		
Bare soil (Italy and France)	1.5	Leafy vegetables	Lettuce	30 60 323-384	37SRX09R04	KCA-6.6.2/02
		Root and tuber vegetables	Carrot tops and roots			
		Cereals	Wheat grain and straw	30 60 201-204 323-384		
Bare soil (Germany, UK, Italy and Spain)	1.13	Oily Crop	Winter and Spring oil seed rape	29-30 59-62 169-171 ~~Study ongoing – will be available Q2 2016~~	IF-14/03024493	KCA-6.6.2/03

An executive summary of the studies submitted for Annex I listing is presented below.

The first field study was conducted in California (Report reference 174-97) and residues were investigated in rotational crops following four applications at seven day intervals of cyprodinil at 561 g/ha as a 75 WG formulation (total application 2.24 kg/ha) to bare soil. Crops of wheat, lettuce and turnips were planted in the treated soil 30, 90, 150 and 210 days after the final application. Samples of lettuce leaves, turnip roots, wheat grain and wheat straw were collected at maturity. Wheat forage was sampled 60 days after planting and at BBCH 31-37, and hay was sampled at BBCH 47 to 85. No residues of cyprodinil above the LOQ (0.01 mg/kg) were found in any of the samples.

In two studies conducted in the UK (Report references 210-99 and 209-99) residues of cyprodinil and selected metabolites were investigated in rotational crops following one application of cyprodinil as a 75 WG formulation at 750 g/ha to wheat at BBCH 30. The wheat crop was ploughed into the plot 15 days after application and crops of wheat, lettuce and radishes were planted 35-37 days after application. Lettuce and radishes were also planted 112-114 days after application, and wheat was planted 314-316 days after application. Crop samples were collected at various intervals after planting and analysed for parent cyprodinil, CGA321915 and NOA422054 (free and/or conjugated).

Cyprodinil was found at 0.01 mg/kg in whole spring wheat plant from the first crop planted 35-37 days after application but was <0.01 mg/kg in all other samples. CGA321915 was found in whole radish plants (0.01 and 0.04 mg/kg) from the first crop, lettuce heads from the second crop (133 DAT) (0.01 mg/kg), whole spring wheat plants from the first crop (0.01 mg/kg) and in spring wheat stalks (aged 135d) from the second crop (0.01 mg/kg). CGA321915 residues were <0.01 mg/kg in all other samples.

NOA422054 was found in radish tops, ranging from <0.01 ppm to 0.04 mg/kg in the first crop (35 –37 DAT planting) and from <0.01 to 0.01 mg/kg in the second crop (112- 114 DAT planting). No residues were found in any of the radish roots. Residues of NOA422054 in lettuce heads ranged from <0.01 to 0.01 mg/kg in both lettuce crops (35-37 and 112-114 DAT plantings). No residues of NOA422054 were found in any wheat commodities from the second crop (316 DAT planting), nor in wheat ears or grain from the first crop (35 DAT planting). Residues of NOA422054 in whole wheat plants from the first crop were 0.03 and 0.07 mg/kg, and residues in wheat stalks from the first crop were 0.01 and 0.02 mg/kg.

In two studies conducted in Switzerland (Report reference 201/00) and Germany (Report reference gr 33800) residues of cyprodinil and selected metabolites were investigated in rotational crops following one application of cyprodinil as a 75 WG formulation at 750 g/ha to spring wheat at BBCH 30. The wheat crop was destroyed 15 days after application and the plot was ploughed. Crops of spring wheat, lettuce and radishes were planted 28-30 days after application. Lettuce and radishes were also planted 120 days after application, and spring wheat was planted in 331-370 days after application. Crop samples were collected at various intervals after planting and analysed for parent cyprodinil, CGA321915 and NOA422054 (free and/or conjugated).

No residues above the LOQ were found in any of the samples from the German trial except for metabolite NOA422054 which was found at 0.01 mg/kg in wheat whole plant (sampled 55 days after application) planted 30 DAT.

In the Switzerland trial, cyprodinil residues were <0.01 mg/kg in all samples. CGA321915 was found in radish leaves (0.03 mg/kg), lettuce head whole plants (0.01 mg/kg) and whole spring wheat plants from the first crop, 30 DAT (0.02 mg/kg). Other samples showed no detectable residues of CGA321915 (i.e. <0.01 mg/kg). NOA422054 was found in whole plant radish (0.02 mg/kg) and radish tops at 0.07-0.08 mg/kg in the first crop (30 DAT) and <0.01 to 0.01 mg/kg in the second crop (112- 114 DAT). Other samples showed no detectable residues of NOA422054 (i.e. <0.01 mg/kg). No residues were found in any of the radish roots and 120 DAT samples of leaves. Residues of NOA422054 in lettuce heads were 0.01 - 0.04 mg/kg in lettuce first crop and <0.01 mg/kg in the second crop (331 DAT). No residues of NOA422054 were found in any wheat samples except in whole plant spring wheat from 30 DAT.

~~Two~~ Six additional field crop rotation studies have also been conducted – two on wheat and four on oil seed rape. These studies were not available during the first EU evaluation of cyprodinil and full summaries are presented here.

Report:	K-CA 6.6.2/01. Chambers J, 2015. Cyprodinil – Residue study on rotational crops in Austria and the United Kingdom in 2009/2010. Battelle UK Ltd, Report Number 37SRX09R03. (Syngenta Regulatory Document No. A8637C_10060)

Guidelines

FAO Guidelines on Producing Pesticide Residues Data from Supervised Trials (Rome, 1990).

Commission of the European Communities, General Recommendations for the Design, Preparation and Realization of Residue Trials; (**SANCO 7029/V1/95 rev. 5 22/7/1997**).

Guidelines and Criteria for the Preparation and Presentation of Complete Dossiers and of Summary Dossiers for the Inclusion of active Substances in Annex I of directive 91/414/EEC (Article 5.3 and 8.2), 1996.

OECD Test Guideline 504: Residues in Rotational Crops (Limited Field Studies) (8 January 2007).

Testing of plant protection products in rotational crops: (**SANCO 7524/V1/95 rev. 2 22/7/1997**).

GLP

The study was carried out according to the principles of Good Laboratory Practice.

EXECUTIVE SUMMARY

Two field trials were conducted during 2009, one in Austria and one in the United Kingdom. Cyprodinil was applied as A8637C, a water dispersible granule (WG) formulation containing 500 g cyprodinil per kg at a rate of 1500 g a.s./ha to bare soil drilled with ryegrass. A representative cereal (wheat), leafy vegetable (lettuce) and root vegetable (carrot) were sown into the soil at nominal rotational intervals of 30, 60, 200 (wheat only) and 365 days after application (DAT). The ryegrass was sprayed off with glyphosate approximately two weeks before sowing the rotational crops. The rotational crops were grown under field conditions and harvested at immature and mature growth stages. After harvest of the rotational crops sown 30 and 60 DAT, the plots were cleared, cultivated and re-sown with ryegrass which was then sprayed off prior to sowing the 200 and 365 DAT crops. Due to poor crop development of the wheat in the 2009 trial, a second plot was sprayed in the same way in 2010 in the UK and the wheat sowings at 30 and 60 DAT were repeated.

Commodities of representative food and feed items (immature whole wheat plants, mature wheat straw and grain; immature and mature lettuce; mature carrot tops and roots) were sampled at intervals after sowing and analysed for residues of cyprodinil with a LOQ of 0.01 mg/kg.

At the rotational interval of 30 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads and mature carrot tops (0.01 mg/kg) in the Austria trial, and mature carrot roots in the UK trial (0.05 mg/kg). At rotational intervals of 60, 200 and 365 DAT, residues of cyprodinil were <0.01 mg/kg in all samples.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Test Material	A8637C
Description	Water dispersible granule formulation containing cyprodinil
Purity	500 g/kg
Batch number	SMO6K782
Stability of test compound	The test substance is assumed to be stable for the period of use in the study

A2. Test System

Trial site	SRK09-040-37FR, Hopton, UK	SRA09-040-37FR, Rohrau, Austria
Soil	Sandy loam	Silty loam
Leafy vegetable	Lettuce (variety: Cosmic)	Lettuce (variety: Santoro)
Cereal	Spring wheat (variety Tybalt) Winter wheat (variety: Diego)	Spring wheat (variety Midas) Winter wheat (variety: Michael)
Root vegetable	Carrot (variety: Maestro F1)	Carrot (variety: VAC 43 81)

A3. Test Facilities

Field trials	Hopton, UK	Rohrau, Austria
Analytical phase	Battelle UK LTD., Battelle house, Fyfield Business and Research Park, Fyfield, road, Ongar, Essex, CM5 0GZ, UK	

B. STUDY DESIGN AND METHODS

B1. Field Phase

In 2009, plots were treated with cyprodinil formulated as a WG at a rate of 1500 g a.s./ha (actual rates were 1492-1560 g a.s./ha) applied to bare soil which had been sown with ryegrass 2-8 days before treatment. The soil was aged for 33, 63, 212 and 365 days (trial SRK09-040-37FR) or 32, 60, 216 and 383 days (trial SRA09-012-37FR) after which the soil was lightly cultivated before drilling representative crops of carrot, lettuce and spring or winter wheat. Due to poor crop development of the rotational wheat crop at trial SRK09-040-37FR, a second plot was sprayed in the same way in the following year (2010) and aged for 29 and 56 days before drilling wheat. The ryegrass was sprayed off with glyphosate approximately two weeks before the rotational crops were planted. The crops were grown outdoors in accordance with usual agricultural practice.

Test Samples

Samples of lettuce (immature and mature heads), carrot (mature roots and tops) and spring/winter wheat (immature whole plant, mature grain and straw) were taken by hand (separated using a hand thresher for wheat grain and straw) and the samples were stored deep frozen at <-18 °C before analysis. Samples were stored for up to 12 months before analysis.

B2. Analytical Phase

Samples were analysed for cyprodinil using method REM 141.10; the LOQ was 0.01 mg/kg for all commodities. A full method description and validation data are presented in document M-CA Section 4, CA 4.1.2.

