A14325E

Cyprodinil 300 g/L EC

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

DOCUMENT M-CP, Section 7

TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Version history[1]

Date	Data points containing amendments or additions and brief description	Document identifier and version number
20 May 2016	CP 7.2.1: addition of exposure calculations according to EFSA guidance CP 7.2.2: addition of exposure calculations according to EFSA guidance CP 7.2.3: addition of exposure calculations according to EFSA guidance (all changes highlighted in yellow)	A14325E_10045 9 October 2015 updated 20/5/16

[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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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCTS

Introduction

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 toxicological studies for the product A14325E containing:

- 300 g/L cyprodinil which 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.

A14325E is an emulsifiable concentrate (EC) containing 300 g/L cyprodinil for use as a fungicide on barley. A14325E was not a representative formulation in the original EU review of cyprodinil. Representative formulations in the original EU review were UNIX 75 WG (A8779A) and CHORUS 50 WG (A8637C).

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 Review Report for cyprodinil (SANCO/4343/2000 final (revised) 28 September 2006), 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 284/2013, and the associated Annex, which repeals Commission Regulation (EU) No 545/2011 which, under Regulation (EC) 1107/2009, replaced the requirements of Annex III to Directive 91/414/EEC
- In scientific and technical knowledge since the approval or last renewal of the approval
- To representative uses

The proposed representative use pattern is included in Document D1.

Each section of this document provides the agreed EU endpoints and if relevant proposals for amended endpoints.

Where new guidance documents have been introduced since the EU review of cyprodinil, an updated evaluation of cyprodinil and A14325E has been included. To adequately assess cyprodinil to the new guidance documents, it may have been necessary to provide new data, if so these are also included.

Information on the detailed composition of A14325E can be found in the confidential dossier of this submission (**Document J**).

Details of all relevant data from the scientific peer reviewed open literature on the active substance, metabolites and breakdown or reaction products and plant protection products containing the active substance have been provided in the **Document M-CA Section 9** and are discussed within the relevant data point of the associated dossier for the active substance, cyprodinil. If the published literature is also relevant to A14325E, it has been discussed within the relevant data point in this document.

CP 7.1 Acute Toxicity

Summary of acute toxicity

A14325E has a low toxicity in respect to acute oral and dermal toxicity. It is not irritating to the rabbit eye, but is moderately irritating to the rabbit skin and is a skin sensitiser in the guinea pig.

The classification according to Regulation (EC) 1272/2008 is given in the table below.

Table 7.1-1: Summary of acute toxicological data obtained with A14325E

Parameter	Species	Result	Classification according to Regulation (EC) No.1272/2008
Acute oral LD50	Rat	>2000 mg/kg	none
Acute dermal LD50	Rat	>2000 mg/kg	none
Acute inhalation LC50	Rat	not required*	none
Acute skin irritation	Rabbit	moderate irritant	none
Acute eye irritation	Rabbit	not irritating	none
Skin sensitisation (Buehler Test)	Guinea Pigs	skin sensitiser	H317

* The criteria for the need for an acute inhalation study are not met for A14325E according to Commission Regulation (EU) No 545/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for plant protection products.

CP 7.1.1 Oral toxicity

Report:	K-CP 7.1.1/01 Straube E (2005). CGA219417 300 g/l EC formulation (A14325E): Acute Oral Toxicity Study in the Rat (Up and Down Procedure). RCC Ltd., Toxicology, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Laboratory Report No. 859442, 23 June 2005. Unpublished. Syngenta File No. CGA219417/1325.

GUIDELINES: OECD 425 (2001): OPPTS 870.1100 (2002). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

In an acute oral toxicity study, five female HanRcc:WIST (SPF) rats were treated with CGA219417 300 g/l EC formulation (A14325E) by gavage at the limit dose of 2000 mg/kg body weight. The undiluted formulation was dosed at a constant concentration of 1.012 g/mL and at a dose volume of 1.98 mL/kg.