II. RESULTS AND DISCUSSION

Method Validation

Procedural recoveries were determined for each commodity and the individual and mean procedural recoveries for these are summarised in Table 6.6.2-2.

Table 6.6.2-2: Summary of procedural recoveries for cyprodinil in following crops

Commodity	Fortification Level (mg/kg)	Cyprodinil		
		Recovery (%)	Mean recovery (%)	RSD (%)
Lettuce heads	0.01	71, 78	75	--
Carrot root	0.01	72, 72	72	--
Carrot tops	0.01	80	80	--
Wheat whole plant	0.01	76, 101, 97, 70	81	18
	0.1	69, 72		
Wheat grain	0.01	75, 73	74	2.4
	0.1	72, 76		
Wheat straw	0.01	84	80	6.8
	0.02	73, 79		
	0.1	85		

Residues in following crops

At the rotational interval of 30 (29-33) DAT, cyprodinil residues in mature lettuce heads (sampled at BBCH 49), immature whole wheat plants (sampled at BBCH 31-39), and mature wheat grain and straw (sampled at BBCH 89) were <0.01 mg/kg in both trials. Cyprodinil residues in immature lettuce heads (sampled at BBCH 45) were also <0.01 mg/kg in both trials. Cyprodinil residues in carrot (sampled at BBCH 48-49) were <0.01 mg/kg in the Austria trial and 0.05 mg/kg in the UK trial for roots, and 0.01 mg/kg in the Austria trial and <0.01 mg/kg in the UK trial for tops. At rotational intervals of 60 (56-63), 200 (212-216) and 365 (365-383) DAT, cyprodinil residues in all samples were <0.01 mg/kg.

The results of the rotational crop trials are presented in Table 6.2.2-3. The results are not corrected for recoveries.

Table 6.2.2-3: Residues of cyprodinil in rotational crops grown in soil treated with cyprodinil at 1500 g a.s/ha

Commodity	Trial SRK09-040-37FR, UK		Trial SRA09-012-37FR, Austria	
	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)
Plant-back interval:	**29/33 days**		**32 days**	
Immature lettuce heads	101	<0.01	67	0.01*
Mature lettuce heads	113	<0.01	75	<0.01
Carrot roots	122	0.05*	127	<0.01*
Carrot tops	122	<0.01	127	0.01*
Immature wheat plants	98	<0.01	70	<0.01
Wheat grain	164	<0.01	122	<0.01
Wheat straw	164	<0.01	122	<0.01
Plant-back interval:	**56/63 days**		**60 days**	
Immature lettuce heads	140	<0.01	107	<0.01
Mature lettuce heads	157	<0.01	119	<0.01
Carrot roots	197	<0.01	157	<0.01
Carrot tops	197	<0.01	157	<0.01
Immature wheat plants	116	<0.01	94	<0.01

Commodity	Trial SRK09-040-37FR, UK		Trial SRA09-012-37FR, Austria	
	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)
Plant-back interval:	**29/33 days**		**32 days**	
Immature wheat plants	125	<0.01	--	--
Wheat grain	181	<0.01	162	<0.01
Wheat straw	181	<0.01	162	<0.01
Plant-back interval:	**212 days**		**216 days**	
Immature wheat plants	410	<0.01	--	--
Wheat grain	487	<0.01	454	<0.01
Wheat straw	487	<0.01	454	<0.01
Plant-back interval:	**365 days**		**383 days**	
Immature lettuce heads	442	<0.01	438	<0.01
Mature lettuce heads	455	<0.01	449	<0.01
Carrot roots	491	<0.01	518	<0.01
Carrot tops	491	<0.01	518	<0.01
Immature wheat plants	434	<0.01	462	<0.01
Wheat grain	490	<0.01	526	<0.01
Wheat straw	490	<0.01	526	<0.01

* Mean of three analyses.

III. CONCLUSIONS

At the rotational interval of 30 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads and mature carrot tops (0.01 mg/kg) in the Austria trial, and mature carrot roots in the UK trial (0.05 mg/kg). At rotational intervals of 60, 200 and 365 DAT, cyprodinil residues in all samples were <0.01 mg/kg.

(Chambers J, 2015)

Report:	K-CA 6.6.2/02. Chambers J, 2015a. Cyprodinil – Residue study on rotational crops in Italy and Southern France in 2009/2010. Battelle UK Ltd, Report Number 37SRX09R04. (Syngenta Regulatory Document No. A8637C_10059)

Guidelines

FAO Guidelines on Producing Pesticide Residues Data from Supervised Trials (Rome, 1990).

Commission of the European Communities, General Recommendations for the Design, Preparation and Realization of Residue Trials; (**SANCO 7029/V1/95 rev. 5 22/7/1997**).

Guidelines and Criteria for the Preparation and Presentation of Complete Dossiers and of Summary Dossiers for the Inclusion of active Substances in Annex I of directive 91/414/EEC (Article 5.3 and 8.2), 1996.

OECD Test Guideline 504: Residues in Rotational Crops (Limited Field Studies) (8 January 2007).

Testing of plant protection products in rotational crops: (**SANCO 7524/V1/95 rev. 2 22/7/1997**).

GLP

The study was carried out according to the principles of Good Laboratory Practice.

EXECUTIVE SUMMARY

Two field trials were conducted during 2009, one in Italy and one in southern France. Cyprodinil was applied as A8637C, a WG formulation containing 500 g cyprodinil per kg at a rate of 1500 g a.s./ha to bare soil drilled with ryegrass. A representative cereal (wheat), leafy vegetable (lettuce) and root vegetable (carrot) were sown into the soil at nominal rotational intervals of 30, 60, 200 (wheat only) and 365 days after application (DAT). The ryegrass was sprayed off with glyphosate approximately two weeks before sowing the rotational crops. The rotational crops were grown under field conditions and harvested at immature and mature growth stages. After harvest of the rotational crops sown 30 and 60 DAT, the plots were cleared, cultivated and re-sown with ryegrass which was then sprayed off prior to sowing the 200 and 365 DAT crops. Due to poor crop development in the 2009 trial, a second plot was sprayed in 2010. Wheat sowings at 30 and 60 DAT and the sowing at 60 DAT in the southern France trial were repeated.

Commodities of representative food and feed items (immature whole wheat plants, mature wheat straw and grain; immature and mature lettuce; mature carrot tops and roots) were sampled at intervals after sowing and analysed for residues of cyprodinil with a LOQ of 0.01 mg/kg.

At the rotational interval of 30 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads, immature wheat whole plants, mature carrot tops (0.01 mg/kg) and mature carrot roots (0.02 mg/kg) in the southern France trial. At the rotational interval of 60 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads, immature wheat whole plants, carrot tops (0.01 mg/kg) and carrot roots (0.03 mg/kg) in the southern France trial. At rotational intervals of 200 (201-204) and 365 (323-384) DAT, cyprodinil residues in all samples were <0.01 mg/kg.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Test Material	A8637C
Description	Water dispersible granule formulation containing cyprodinil
Purity	500 g/kg
Batch number	SMO6K782
Stability of test compound	The test substance is assumed to be stable for the period of use in the study

A2. Test System

Trial site	SRI09-368-37FR, Castagnito d'Alba, Italy	SRF09-002-37FR, Nimes, France
Soil	Loamy	Silty clay
Leafy vegetable	Lettuce (varieties: Icaro and Ballerina)	Lettuce (variety: Pitice)
Cereal	Spring wheat (variety Valbona) Winter wheat (varieties: Bologna and Sirtaki)	Spring wheat (varieties Courtot and Arbon) Winter wheat (variety: Isidor)
Root vegetable	Carrot (variety: Nantese di Chioggia)	Carrot (variety: Maestro)

A3. Test Facilities

Field trials	Castagnito d'Alba, Italy	Nimes, southern France
Analytical phase	Battelle UK LTD., Battelle house, Fyfield Business and Research Park, Fyfield, road, Ongar, Essex, CM5 0GZ, UK	

B. STUDY DESIGN AND METHODS

B1. Field Phase

In 2009, plots were treated with cyprodinil formulated as a WG at a rate of 1500 g a.s./ha (actual rates were 1438-1593 g a.s./ha) applied to bare soil which had been sown with ryegrass on the day of treatment or 9 days before treatment. The soil was aged for 30, 60, 204 and 327/384 days (trial SRI09-368-37FR) or 28, 61, 201 and 323/364 days (trial SRF09-002-37FR) after which the soil was lightly cultivated before drilling representative crops of carrot, lettuce and spring or winter wheat. Due to poor crop development of the rotational wheat crop at trial SRI09-368-37FR, a second plot was sprayed in the same way in the following year (2010) and aged for 25 and 55 days before drilling wheat. Due to poor crop development of the rotational wheat and carrot crops at trial SRF09-002-37FR, a second plot was sprayed in the same way in the following year (2010) and aged for 33 and 65 days before drilling wheat and carrot. The ryegrass was sprayed off with glyphosate approximately two weeks before the rotational crops were planted. The crops were grown outdoors in accordance with usual agricultural practice.

Test Samples

Samples of lettuce (immature and mature heads), carrot (mature roots and tops) and spring/winter wheat (immature whole plant, mature grain and straw) were taken by hand (separated using a hand thresher for wheat grain and straw) and the samples were stored deep frozen at <-18 °C before analysis. Samples were stored for up to 12 months before analysis.

B2. Analytical Phase

Samples were analysed for cyprodinil using method REM 141.10; the LOQ was 0.01 mg/kg for all commodities. A full method description and validation data are presented in document M-CA Section 4, CA 4.1.2.

II. RESULTS AND DISCUSSION

Method Validation

Procedural recoveries were determined for each commodity and the individual and mean recoveries are summarised in Table 6.6.2-4.

Table 6.6.2-4: Summary of procedural recoveries for cyprodinil in following crops

Commodity	Fortification Level (mg/kg)	Cyprodinil		
		Recovery (%)	Mean recovery (%)	RSD (%)
Lettuce heads	0.01	81, 69	76	8.1
	0.10	77		
Carrot root	0.01	71, 75, 70	73	4.9
	0.10	70, 78		
Wheat whole plant	0.01	75, 74, 78, 80, 82, 78	77	4.9
	0.10	73, 72, 82		
Wheat grain	0.01	67, 77, 88, 87, 70	75	12
	0.10	72, 66		
Wheat straw	0.01	89, 86, 84, 90, 89	88	2.9

Residues in following crops

At the rotational interval of 30 (25-33) DAT, cyprodinil residues in mature lettuce heads (sampled at BBCH 49), and mature wheat grain and straw (sampled at BBCH 89) were <0.01 mg/kg in both trials. Cyprodinil residues in immature lettuce heads (sampled at BBCH 45-46), immature wheat whole plants (sampled at BBCH 31-55) and carrot tops (sampled at BBCH 48-49) were 0.01 mg/kg in the southern France trial and <0.01 mg/kg in the Italy trial. Cyprodinil residues in carrot roots (sampled at BBCH 48-49) were 0.02 mg/kg in the southern France trial and <0.01 mg/kg in the Italy trial.

At the rotational interval of 60 (55-65) DAT, cyprodinil residues in mature lettuce heads (sampled at BBCH 49), and mature wheat grain and straw (sampled at BBCH 89) were <0.01 mg/kg in both trials. Cyprodinil residues in immature lettuce heads (sampled at BBCH 45-46), immature wheat whole plants (sampled at BBCH 31-55) and carrot tops (sampled at BBCH 48-49) were 0.01 mg/kg in the southern France trial and <0.01 mg/kg in the Italy trial. Cyprodinil residues in carrot roots (sampled at BBCH 48-49) were 0.03 mg/kg in the southern France trial and <0.01 mg/kg in the Italy trial.

At rotational intervals of 200 (201-204) and 365 (323-384) DAT, cyprodinil residues in all samples were <0.01 mg/kg.

The results of the rotational crop trials are presented in Table 6.2.2-5. The results are not corrected for procedural recoveries.

Table 6.2.2-5: Residues of cyprodinil in rotational crops grown in soil treated with cyprodinil at 1.50 kg a.s/ha

Commodity	Trial SRI09-368-37FR, Italy		Trial SRF09-002-37FR, Southern France	
	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)
Plant-back interval:	**25/30 days**		**28/33 days**	
Immature lettuce heads	78	<0.01	70	0.01*

Commodity	Trial SRI09-368-37FR, Italy		Trial SRF09-002-37FR, Southern France	
	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)	Interval: Treatment to Sampling (days)	Cyprodinil Residues (mg/kg)
Plant-back interval:	**25/30 days**		**28/33 days**	
Mature lettuce heads	85	<0.01	76	<0.01
Carrot roots	157	<0.01	145	0.02*
Carrot tops	157	<0.01	145	0.01*
Immature wheat plants	86	<0.01	117	0.01*
Immature wheat plants	86	<0.01	--	--
Wheat grain	142	<0.01	182	<0.01
Wheat straw	142	<0.01	182	<0.01
Plant-back interval:	**55/60 days**		**61/65 days**	
Immature lettuce heads	113	<0.01	130	0.01*
Mature lettuce heads	116	<0.01	141	<0.01
Carrot roots	183	<0.01	187	0.03*
Carrot tops	183	<0.01	187	0.01*
Immature wheat plants	99	<0.01	139	0.01*
Wheat grain	163	<0.01	194	<0.01
Wheat straw	163	<0.01	194	<0.01
Plant-back interval:	**204 days**		**201 days**	
Immature wheat plants	386	<0.01	357	<0.01
Wheat grain	453	<0.01	431	<0.01
Wheat straw	453	<0.01	431	<0.01
Plant-back interval:	**327/384 days**		**323/364 days**	
Immature lettuce heads	419	<0.01	406	<0.01
Mature lettuce heads	425	<0.01	418	<0.01
Carrot roots	495	<0.01	489	<0.01
Carrot tops	495	<0.01	489	<0.01
Immature wheat plants	406	<0.01	406	<0.01*
Wheat grain	462	<0.01	452	<0.01
Wheat straw	462	<0.01	452	<0.01

* Mean of three analyses.

III. CONCLUSIONS

At the rotational interval of 30 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads, immature wheat whole plants, mature carrot tops (0.01 mg/kg) and mature carrot roots (0.02 mg/kg) in the southern France trial. At the rotational interval of 60 DAT, cyprodinil residues in all samples were <0.01 mg/kg except for immature lettuce heads, immature wheat whole plants, carrot tops (0.01 mg/kg) and carrot roots (0.03 mg/kg) in the southern France trial. At rotational intervals of 200 (201-204) and 365 (323-384) DAT, cyprodinil residues in all samples were <0.01 mg/kg.

(Chambers J, 2015a)

Report:	K-CA 6.6.2/03. Ziske, J., Bodsch, J. (2016) Cyprodinil – Residue study on rotational crops in Germany, United Kingdom, Italy and Spain in 2014. SGS Institut Fresenius GmbH, Report Number IF-14/03024493. (Syngenta File No. A9219B_12328)

Guidelines

Guidelines for the generation of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market, **EU 1999: 1607/VI/97 (rev. 2)**.

European Commission Guidance for Generating and Reporting Methods of Analysis in Support of Pre-registration Requirements for Annex II (Part A, Section 4) of Directive 91/414, **SANCO/3029/99 rev. 4** (11 Jul 2000).

European Commission Guidance Document on Residue Analytical Method, **SANCO/825/00 revision 8.1** (16 Nov 2010).

Commission of the European Communities, General Recommendations for the Design, Preparation and Realization of Residue Trials; **7029/VI/95 (rev. 5, working document)**.

Regulations (EU) **283/2013** and **284/2013** implementing 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 and repealing Council Directives 79/117/EEC and 91/414/EEC.

OECD Test Guideline 504: Residues in Rotational Crops (Limited Field Studies).

Commission of the European Communities, Rotational Studies, Guidance document on testing of plant protection products in rotational crops; **7524/VI/95 (rev.2, 1997)**.

The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies, **ENV/JM/MONO (2002) 9**.

The national requirements are based on the OECD Principles of Good Laboratory Practice, which are accepted by regulatory authorities throughout the European Community, the United States of America (FDA and EPA) and Japan (MHW, MAFF and METI) on the basis of intergovernmental agreements. FAO Guidelines on Producing Pesticide Residues Data from Supervised Trials (Rome, 1990).

GLP

The study was carried out according to the principles of Good Laboratory Practice.

EXECUTIVE SUMMARY

Four field trials were conducted during 2014, one in Germany, one in the United Kingdom, one in Italy and one in Spain. Cyprodinil was applied as A9219B, a WG formulation containing 375 g cyprodinil per kg at a rate of 1125 g a.s./ha to bare soil. Application was made 29-30, 59-62 and 169 – 171 days prior to planting oilseed rape.

Commodities of rape seed after sowing and analysed for residues of cyprodinil at NCH with a LOQ of 0.01 mg/kg.

I. MATERIALS AND METHODS

A. MATERIALS

A1. Test Materials

Test Material	A9219B
Description	Water dispersible granule formulation containing cyprodinil
Purity	375 g/kg
Batch number	SMO0L138

Stability of test compound	The test substance is assumed to be stable for the period of use in the study

A2. Test System

Trial site	14-00834-01 Vechta, Germany	14-00834-02 Banbury, UK	14-00834-03 Lombardia, Italy	14-00834-04 Andalucia, Spain
Soil	Sandy loam	Clay	Sandy loam	Clay loam
Oil seed rape	Plots C, P2 and P3 – Winter rape (variety Lorenz) Plot P4 – Spring rape (variety Campino)	Plots C, P2 and P3 – Winter rape (variety Excel) Plot P4 – Spring rape (variety Heros)	Plots C, P2 and P3 – Winter rape (variety Excalibur) Plot P4 – Spring rape (variety Marathon)	Plots C, P2 and P3 – Winter rape (variety Visby) Plot P4 – Spring rape (variety Jura)

A3. Test Facilities

Field trials	Vechta, Germany Banbury, UK Lombardia, Italy Andalucia, Spain
Analytical phase	SGS INSTITUT FRESENIUS GmbH, Im Maisel 14, Taunusstein, Germany

B. STUDY DESIGN AND METHODS

B1. Field Phase

In 2014, plots were treated with cyprodinil formulated as a WG at a rate of 1125 g a.s./ha (actual rates were 1081-1163 g a.s./ha) applied to bare soil in a spray solution. The soil was aged for 30, 60, and 170 days after which the soil was lightly cultivated before drilling with winter or spring oil seed rape which was grown in accordance with usual agricultural practice.

Test Samples

Samples were taken by hand (pods were cut and separated either by beating in a paper bag followed by wind sifting in trial 14-00834-01, or threshed and cleaned using a thresher in trials 14-00834-02 and 14-00834-03, or using a minibatt in trial 14-00834-04) and the samples were stored deep frozen at <-18 °C before analysis. Samples were stored for up to 280 days before analysis.

B2. Analytical Phase

Samples were analysed for cyprodinil using method GRM010.02A; the LOQ was 0.01 mg/kg. A full method description and validation data are presented in document M-CA Section 4, CA 4.1.2.

II. RESULTS AND DISCUSSION

Method Validation

Procedural recoveries were determined for each commodity and the individual and mean recoveries are summarised in Table 6.6.2-6.

Table 6.6.2-6: Summary of procedural recoveries for cyprodinil in following crops

Commodity	Fortification Level (mg/kg)	Cyprodinil		
		Recovery (%)	Mean recovery (%)	RSD (%)
Oilseed rape	0.01	75	75	0.7
	0.10	75		
	1.1	74		

The study report also includes method validation data for GRM010.02A in oilseed rape and this is summarised in table 6.6.2-7 below.