The animals were examined at least once per day for mortality / viability and clinical signs for a total of 15 days. Body weights were recorded at intervals throughout the study and all animals were given a gross examination *post mortem.*

There were no mortalities. Clinical signs included slightly ruffled fur and hunched posture, but no clinical signs were recorded after day 4. There was no effect on bodyweight. Congested lungs were noted in one animal at scheduled necropsy.

The acute oral LD_{50} of CGA219417 300 g/l EC formulation (A14325E) to female rats is in excess of 2000 mg/kg bw.

The acute oral toxicity was greater than 2000 mg/kg therefore no classification is required for acute oral toxicity of A14325E according to Regulation (EC) No.1272/2008.

MATERIALS AND METHODS

Test Material:	CGA219417 (cyprodinil) 300 g/l EC formulation (A14325E)
Description:	Formulation, yellow liquid
Lot/Batch #:	SMU5BP002
Purity:	303 g/l corresponding to 29.9 % w/w
Stability of test compound:	Stable at <30ºC, light protected

Vehicle and/or positive control: None

Test Animals:

Species	Rat
Strain	HanRcc:WIST (SPF)
Age/weight at dosing	11-13 weeks / 178-185g
Source	RCC Ltd., Laboratory Animal Services, CH-4414 Füllinsdorf, Switzerland
Housing	Individually in Makrolon type-3 cages with standard softwood bedding
Acclimatisation period	6 days
Diet	Pelleted standard Provimi Kliba 3433 rat/mouse maintenance diet *ad libitum* (except during the pre-dose fast)
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 22 ± 3°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

In-life dates: Start: 19 April 2005 End: 20 May 2005

Animal assignment and treatment: Five female HanRcc:WIST (SPF) rats were treated, sequentially, with undiluted CGA219417 300 g/l EC formulation (A14325E) by gavage at a limit dose of 2000 mg/kg. The animals were examined daily during the acclimatisation period and mortality, viability and clinical signs were recorded. All animals were examined for clinical signs once during the first 30 minutes after application and at approximately 1, 2, 3 and 5 hours after treatment on day 1 and once daily during test days 2-15. Mortality/viability was recorded once during the first 30 minutes after dosing and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2-15. Body weights were recorded on day -1 (prior to removal of food), day 1 (prior to administration) and on days 8 and 15. All animals were necropsied and examined macroscopically on day 15.

Statistics: The acute oral LD_{50} was estimated from the mortality data (limit test, no deaths).

RESULTS AND DISCUSSION

Mortality: There were no mortalities.

Clinical observations: Slightly ruffled fur was noted in four animals from the 30 minute or 2-hour examination to the 3 or 5 hour examination, or to test day 2 or 4. Hunched posture was noted in three animals from the 30 minutes or 2-hour examination to the 3 or 5 hour examination, or to test day 3. No clinical signs were observed in one animal during the course of the study.

Body Weight: The body weights were within the range commonly recorded for this age and strain of rats.

Necropsy: Congested lungs were noted in one animal at the scheduled necropsy. No macroscopic findings were recorded for all other animals at necropsy.

CONCLUSIONS

The acute oral LD_{50} of CGA219417 300 g/l EC formulation (A14325E) to female rats was in excess of 2000 mg/kg.

The acute oral toxicity was greater than 2000 mg/kg therefore no classification is required for acute oral toxicity of A14325E according to Regulation (EC) No.1272/2008.

(Straube E, 2005a)

CP 7.1.2 Dermal toxicity

Report:	K-CP 7.1.2/01 Straube E (2005a). CGA219417 300 g/l EC formulation (A14325E): Acute Dermal Toxicity Study in Rats. RCC Ltd., Toxicology, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Laboratory Report No. 859443, 23 June 2005. Unpublished. Syngenta File No. CGA219417/1326.