Table 6.6.2-7: Summary of method validation for cyprodinil in oil seed rape using GRM010.02A

Matrix	Fortification Level (mg/kg)	Recovery (%)	n	Mean (%)	RSD (%)	Range (%)	Recovery (%)	n	Mean (%)	RSD (%)	Range (%)
		Primary transition m/z 226 → 93					Confirmatory transition m/z 226 → 77				
Rape (seed)	0.01*	81, 79, 78, 75, 75	5	78	3.4	75 - 81	81, 79, 78, 75, 75	5	79	4.1	74 - 82
	0.10	70, 70, 72, 72, 72	5	71	1.8	70 - 72	70, 70, 72, 72, 72	5	71	1.8	69 - 72
	Overall	--	10	74	5.3	70 - 81	--	10	75	6.2	69 - 82

Residues in following crops

Treated and untreated samples of rape (seed) were taken at normal commercial harvest (NCH). All samples (seeds) were analysed. Rape (seed) samples taken from plot P2, plot P3 and plot P4 showed no residues of cyprodinil at or above the LOQ (0.01 mg/kg) at 30 days, 60 days or 170 days plant back interval. No residues of cyprodinil were found at or above the LOQ (0.01 mg/kg) in any of the untreated samples.

III. CONCLUSIONS

Cyprodinil residues in all samples were <0.01 mg/kg at all plant back intervals in all trials.

(Ziske J, Bodsch J, 2016)

Summary of residues in succeeding crops

The metabolism of cyprodinil in rotational crops is sufficiently elucidated. When radiolabelled cyprodinil was applied to a primary crop (spring wheat) at an application rate of 1.25 kg a.s./ha, no significant cyprodinil residues (TRR<0.01 mg/kg) were found in any of the edible parts of the succeeding crops tested. When cyprodinil was applied to bare soil, four major metabolites were identified in succeeding crops; CGA321915, CGA249287, NOA422054, and CGA263208. The EU evaluation concluded that as CGA 249287 and NOA 422054 were not found to be of toxicological concern, they do not need to be included in the residue definition for plants (**Vol.3, Annex B, Section B.7.7, November 2003**). Residues of CGA263208 were seen only after application to bare soil at exaggerated rates and absolute levels are low. The proposed definition of the residue in succeeding crops is therefore parent cyprodinil only, consistent with the definition of the residue in primary crops.

The representative crops supported in this dossier are apple and barley. Cyprodinil is recommended on these crops at a maximum total dose of 1.125 kg a.s./ha (apple) and 0.90 kg a.s./ha (barley). In practice, apple as a perennial crop is not followed in rotation by succeeding crops and so consideration of potential residues in succeeding crops is relevant following the use of cyprodinil on barley. In barley, applications of cyprodinil are recommended up to BBCH 61 which normally occurs in May/June.

In field studies, cyprodinil was applied at 2.24 kg a.s./ha in the US (one trial), 0.75 kg a.s./ha in the UK, Switzerland and Germany in 1999 and 2000 (4 trials), and 1.5 kg a.s./ha in the UK, Austria, Italy and southern France in 2009 (4 trials).

As the proposed definition of the residue in plants including rotational crops is parent cyprodinil alone, residues of the metabolites as measured in the 1999 and 2000 trials in the EU are not considered further.

In the four trials in northern EU carried out from 1999 to 2000, no residues of cyprodinil above the LOQ (0.01 mg/kg) were found in succeeding crops of wheat, lettuce or radish (other than in one sample of immature whole wheat) planted 28-37 days after application of cyprodinil at 0.75 kg a.s/ha, slightly less than but within 25% of the maximum rate recommended for barley. No residues of cyprodinil above the LOQ were found in any of the succeeding crops planted 120 days or more after application.

In the four trials in northern and southern EU carried out in 2009, residues of cyprodinil following application of cyprodinil at 1.5 kg a.s/ha (approximately 1.7 times the maximum rate recommended in barley) were found in succeeding crops of immature lettuce heads in two trials (0.01 mg/kg), immature wheat whole plants in one trial (0.01 mg/kg), mature carrot tops in one trial (0.01 mg/kg) and carrot roots in two trials (0.02-0.05 mg/kg). No residues of cyprodinil above the LOQ (0.01 mg/kg) were found in succeeding crops of wheat, lettuce and carrot planted 60 after application of cyprodinil at 1.5 kg a.s/ha other than in one sample of immature lettuce heads (0.01 mg/kg), one sample of immature whole wheat plants (0.01 mg/kg), one sample of mature carrot tops (0.01 mg/kg) and one sample of mature carrot roots (0.03 mg/kg). At rotational intervals of 200 and 365 DAT in these trials, cyprodinil residues in all succeeding crops were <0.01 mg/kg.

In the US trial, no residues of cyprodinil above the LOQ (0.01 mg/kg) were found in rotated crops of wheat, lettuce and turnips planted 30 or more days after application of cyprodinil at 2.24 kg a.s/ha (approximately 2.5 times the maximum rate recommended in barley). Climatic conditions in California are not necessarily comparable with those in the EU; however the trial provides supporting evidence.

In four EU trials where oil seed rape was planted back after 30, 60 and 170 days no residues of cyprodinil were found in oil seed above the LOQ (0.01mg/kg).

The results of the trials in the EU are summarised in Table 6.2.2-~~6~~8.

Table 6.2.2-6 8:Summary of residues of cyprodinil in rotational crops grown in EU trials

Commodity			Cyprodinil Residues in Rotational Crops (mg/kg)							
	Application rate:	1500 g a.s./ha				1125 g a.s./ha	750 g a.s./ha			
	Plant-back interval (days)	UK SRK09-040-37FR	Austria SRA09-012-37FR	Italy SRI09-368-37FR	Southern France SRF09-002-37FR	Germany, Italy, UK, Spain IF14-00834	UK 210-99	UK 209-99	Switzerland 201/00	Germany gr 33800
Immature lettuce heads	25-37	<0.01	**0.01**	<0.01	**0.01**	-	<0.01	<0.01	<0.01	<0.01
	55-65	<0.01	<0.01	<0.01	**0.01**	-	-	-	-	-
	112-120	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	314-384	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
Mature lettuce heads	25-37	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
	55-65	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	112-120	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	314-384	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
Carrot roots	25-33	**0.05**	<0.01	<0.01	**0.02**	-	-	-	-	-
	55-65	<0.01	<0.01	<0.01	**0.03**	-	-	-	-	-
	323-384	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
Carrot tops	25-33	<0.01	**0.01**	<0.01	**0.01**	-	-	-	-	-
	55-65	<0.01	<0.01	<0.01	**0.01**	-	-	-	-	-
	323-384	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
Immature radish plants	28-37	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	112-120	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
Immature and mature radish roots*	28-37	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	112-120	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
Immature and mature radish tops*	28-37	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
	112-120	-	-	-	-	-	<0.01	<0.01	<0.01	<0.01
Immature wheat plants	25-37	<0.01	<0.01	<0.01	0.01	-	<0.01	**0.01**	<0.01	<0.01

Commodity			Cyprodinil Residues in Rotational Crops (mg/kg)								
	Application rate:		1500 g a.s./ha				1125 g a.s./ha	750 g a.s./ha			
	Plant-back interval (days)	UK SRK09-040-37FR	Austria SRA09-012-37FR	Italy SRI09-368-37FR	Southern France SRF09-002-37FR	Germany, Italy, UK, Spain IF14-00834	UK 210-99	UK 209-99	Switzerland 201/00	Germany gr 33800
	55-65	<0.01	<0.01	<0.01	0.01	-	-	-	-	-
	201-216	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	314-384	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
Wheat grain/ears	25-37	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
	55-65	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	201-216	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	314-384	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
Wheat straw/stalks	25-37	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
	55-65	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	201-216	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-
	314-384	<0.01	<0.01	<0.01	<0.01	-	<0.01	<0.01	<0.01	<0.01
Oil seed rape (seed)	29-30	-	-	-	-	<0.01	-	-	-	-
	59-62	-	-	-	-	<0.01	-	-	-	-
	169-171	-	-	-	-	<0.01	-	-	-	-

* Highest value measured in either immature or mature commodity presented.
Values above the LOQ are in bold.

Following barley harvest, cereals, oilseed rape, root crops (e.g. carrot, turnip), leafy vegetables (e.g. kale, lettuce) may potentially be planted in the autumn a minimum of 60 days after application of cyprodinil to barley in the spring (based on a minimum pre-harvest interval of 45 days plus 15 days for soil preparation). Other crops would not be planted until the following spring, and across the EU this would be expected to be approximately 200 days or more after application of cyprodinil to barley. These intervals also take account of replanting after crop failure as in practice a barley crop is unlikely to fail once the crop has become established and after cyprodinil has been applied (at BBCH 30-61). If the crop did fail at this late stage, a succeeding crop would not be planted until the autumn.

The studies in the EU are relevant for the proposed use of cyprodinil in barley and the results indicate that residues of cyprodinil are not expected in succeeding crops planted in the spring after application to barley in the previous year. However, low residues of cyprodinil may occur in some crops planted in the autumn, e.g. carrot, planted 30 to 60 days after application.

Where residues of cyprodinil were found in rotational crops planted 30-60 days after application, values were very low (0.01 – 0.03 mg/kg) and within existing EU MRLs for root crops (2 mg/kg for carrot, horseradish and parsnip, 1 mg/kg for beetroot, 0.3 mg/kg for celeriac, 0.08 mg/kg for radish, 0.05 mg/kg for other root crops), leafy brassicas (0.05 mg/kg), and lettuces and salad plants (15 mg/kg). Therefore, it is not necessary to set a minimum interval before planting succeeding crop and it is not necessary to set new MRLs to take account of residues in succeeding crops.

In the opinion on the Article 12 MRL review, EFSA recommended that Member States granting authorisations should consider a pre-plant interval of at least 120 days in order to avoid residues of cyprodinil metabolites in rotational crops. This recommendation is not relevant ~~here~~ as the metabolites do not form part of the residue definition. The residue definition of parent cyprodinil only for rotated crops is appropriate as the metabolites CGA 249287 and NOA 422054 have been demonstrated to be non-toxicologically relevant (see Table 6.7.1-2 below).

According to the rotational crop studies provided residues of cyprodinil are expected to be very low and within EU MRLs for root crops, leafy brassicas, oilseeds and lettuce and salad plants. ~~Limited field studies are underway to investigate potential residues of cyprodinil which may occur in an oily rotational crop, and will be reported as soon as available.~~

CA 6.7 Proposed Residue Definitions and Maximum Residue Levels

CA 6.7.1 Proposed residue definitions

EU documents: EFSA, 2013, France, 2010, France, 2005

Plant products

The plant metabolism studies are fully summarised in Sections CA 6.2.1 and CA 6.6.1. A brief summary on each metabolite is given below and toxicology data that is available for each is summarised in Table 6.7.1-2. ~~The residue definitions are pending confirmation of the ongoing genotoxicity testing of metabolites NOA422054, CGA321915, GA253208 and CGA304075~~. Genotoxicity testing has confirmed that metabolites NOA422054, CGA321915, GA253208 and CGA304075 are not of toxicological concern.

CGA249287 – detected in rotational crop metabolism studies. Not of toxicological concern.

NOA422054 - unique to rotational crops and represented up to 46.2% of the total radioactive residue (0.71 mg/kg) and 1.5 mg/kg (12.8% TRR) in respectively, 365 DAT radish leaves and 120 DAT mature wheat straw. Not of toxicological concern.
CGA321915 - detected in rotational crop metabolism studies. Absolute residue levels in succeeding crops are low and not expected.
CGA232449 – detected in crop metabolism studies. Found in the rat metabolism study.
CGA263208 - Absolute residue levels in succeeding crops are low and not expected.
CGA304075 – found in the rat and are covered by the toxicological profile of cyprodinil.
CGA304076 - found in the rat and are covered by the toxicological profile of cyprodinil.

The residue definition in plant commodities for both risk assessment and monitoring is proposed as parent cyprodinil only. Metabolites seen during metabolism and field studies are either considered not toxicologically relevant or are likely to be at low absolute levels.

This is in keeping with the residue definition for both enforcement and risk assessment derived in the framework of the Annex I inclusion (**Vol.3, Annex B, Section B.7.3, November 2003**). This definition was supported by EFSA in the Conclusion on the peer review of cyprodinil (EFSA Scientific Report (2005) 51, 1-78), the Article 12 review of Regulation (EC) No 396/2005 (EFSA Journal 2013; 11(10):3406) and the Reasoned opinion on the modification of the existing MRL for celery (EFSA Journal 2015;13(3):4046).

~~No changes to the definition of the residue are proposed.~~

Animal products

The residue definition for both enforcement and risk assessment previously derived in the framework of the Annex I inclusion was the sum of cyprodinil + metabolite CGA304075 (free and conjugated) expressed as cyprodinil (**Vol.3, Annex B, Section B.7.3, November 2003**). This definition was supported by EFSA in the Conclusion on the peer review of cyprodinil (EFSA Scientific Report (2005) 51, 1-78).

The metabolism studies in both ruminants and poultry show that cyprodinil is extensively metabolised and proceeds predominantly via hydroxylation of the phenyl and pyrimidine rings and conjugation with sulphate or glucuronic acid. The majority of the radioactivity was eliminated in the urine and faeces. CGA304075 is a major metabolite in products of animal origin in both its free and conjugated form. In the goat metabolism whilst CGA304075 was the main metabolite in liver and kidney, the glucuronide conjugated form was the main metabolite found in milk. Other metabolites found at significant levels include CGA304076, CGA232449, and CGA249287. All these metabolites were found in the rat metabolism study.

In the Article 12 review of Regulation (EC) No 396/2005 (EFSA Journal 2013; 11(10):3406), EFSA reconsidered the metabolism data and considered whether the conjugate of CGA304075 needed to be included in the residue definition. It was noted that whilst conjugation does occur in hens, no significant residues in poultry are expected. Significant residues in poultry are also not expected following the representative uses on apple and barley supported in this dossier. The cow feeding studies (see section CA 6.4) confirmed the presence of CGA304075 (and parent cyprodinil to a lesser extent) in ruminant tissues. Residues of CGA304075 were not detected in milk at the lowest dose of the feeding study. On the basis of the findings of the livestock metabolism studies, free CGA304075 would not be expected to be detected in the milk however conjugated residues of CGA304075 might be expected.

The method of analysis used in the feeding studies (GRM 010.01A – see CA 4.1.2) includes a hydrolysis step with 0.5M hydrochloric acid that converts conjugated CGA304075 into its free form. Method development using animal products from a radiolabelled study (see section CA 6.2.3) indicated that this hydrolysis step is effective at releasing the conjugated CGA 304075. Therefore the levels determined in the feeding studies are of the free & conjugated metabolite.

Although feeding studies indicate that residues of both free and conjugated CGA304075 in milk will be <LOQ at relevant dosing levels, the metabolism studies do indicate that any cyprodinil residues present in milk at significant levels will be present as conjugated CGA304075 and the definition of the residue for milk should reflect this.

Therefore, the proposed residue definitions for enforcement and risk assessment in all commodities of animal origin (except milk) are:

The sum of cyprodinil and CGA304075 expressed as cyprodinil.

The proposed residue definitions for enforcement and risk assessment in milk are:

The sum of cyprodinil and CGA304075 (free and conjugated) expressed as cyprodinil.

EFSA stated further that the residue definition might require further consideration in the future if the dietary burden of poultry is increased. Based on the calculations presented here (see C.A 6.4), the dietary burden in poultry is 0.04-0.08 mg/kg bw/day, comparable to the intake calculated by EFSA, and consequently the definition of the residue in poultry (and all other animal products other than milk) is proposed as the sum of cyprodinil and CGA304075 (free) expressed as cyprodinil.

Table 6.7.1-1: Summary of the definitions of residue

Endpoint	Proposed EU endpoints
Definition of the residue in crops for enforcement purposes	Cyprodinil
Definition of the residue in crops for risk assessment purposes	Cyprodinil
Definition of the residue in animal products for enforcement purposes	Sum of cyprodinil + metabolite CGA304075 (free) expressed as cyprodinil. Milk only: Sum of cyprodinil + metabolite CGA304075 (free and conjugated) expressed as cyprodinil.
Definition of the residue in animal products for risk assessment purposes	Sum of cyprodinil + metabolite CGA304075 (free) expressed as cyprodinil. Milk only: Sum of cyprodinil + metabolite CGA304075 (free and conjugated) expressed as cyprodinil.
Fat soluble residue?	No. The P_{ow} of cyprodinil is higher than 3, however the distribution of CGA304075 in animal tissues indicates that the metabolite does not accumulate in fat tissues. Furthermore, the results of the cow feeding study shows those levels of either cyprodinil or CGA304075 were not found in milk and fat at an exaggerated dose rate, indicating that residues of cyprodinil are not necessarily expected to accumulate in fat tissues.

The table below summarises the toxicology studies available on dietary metabolites as detailed in MCA Section 5.8.1.

Table 6.7.1-2: Summary of the available toxicology data for cyprodinil metabolites seen in dietary studies

Metabolite	Where detected	Toxicology Study Type	Toxicology Outcome
CGA249287	Crop rotation metabolism studies Field crop rotation studies Poultry metabolism study Ruminant metabolism study (milk, liver and kidney) Detected in ADME rat study	Bacterial reverse mutation assay	Negative (±S9)
		Gene mutation in mammalian cells	Negative (±S9)
		In vitro cytogenetic test	Negative (±S9)
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
		90 Day Dietary Toxicity Rat	NOEL: 1000 ppm
NOA422054	Crop rotation metabolism studies Field crop rotation studies Not present in rat metabolism study	Bacterial reverse mutation assay	Negative (±S9)
		Gene mutation in mammalian cells	~~TBD~~ Negative (±S9)
		In vitro micronucleus assay	~~TBD~~ Negative (±S9)
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
CGA321915	Crop rotation metabolism studies Field crop rotation studies Not present in rat metabolism study	Bacterial reverse mutation assay	Negative (±S9)
		Gene mutation in mammalian cells	~~TBD~~ Negative (±S9)
		In vitro micronucleus assay	~~TBD~~ Negative (±S9)
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
CGA232449	Crop metabolism study Crop rotation metabolism studies Ruminant metabolism study Detected in ADME rat study	Bacterial reverse mutation assay	Negative (±S9)
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
CGA263208	Identified in crop metabolism study Found in rotational crops Not present in rat metabolism study	Bacterial reverse mutation assay	Negative (±S9)
		Bacterial reverse mutation assay	Negative (±S9)
		Gene mutation in mammalian cells	~~TBD~~ Negative (±S9)
		In vitro cytogenetic test	Negative (±S9)
		Micronucleus Assay in Bone Marrow Cells of the Rat	Negative
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
		90 Day Dietary Toxicity Rat	NOAEL: 300 ppm
		Pre-natal Developmental Toxicity Rat	Maternal NOAEL: 200 mg/kg bw/day Foetal NOAEL: 200 mg/kg bw/day
CGA304075	Identified in crop metabolism study Identified in poultry metabolism study Identified in ruminant metabolism study Crop metabolism study Detected in ADME rat study	Bacterial reverse mutation assay	Negative (±S9)
		Gene mutation in mammalian cells	~~TBD~~ Negative (±S9)
		In vitro micronucleus assay	~~TBD~~ Negative (±S9)
		Acute Oral LD_{50} Rat	LD50 > 2000 mg/kg bw
CGA304076	Identified in crop metabolism study Identified in ruminant metabolism study Crop metabolism study Detected in ADME rat study	A major metabolite seen in the rat metabolism study. Structurally very similar to CGA304075	

CA 6.7.2 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed

EU MRLs for cyprodinil are currently detailed in Annexes of Regulation (EC) No 396/2005. EU MRLs for commodities relevant to this submission are detailed in Table 6.7.2–1. The residue values used and the calculations for MRLs are presented in Section CA 6.3. The calculations for MRLs for animal commodities are presented in Section CA 6.4.5.