GUIDELINES: OECD 402 (1987): OPPTS 870.1200 (1998): 92/69/EEC B.3 (1992). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

In an acute dermal toxicity study, five male and five female HanRcc:WIST (SPF) rats were treated with CGA219417 300 g/l EC formulation (A14325E) by dermal application at a limit dose of 2000 mg/kg body weight. The undiluted formulation was applied at a dosage volume of 1.98 ml/kg for 24 hours to an area of shaved skin approximately 20 cm2 for males and approximately 16 cm2 for females and covered with a semi-occlusive dressing. After the 24 hour application period, the skin was cleansed with lukewarm tap water.

The animals were examined at least once per day for mortality / viability and clinical signs for a total of 15 days. Body weights were recorded at intervals throughout the study and all animals were given a gross examination post mortem.

There were no mortalities. No clinical signs of toxicity were observed. Slight general erythema was noted in all animals on days 2 and 3 and persisted up to day 6 in 8 animals. Slight crust formation was observed in six animals, starting on or after day 4 but had cleared by day 10. Scaling was seen in 3 females starting on day 5 or later, but had cleared by day 13.

The acute dermal LD_{50} of CGA219417 300 g/l EC formulation (A14325E) to male and female rats is in excess of 2000 mg/kg bw.

The acute dermal toxicity was greater than 2000 mg/kg therefore no classification is required for acute dermal toxicity of A14325E according to Regulation (EC) No.1272/2008.

MATERIALS AND METHODS

Test Material:	CGA219417 (cyprodinil) 300 g/l EC formulation (A14325E)
Description:	Formulation, yellow liquid
Lot/Batch #:	SMU5BP002
Purity:	303 g/l corresponding to 29.9 % w/w
Stability of test compound:	Stable at <30ºC, light protected

Vehicle and/or positive control: None

Test Animals:

Species	Rat
Strain	HanRcc:WIST (SPF)
Age/weight at dosing	Males 8-9 weeks, females 11-12 weeks / males 231-262g, females 187-202g
Source	RCC Ltd., Laboratory Animal Services, CH-4414 Füllinsdorf, Switzerland
Housing	Individually in Makrolon type-3 cages with standard softwood bedding
Acclimatisation period	6 days
Diet	Pelleted standard Provimi Kliba 3433 rat/mouse maintenance diet *ad libitum*
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 22 ± 3°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

In-life dates: Start: 20 April 2005 End: 4 May 2005

Animal assignment and treatment: Five male and five female HanRcc:WIST (SPF) rats were treated with undiluted CGA219417 300 g/l EC formulation (A14325E) by dermal application to an area of shorn skin at a limit dose of 2000 mg/kg. The undiluted formulation was applied at a dosage volume of 1.98 ml/kg for 24 hours to an area of shaved skin approximately 20 cm2 for males and approximately 16 cm2 for females and covered with a semi-occlusive dressing. After the 24 hour application period, the skin was cleansed with lukewarm tap water.

The animals were examined daily during the acclimatisation period and mortality, viability and clinical signs were recorded. All animals were examined for clinical signs once during the first 30 minutes after administration and at approximately 1, 2, 3 and 5 hours after administration on day 1 and once daily during test days 2-15. Mortality/viability was recorded once during the first 30 minutes after administration and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2-15. Body weights were recorded on day 1 (prior to administration) and on days 8 and 15. All animals were necropsied and examined macroscopically.

Statistics: The acute dermal LD_{50} was estimated from the mortality data (limit test, no deaths).

RESULTS AND DISCUSSION

Mortality: There were no mortalities.

Clinical observations: No clinical signs were observed during the course of the study. Slight general erythema was noted in all animals on days 2 and 3, persisting up to day 4 or 5 in 7 animals and to day 6 in 1 animal. Slight crust formation was observed in six animals, starting on or after day 4 but had cleared by day 10. Scaling was seen in 3 females starting on day 5 or later, but had cleared by day 13.

Body Weight: The body weights were within the range commonly recorded for this age and strain of rats.