No changes to the current EFSA EU MRLs for apple, barley grain and animal commodities are proposed as a result of this submission.

Table 6.7.2–1: Established and proposed MRLs for cyprodinil for commodities in this submission

Code	Commodity	Current EU MRL[1] (mg/kg)	Proposed EU MRL (mg/kg)
0130010	Apple (fruit)	1.5#	No changes are proposed.
0500010	Barley (grain)	4.0	
1011000 1016000 1020000 1030000	Swine tissues Poultry tissues Milk Birds eggs	0.02*	
1012030 1012040 1013030 1013040 1014030 1014040 1015030 1015040 1017030 1017040	Bovine liver Bovine kidney Sheer liver Sheep kidney Goat liver Goat kidney Horse liver Horse kidney Other farm animals liver Other farm animals kidney	0.05	
1012010 1012020 1012050 1012990 1013010 1013020 1013050 1013990 1014010 1014020 1014050 1014990 1015010 1015020 1015050 1015990 1017010 1017050 1017990	Bovine meat Bovine fat Bovine edible offal Bovine others Sheep meat Sheep fat Sheep edible offal Sheep others Goat meat Goat fat Goat edible offal Goat others Horse meat Horse fat Horse edible offal Horse others Other farm animals meat Other farm animals fat Other farm animals others	0.02*	

[1] – MRLs as given in Commission Regulation (EU) 400/2015

* LOQ.

The data on apple presented in this submission support a MRL of 1 mg/kg however this is based on a less critical GAP than considered by EFSA.

CA 6.7.3 Proposed maximum residue levels (MRLs) and justification of the acceptability of the levels proposed for imported products (import tolerance)

Not applicable.

CA 6.8 Proposed Safety Intervals

Pre-harvest intervals

Proposed pre-harvest intervals for the use of cyprodinil on the representative use crops (apple and barley) are detailed in Table 6.8-1.

Table 6.8-1: Proposed Pre-harvest Intervals

Crop	Application method	Pre-Harvest Interval (days)
Apple	Foliar spray (BBCH 10-71)	21
Barley	Foliar spray (BBCH 30-61)	45[(a)]

(a) It is more appropriate to base the application timing on cereal crops on growth stage rather than a pre-harvest interval; however this PHI is given as an indication.

Re-entry intervals for livestock to areas to be grazed

A re-entry interval for livestock is not applicable as apple and barley are not grazed.

Re-entry period for man into treated areas

The worker re-entry risk assessments for the representative uses have been presented in Section MCP 7.2.3 of the dossiers for products A14325E and A8637C. No re-entry period is required for scouting activities for the proposed uses or for harvesting at the proposed PHIs.

Withholding periods for animal feeding stuffs

An additional period of withholding after harvest is not required for livestock feed commodities.

Waiting period between last application and sowing or planting the crops to be protected

As cyprodinil is applied post-emergence to crops no waiting period is required.

Waiting period between last application and handling treated products

The worker re-entry risk assessments for the representative uses have been presented in document MCP Section CP 7.2.3 of the dossiers for products A14325E and A8637C. No re-entry period is required for scouting activities for the proposed uses or for harvesting at the proposed PHIs.

Waiting periods between last application and sowing or planting succeeding crops

The rotational crop studies showed that even at a 60 day plant back interval residues of cyprodinil in succeeding crops were very low and within existing MRLs. Thus, a waiting period is not required.

CA 6.9 Estimation of the Potential and Actual Exposure through Diet and other Sources

Acceptable Daily Intake (ADI) and Dietary Exposure Calculation

No change from the existing EU ADI of 0.03 mg/kg body weight/day for cyprodinil is proposed (see EFSA report for cyprodinil (**EFSA Scientific Report (2005) 51, 1-78)** and **Document M-CA, Section 5** of this submission).

Long-term consumer exposure to potential residues of cyprodinil resulting from the proposed representative use of cyprodinil is estimated according to the EFSA PRIMo model[1] for chronic risk assessment.

The TMDI values are calculated based on MRL values as listed in Table 6.9-1. The residues as entered into the EFSA model are for apple, barley grain and animal commodities.

Table 6.9-1: Input values for TMDI calculations

Commodity Code	Commodity	Input value (mg/kg)	Comment*
0130010	Apple	1.5	EU MRL
0500010	Barley	4	EU MRL
1011000	Swine tissues	0.02	EU MRL
1012010 1012020 1012050 1012990 1013010 1013020 1013050 1013990 1014010 1014020 1014050 1014990 1015010 1015020 1015050 1015990 1017010 1017050 1017990	Bovine meat Bovine fat Bovine edible offal Bovine others Sheep meat Sheep fat Sheep edible offal Sheep others Goat meat Goat fat Goat edible offal Goat others Horse meat Horse fat Horse edible offal Horse others Other farm animals meat Other farm animals fat Other farm animals others	0.02	EU MRL
1012030 1012040 1013030 1013040 1014030 1014040 1015030 1015040 1017030 1017040	Bovine liver Bovine kidney Sheer liver Sheep kidney Goat liver Goat kidney Horse liver Horse kidney Other farm animals liver Other farm animals kidney	0.05	EU MRL
1016000	Poultry tissues	0.02	EU MRL
1020000	Milk and cream	0.02	EU MRL
1030000	Birds eggs	0.02	EU MRL

* MRLs in Commission Regulation 2015/400 of 396/2005

[1] Revision 2.0 of the EFSA model. Reasoned Opinion on the Potential Chronic and Acute Risk to Consumers' Health Arising from Proposed Temporary EU MRLs According to Regulation (EC) No 396/2005 on Maximum Residue Levels of Pesticides in Food and Feed of Plant and Animal Origin, European Food Safety Authority, 15 March 2007

The TMDI calculations give unrealistic worst-case estimates of intake because they assume that all commodities with proposed uses will contain residues at the MRL. No account is taken of the potential reduction in residues during transport and storage or during commercial and domestic processing. In practice, the actual intake is likely to be much lower than the calculated values.

The TMDI calculation for cyprodinil using the EFSA PRIMo model is presented in Table 6.9-1. The highest TMDI for cyprodinil is for a German child and represents 61.6% of the ADI.

Table 6.9-1: TMDI for cyprodinil using the EFSA Model Rev 2.0

The output is taken directly from the EFSA spreadsheet. The proposed EU MRL values have been used.

Cyprodinil			
Status of the active substance:		Code no.	
LOQ (mg/kg bw):		proposed LOQ:	
Toxicological end points			
ADI (mg/kg bw/day):	**0.03**	ARfD (mg/kg bw):	**n.n.**
Source of ADI:	**EFSA**	Source of ARfD:	
Year of evaluation:	**2005**	Year of evaluation:	

Prepare workbook for refined calculations

Undo refined calculations

Explain choice of toxicological reference values.
The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL).
The pTMRLs have been submitted to EFSA in September 2006.

Chronic risk assessment

TMDI (range) in % of ADI minimum - maximum	
3	62
No of diets exceeding ADI:	---

Highest calculated TMDI values in % of ADI	MS Diet	Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)
61.6	DE child	60.3	Apples	1.0	Milk and cream,	0.2	Barley	
34.3	NL child	31.7	Apples	2.0	Milk and cream,	0.3	Barley	
21.1	IE adult	16.5	Barley	4.1	Apples	0.2	Milk and cream,	
16.0	FR toddler	13.1	Apples	2.6	Milk and cream,	0.1	Bovine: Meat	
15.5	WHO cluster diet E	10.8	Barley	4.2	Apples	0.2	Milk and cream,	
14.3	FR infant	12.5	Apples	1.7	Milk and cream,	0.0	Bovine: Meat	
12.7	DK child	11.6	Apples	0.8	Milk and cream,	0.1	Swine	
11.8	WHO Cluster diet F	8.0	Barley	3.3	Apples	0.3	Milk and cream,	
11.5	NL general	5.9	Apples	5.0	Barley	0.4	Milk and cream,	
10.9	ES adult	6.6	Barley	3.8	Apples	0.3	Milk and cream,	
10.5	LT adult	9.3	Apples	0.8	Barley	0.3	Milk and cream,	
10.5	UK Infant	7.8	Apples	2.6	Milk and cream,	0.1	Birds' eggs	
10.2	PL general population	10.2	Apples		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)	
10.2	UK Toddler	8.5	Apples	1.4	Milk and cream,	0.2	Barley	
9.3	WHO Cluster diet B	5.0	Apples	3.7	Barley	0.2	Milk and cream,	
8.4	WHO regional European diet	4.4	Barley	3.3	Apples	0.3	Milk and cream,	
6.9	ES child	5.7	Apples	0.8	Milk and cream,	0.1	Bovine: Meat	
6.7	WHO cluster diet D	3.3	Apples	2.9	Barley	0.3	Milk and cream,	
6.1	SE general population 90th percentile	5.3	Apples	0.8	Milk and cream,	0.1	Birds' eggs	
5.7	PT General population	5.3	Apples	0.4	Barley		FRUIT (FRESH OR FROZEN)	
4.6	IT kids/toddler	4.4	Apples	0.1	Barley		FRUIT (FRESH OR FROZEN)	
4.4	DK adult	3.9	Apples	0.4	Milk and cream,	0.1	Swine	
4.1	IT adult	4.0	Apples	0.1	Barley		FRUIT (FRESH OR FROZEN)	
3.5	UK vegetarian	3.0	Apples	0.3	Barley	0.2	Milk and cream,	
2.8	FI adult	2.0	Apples	0.4	Milk and cream,	0.3	Barley	
2.8	FR all population	2.4	Apples	0.2	Milk and cream,	0.1	Barley	
2.7	UK Adult	2.1	Apples	0.4	Barley	0.2	Milk and cream,	

Conclusion:
The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.
A long-term intake of residues of Cyprodinil is unlikely to present a public health concern.

Acute Reference Dose (ARfD) and Dietary Exposure Calculation

No acute reference dose (ARfD) for cyprodinil has been set in the EU (**EFSA Scientific Report (2005) 51, 1-78**). Therefore, calculations of the short-term intake are not required.

CA 6.10 Other Studies

CA 6.10.1 Effect on the residue level in pollen and bee products

The data requirement objective of these studies is to determine the residue in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom.

Document SANCO/10181/2013 Rev. 2.1, 13 May 2013 states: "*In some cases, agreed test methods or guidance documents are not yet available for particular data requirements. In these cases, waiving of these particular data requirement points is considered acceptable as long as no test methods or guidance documents are published in the form of an update of the Commission Communications 2013/C 95/01 and 2013/C 95/02.*"

The notifier's current understanding is that there is no guidance yet finalised for assessing residue levels in pollen and bee product studies (suitable for human consumption assessment purposes). It is also noted in Section A.24 of the summary from the SCOPAFF meeting on 24 – 25 November 2014 that "*the Commission working document is not yet finalised and ready to be noted as a guidance document.*" Additionally, *"...the Commission emphasised that for the time being there are no agreed test guidelines and that hence the pertinent data requirements can be waived.*"

There is no guidance yet finalised for conducting studies to determine the residues in bee products.

Therefore, no studies have been conducted investigating residues of cyprodinil in pollen and bee products.

The representative uses for cyprodinil presented in this dossier are on barley and pome fruit. Barley is of low attractiveness to bees (**EFSA Guidance Document on the risk assessment of plant protection products on bees, Table D1, EFSA Journal 2013; 11(7):3295**). Pome fruit may be attractive to bees and the representative use of A8637C may be applied during flowering and therefore available in pollen or nectar collected by foraging bees. As discussed above no residue trials investigating residues of cyprodinil in bee products have been undertaken due to lack of finalised guidance into how the trials are to be conducted, however EFSA monitoring data is available for 2010 to 2013 (see the table below) demonstrating that residues of cyprodinil in honey are likely to be below the LoQ. Residues of cyprodinil are detected in pome fruit when included in the monitoring program showing cyprodinil is used on apple and pear, however no residues of cyprodinil have been detected in samples of honey. Residues of cyprodinil are unlikely to occur in bee products above the LoQ through the representative uses discussed in this dossier, and there is no risk to the consumer.

Table 6.10-1: Summary of European Union Report on Pesticide Residues in Food data on Cyprodinil in pome fruit and honey

Report Year	Cyprodinil residue detected in apple?	Cyprodinil residue detected in pear?	Cyprodinil residue detected in honey?
2010[1]	YES	n/a	NO
2011[2]	n/a	YES	NO
2012[3]	Pome fruit not included in the program		NO
2013[4]	YES	n/a	NO

[1] The 2010 European Union Report on Pesticide Residues in Food (EFSA Journal 2013; 11(3); 3130)
[2] The 2011 European Union Report on Pesticide Residues in Food (EFSA Journal 2014; 12(5); 3694)
[3] The 2012 European Union Report on Pesticide Residues in Food (EFSA Journal 2014; 12(12); 3942)
[4] The 2013 European Union Report on Pesticide Residues in Food (EFSA Journal 2015; 13(3); 4038)

Summary of residue behaviour

The stability of residues of cyprodinil and CGA304075 during storage was investigated in various commodities.

Cyprodinil was stable in crops representing the high water, high starch and high acid crop groups, plus wheat stalks and wine, for 24-26 months. Residues of cyprodinil were stable in products of animal origin for 18-19 months. CGA304075 was stable in products of animal origin for 3-6 months.

The metabolism of cyprodinil has been investigated in potato, tomato, apple, peach and wheat. These crops are representative of root vegetables, fruits and cereals. The metabolism was essentially similar in all crops and the residue definitions for both risk assessment and monitoring is cyprodinil (parent compound) only.

The metabolism studies in both ruminants and poultry show that cyprodinil is extensively metabolised and proceeds predominantly via hydroxylation of the phenyl and pyrimidine rings and conjugation with sulphate or glucuronic acid. The majority of the radioactivity was eliminated in the urine and faeces. CGA304075 is a major metabolite in in products of animal origin in both its free and conjugated form. In the goat metabolism whilst the CGA304075 was the main metabolite in liver and kidney, the glucuronide conjugated form was the main metabolite found in milk. Other metabolites found at significant levels include CGA304076, CGA232449, and CGA249287. All these metabolites were found in the rat metabolism study.

The proposed residue definitions for enforcement and risk assessment in all commodities of animal origin (except milk) are the sum of cyprodinil and CGA304075 expressed as cyprodinil. The proposed residue definition for enforcement and risk assessment in milk is the sum of cyprodinil and CGA304075 (free and conjugated) expressed as cyprodinil.

Residue trials in apple and barley were conducted in the EU and are used to support the proposed EU GAP.

Twenty five supervised residue trials were conducted on apple in northern and southern Europe. Treatments with cyprodinil were applied as three post-emergence foliar sprays (BBCH 71-87) at a nominal application rate of 375 g a.s./ha. Samples were analysed for residues of cyprodinil with a LOQ of 0.01 mg/kg. The available trials are sufficient to support the EU proposed GAP for apple. Residues found

in the trials from northern and southern Europe were comparable, leading to the similar STMR and HR values. The data indicated that residues will be within the existing EU MRL of 1.0 mg/kg.

Fourteen supervised residue trials were conducted on barley in northern and southern Europe. Treatments with cyprodinil were applied as two post-emergence foliar sprays (BBCH 24-31) at a nominal application rate of 450 g a.s./ha. Samples were analysed for residues of cyprodinil with a LOQ of 0.01 mg/kg. The available trials are sufficient to support the EU proposed GAP for barley. The data indicated that residues will be within the existing EU MRL of 3 mg/kg and support the recently proposed EU MRL of 4 mg/kg.

The potential dietary exposure of livestock to cyprodinil residues in the supported representative crops of apple and barley, and their processed products has been calculated.

The maximum dietary burden of residues of cyprodinil in livestock was 0.024-0.097 mg/kg bw/day for the different species. For poultry, based on the hen metabolism studies residues of cyprodinil (cyprodinil + CGA304075) will not occur in poultry products at levels above the combined LOQs of cyprodinil and CGA304075 (0.02 mg/kg). For ruminants and pigs, based on feeding studies in cattle, residues of cyprodinil and CGA304075 are not expected above the LOQ in animal tissues based on the representative uses. MRL, STMR and HR values for all animal commodities based on the representative uses supported in this document are therefore equivalent to the sum of the LOQs for cyprodinil and CGA304075 and within existing/proposed values.

The hydrolytic stability of cyprodinil was investigated under conditions typical of those found in industrial and household processes such as pasteurisation, boiling and sterilisation. No breakdown or reaction products were formed during hydrolysis of cyprodinil under representative processing conditions. Thus, it was concluded that for processed crop commodities the same residue definition (parent cyprodinil) would be applicable.

The magnitude of cyprodinil residues in processed apple and barley was investigated. In apple, cyprodinil residues would be expected to concentrate in wet and dry pomace but not in juice or puree. Little of the cyprodinil residue was removed from the fruit by washing. In barley, residues of cyprodinil did not concentrate in malt germ, spent grain, flocs, yeast wort, beer or pearl barley. Residues of cyprodinil did concentrate in malt and pearling dust. Suitable transfer factors have been derived for these commodities.

The metabolism of cyprodinil in rotational crops is sufficiently elucidated. When radiolabelled cyprodinil was applied to a primary crop (spring wheat) at an application rate of 1.25 kg a.s./ha, no significant cyprodinil residues (TRR<0.01 mg/kg) were found in any of the edible parts of the succeeding crops tested. When cyprodinil was applied to bare soil, four major metabolites were identified in succeeding crops CGA321915, CGA249287, NOA422054, and CGA263208. The EU evaluation concluded that as CGA 249287 and NOA 422054 were not found to be of toxicological concern, and residues of CGA263208 were seen only after application to bare soil at exaggerated rates and absolute levels are low, they do not need to be included in the residue definition for plants (**Vol.3, Annex B, Section B.7.7, November 2003)**.

In rotational crop field studies, cyprodinil was applied to bare soil at 2.24 kg a.s./ha in the US (one trial), 0.75 kg a.s./ha in the UK, Switzerland and Germany in 1999 and 2000 (4 trials), and 1.5 kg a.s./ha in the UK, Austria, Italy and southern France in 2009 (4 trials). Low residues (0.01 – 0.03 mg/kg) of cyprodinil were occasionally found in rotational crops planted 30-60 days after application but not following longer intervals. The levels of residues found were within existing EU MRLs for root crops (2 mg/kg for carrot, horseradish and parsnip, 1 mg/kg for beetroot, 0.3 mg/kg for celeriac, 0.08 mg/kg for radish, 0.05 mg/kg for other root crops), leafy brassicas (0.05 mg/kg), and lettuces and salad plants (15 mg/kg). Therefore, it is not necessary to set a minimum interval before planting succeeding crop and it is not necessary to set new MRLs to take account of residues in succeeding crops.

Long-term consumer exposure to potential residues of cyprodinil resulting from the proposed representative uses of cyprodinil has been estimated according to the EFSA PRIMo model for chronic risk assessment. No change from the existing EU ADI of 0.03 mg/kg body weight/day for cyprodinil is proposed. The highest TMDI for cyprodinil was for a German child and represented 61.6% of the ADI.

Therefore, there is no unacceptable chronic risk to human health from the consumption of commodities containing residues of cyprodinil arising from apple and barley treated with cyprodinil according to the proposed uses. Short-term consumer exposure to potential cyprodinil residues is not relevant as an ARfD has not been set for cyprodinil.

References

France, 2005. Draft assessment report on the active substance cyprodinil prepared by the rapporteur Member State France in the framework of Council Directive 91/414/EEC, November 2003.

EFSA (European Food Safety Authority), 2005a. Conclusion on the peer review of the pesticide risk assessment of the active substance cyprodinil. *EFSA Scientific Report* (2005) 51, 1-78.

France, 2010. Addendum to the draft assessment report on the active substance cyprodinil prepared by the rapporteur Member State France in the framework of Council Directive 91/414/EEC, October 2009.