Necropsy: No macroscopic abnormalities were detected in any animal at gross examination *post mortem*.

CONCLUSIONS

The acute dermal LD_{50} of CGA219417 300 g/l EC formulation (A14325E) to male and female rats is in excess of 2000 mg/kg bw.

The acute dermal toxicity was greater than 2000 mg/kg therefore no classification is required for acute dermal toxicity of A14325E according to Regulation (EC) No.1272/2008.

(Straube E, 2005a)

CP 7.1.3 Inhalation toxicity

According to Commission Regulation (EU) No 284/2013, an acute inhalation test must be carried out where the plant protection product:

- is a gas or liquified gas,
- is a smoke generating formulation of fumigant,
- is used with fogging equipment,
- is a vapour releasing plant protection product,
- in supplied in an aerosol dispenser,
- is in the form of a powder or granule containing a significant proportion of particles of diameter < 50µm (> 1% on a weight basis),
- is to be applied from aircraft in cases were inhalation exposure is relevant,
- contains an active substance with a vapour pressure > 1 x 10^{-2} Pa and is to be used in enclosed spaces such as warehoused or glasshouses,
- is to be applied by spraying.

A14325E will be applied by spraying but the nature of application would not be expected to produce inhalable droplets. A14325E will be applied by professional applicators using tractor mounted boom sprays, the spraying will therefore be directed down; therefore ensuring any exposure to the spray dilution is minimal. In addition, neither cyprodinil nor the inert ingredients in the formulation are toxic by the inhalation route (see **Document J confidential information CP 7.4**).

It is concluded that an inhalation study is not required for A14325E.

CP 7.1.4 Skin irritation

Report:	K-CP 7.1.4/01 Straube E (2005b). CGA219417 300 g/l EC formulation (A14325E): Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application). RCC Ltd., Toxicology, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Laboratory Report No. 859444, 23 June 2005. Unpublished. Syngenta File No. CGA219417/1328.

GUIDELINES: OECD 404 (2002): OPPTS 870.2500 (1998): 2004/73/EC B.4 (2004). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

In a primary dermal irritation study, CGA219417 300 g/l EC formulation (A14325E) was applied, undiluted (0.5ml), on a gauze patch, to a 2.5cm x 2.5cm area of shaved, intact skin on each of a group of three (one male and two female), New Zealand White rabbits and covered with semi-occlusive dressings. The dressing was left in place for 4 hours after which it was removed and the skin cleansed with lukewarm tap water. As it was suspected that the test item might produce irritancy, a single animal was treated first. As no corrosive effect was observed after the 4-hour exposure, the test was completed using the two remaining animals for an exposure period of four hours. The skin reactions were scored (according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004) 1, 24, 48 and 72 hours, as well as 7, 10, 14, 17 and 21 days after removal of the dressings.

The application of CGA219417 300 g/l EC formulation (A14325E) to rabbit skin resulted in mild to moderate, early-onset and transient signs of irritation such as erythema, oedema and scaling. These effects were reversible and were no longer evident 17 days after treatment. There were no corrosive effects and no clinical signs were observed. According to the ***Draize (1959)*** classification criteria CGA219417 300 g/l EC formulation (A14325E) is considered to be "moderately irritant" to rabbit skin.

The application of CGA219417 300 g/l EC formulation (A14325E) to the intact skin resulted in mild to moderate, early-onset and transient signs of irritation. These effects were reversible within 17 days. According to the Draize classification criteria this formulation is considered to be moderately irritant to rabbit skin.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) No 1272/2008 as amended. Therefore, no classification is required for skin irritating properties of A14325E.