EFSA, 2013. Evaluation Report prepared under Article 12 of Regulation (EC) No 396/2005. Authorised uses to be considered for the review of the existing MRLs for cyprodinil, July 2013.

The 2010 European Union Report on Pesticide Residues in Food (EFSA Journal 2013; 11(3); 3130)

The 2011 European Union Report on Pesticide Residues in Food (EFSA Journal 2014; 12(5); 3694)

The 2012 European Union Report on Pesticide Residues in Food (EFSA Journal 2014; 12(12); 3942)

The 2013 European Union Report on Pesticide Residues in Food (EFSA Journal 2015; 13(3); 4038)

Appendix 1: Example calculation of residue values by extrapolation

Trial: trial 02-2154
Residue: cyrpodinil

Data

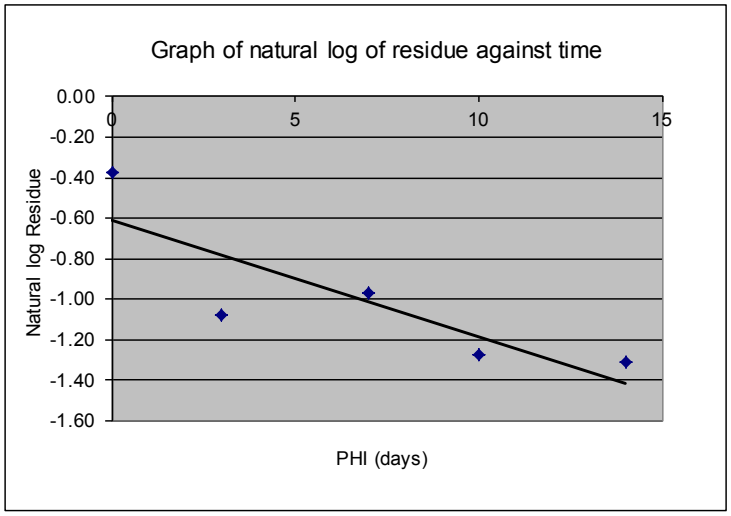
Days	Residue	Natural log Residue
0	0.69	-0.37106
3	0.34	-1.07881
7	0.38	-0.96758
10	0.28	-1.27297
14	0.27	-1.30933

Statistics

Slope	Intercept	R^2 fit
-0.0576	-0.6084	0.7106

Extrapolation

Days	Extrapolated Residue Prediction
21	0.162



Appendix 2: Tables from Plant and Animal Metabolism Studies

In response to requests from the RMS –

"IIA 6.1.3.3/01, Stingelin J. 1993, addendum no. 1 to project report 91JS15PR1, Syngenta file No CGA219417/0199: Please submit table II "quantification of metabolite fraction (Analytical System I) in various plant parts of apple tree at maturity, 61 days after the third application of {2-14C-pyrimidine}CGA219417 in a Word format."

Table II: Quantitation of Metabolite Fraction (Analytical System I) in Various Plant Parts of Apple Tree at Maturity, 61 Days after the third Application of [2-14C-Pyrimidine] CGA 219417

Plant Part	Total Residues [ppm][1]	Original & uncleaved metabolite fractions[2,3,4] [%]															Soxhlet [%][2]	NE [%][2]	Total [%][2]
		I_1	I_3	I_{4a}	I_4	I_6	I_{10}	I_{10a}	I_{10b}	I_{11a}	I_{12b}	I_{13}	I_{13c}	I_{14d}	I_{15}	Unresolved	Sub-Total			
Peel	3.461	2.5	2.0	1.1	1.7	--	1.0	6.3	--	2.0	2.0	1.0	--	1.2	9.7	7.8	38.3	7.2	46.4	91.9
Pulp	0.173	16.0	0.6	1.1	0.9	--	1.5	9.2	0.6	0.8	2.7	8.1	1.5	1.3	11.2	23.8	79.3	0.7	11.0	91.0
Whole Fruit[5]	0.798	4.8	1.7	1.1	1.5	--	1.1	6.6	0.1	1.7	2.1	2.2	0.3	1.2	11.1	10.4	45.8	5.9	38.9	90.6
Leaves	49.324	--	8.9	1.8	2.2	1.4	9.5	2.7	--	8.5	4.7	--	--	0.5	12.1	15.7	68.0	4.0	22.6	94.6

[1] in equivalents of CGA 219417
[2] given in % of the total residues determined by combustion, except for the plant part *wholefruit*, where the total residues were calculated by the ∑ surface rad. + penetrated rad$_{[comb]}$
[3] Quantification was done by 2-dim. TLC, using *analytical system I* (SS79/SS28). For parent determination *analytical system II* (SS126) was used.
[4] Denomination of the metabolite fractions was done in accordance with the projects 90DG40 (CGA 219417 in spring wheat), and 91CN03 (CGA 219417 in tomatoes)
[5] including parent content of the surface radioactivity

☐ characterized or identified metabolites:

I_{10} co-chromatographs with CGA 232449 after cellulose treatment
I_{10a} was identified as the N-glucose conjugate of CGA 219417
I_{11a} was identified as CGA 304075 after cellulose treatment
I_{12b} was identified as glucose conjugate of N-(2-hydroxyphenyl)-4-cyclopropyl-6-methyl-2-pyrimidinamine
I_{13} co-chromatographs with CGA 249287
I_{15} co-chromatographs with CGA 219417

In response to requests from the RMS –

"Study in the original DAR IIA6.2.2.1/02, Neumann, CH., 1994, Project report 91CN04PR1, Syngenta File No 219417/0257: Please submit in a word format the following table:

- *Table VII : Quantitative distribution of metabolites in liver, kidney, muscle, milk and urine of goats after oral administration of [14C]CGA219417 in % of tissues residues (low dose experiments)*
- *Table VIII : Quantitative distribution of metabolites in liver, kidney, muscle and milk of goats after oral administration of [14C]CGA219417 in ppm parent equivalents"*

Table VII: Quantitative Distribution of Metabolites in Liver, Kidney, Muscle, Milk and Urine of Goats after Oral Administration of [14C] CGA 219417 in % of Tissue Residues (low dose experiments)

Sample	Label	Metabolite Fractions [%]																	Non- extr.	total
		I_1 (Start)	I_2 (1G)	I_{2a}	I_3 (3U)	I_4	I_{4a}	I_{4b}	I_5	I_6	I_7	I_{7a}	I_8	I_9 (CGA 249287)	I_{10} (CGA 304075)	I_{11} (CGA 219417)	Unresolved	Subtotal		
Urine	^{14}C-Phenyl	0.7	--	--	28.1	--	--	--	1.2	6.0	--	--	--	--	17.7	--	37.6	91.4	--	91.4
	^{14}C-Pyrimidine	1.2	--	--	8.1	--	--	--	--	9.1	--	--	--	--	22.2	--	49.4	90.0	--	90.0
Milk	^{14}C-Phenyl	9.1	15.2	--	2.1	--	--	--	4.1	19.1	3.3	--	1.5	--	--	--	17.4	71.8	20.2	92.0
	^{14}C-Pyrimidine	10.3	27.3	--	3.0	5.5	--	--	3.1	11.7	3.5	--	2.1	2.1	--	--	15.4	84.0	14.5	98.5
Muscle	^{14}C-Phenyl	No quantification possible																		
	^{14}C-Pyrimidine	No quantification possible																		
Kidney	^{14}C-Phenyl	3.9	--	2.6	1.2	--	n.q.	--	6.8	5.6	--	2.5	--	--	18.3	--	17.7	57.3	12.2	69.5
	^{14}C-Pyrimidine	0.4	--	--	6.9	--	n.q.	2.2	2.8	8.0	--	--	--	5.8	17.7	--	27.0	70.8	11.9	82.7
Liver	^{14}C-Phenyl	0.6	--	1.9	n.q.	--	1.4	--	1.4	2.4	--	3.8	--	--	--	1.5	44.6	53.7	40.7	94.4
	^{14}C-Pyrimidine	0.1	--	--	2.0	--	n.q.	1.1	n.q.	2.8	--	--	--	4.2	2.7	5.7	40.8	59.4	33.7	93.1

Table VIII: Quantitative Distribution of Metabolites in Liver, Kidney, Muscle and Milk of Goats after Oral Administration of [14C]CGA 219417 in ppm parent equivalents1

Sample	Label	Residues (ppm)	Metabolite Fractions [ppm]															Non-extr.
			I_1 (start)	I_2 (1G)	I_{2a}	I_3 (3U)	I_4	I_{4a}	I_{4b}	I_5	I_6 (2U)	I_7	I_{7a}	I_8	I_9 (CGA 249287)	I_{10} (CGA 304075)	I_{11} (CGA 219417)	Unresolved	
Milk	^{14}C-Phenyl	0.015	0.001	0.002	--	<0.001	--	--	--	<0.001	0.003	0.001	--	<0.001	--	--	--	0.003	0.004
	^{14}C-Pyrimidine	0.048	0.005	0.013	--	0.001	0.003	--	--	0.001	0.006	0.002	--	0.001	0.001	--	--	0.007	0.007
Muscle	^{14}C-Phenyl	0.007	No quantification possible																
	^{14}C-Pyrimidine	0.006	No quantification possible																
Kidney	^{14}C-Phenyl	0.234	0.009	--	0.006	0.003	--	n.q.	--	0.016	0.013	--	0.006	--	--	0.041	--	0.038	0.029
	^{14}C-Pyrimidine	0.216	<0.001	--	--	0.015	--	n.q.	0.005	0.006	0.017	--	--	--	0.013	0.038	--	0.058	0.026
Liver	^{14}C-Phenyl	0.172	0.001	--	0.003	n.q.	--	0.002	--	0.002	0.004	--	0.007	--	--	--	0.003	0.077	0.070
	^{14}C-Pyrimidine	0.277	<0.001	--	--	0.006	--	n.q.	0.003	n.q.	0.008	--	--	--	0.012	--	0.016	0.113	0.093

n .q. = not quantified