MATERIALS AND METHODS

Test Material:	CGA219417 (cyprodinil) 300 g/l EC formulation (A14325E)
Description:	Formulation, yellow liquid
Lot/Batch #:	SMU5BP002
Purity:	303 g/l corresponding to 29.9 % w/w
Stability of test compound:	Stable at <30ºC, light protected

Vehicle and/or positive control: None

Test Animals:

Species	Rabbit
Strain	New Zealand White (SPF)
Age/weight at dosing	11-12 weeks / male 2410g, females 2401g, 2460g
Source	Charles River Laboratories France, BP 0109, F-69592 L'Arbresle
Housing	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls.
Acclimatisation period	5 or 6 days
Diet	Pelleted standard Provimi Kliba 3418 rabbit maintenance diet *ad libitum*
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 17-23°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

In-life dates: Start: 5 April 2005 End: 27 April 2005

Animal assignment and treatment: CGA219417 300 g/l EC formulation (A14325E) was applied, undiluted (0.5ml), on a gauze patch, to a 2.5cm x 2.5cm area of shaved, intact skin on each of a group of three (one male and two female), New Zealand White rabbits and covered with semi-occlusive dressings. The dressing was left in place for 4 hours after which it was removed and the skin cleansed with lukewarm tap water. As it was suspected that the test item might produce irritancy, a single animal was treated first. As no corrosive effect was observed after the 4-hour exposure, the test was completed using the two remaining animals for an exposure period of four hours. The skin reactions were scored (according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004) 1, 24, 48 and 72 hours, as well as 7, 10, 14, 17 and 21 days after removal of the dressings.

RESULTS AND DISCUSSION

Very slight to well-defined erythema was noted in all animals from the 1 hour reading to day 7 and persisted as slight erythema in one animal until day 10. Slight oedema was seen in all animals at the 1 hour reading and persisted as very slight to slight oedema in two animals until the 72 hour reading. Scaling was observed in two animals from day 7 to 10 and in the third animal from day 7 to 14. All skins had fully recovered by day 17. There were no corrosive effects seen.

There were no clinical signs of systemic toxicity and no effects on bodyweight.

Table 7.1.4-1: Individual and mean skin irritation scores of CGA219417 300 g/l EC formulation (A14325E) according to the Draize scheme

Time	Erythema			Oedema		
Animal number	**97**	**98**	**99**	**97**	**98**	**99**
after 1 hour	2	2	2	2	2	2
after 24 hours	2	2	1	2	1	0
after 48 hours	2	2	1	2	1	0
after 72 hours	2	2	1	1	1	0
mean score 24-72 h	2.0	2.0	1.0	1.7	1.0	0
after 7 days	1s	1s	1s	0	0	0
after 10 days	0s	1s	0s	0	0	0
after 14 days	0	0	0s	0	0	0
after 17 days	0	0	0	0	0	0
after 21 days	0	0	0	0	0	0

s scaling

CONCLUSIONS

The application of CGA219417 300 g/l EC formulation (A14325E) to the intact skin resulted in mild to moderate, early-onset and transient signs of irritation. These effects were reversible within 17 days. According to the Draize classification criteria this formulation is considered to be moderately irritant to rabbit skin.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) No 1272/2008 as amended. Therefore, no classification is required for skin irritating properties of A14325E.

REFERENCES

Draize JH (1959). Dermal Toxicity. In Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, pp 46-49. Austin, Texas: Association of Food and Drug Officials of the United States.

(Straube E, 2005b)

CP 7.1.5 Eye irritation

Report:	K-CP 7.1.5/01 Straube E (2005c). CGA219417 300 g/l EC formulation (A14325E): Primary Eye Irritation Study in Rabbits. RCC Ltd., Toxicology, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Laboratory Report No. 859446, 23 June 2005. Unpublished. Syngenta File No. CGA219417/1327.

GUIDELINES

OECD 404 (2002): OPPTS 870.2500 (1998): 2004/73/EC B.4 (2004). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

In a primary eye irritation study, 0.1 ml of undiluted CGA219417 300 g/l EC formulation (A14325E) was instilled into the conjunctival sac of the left eye of each of a group of three, young adult (one male and two female) New Zealand White rabbits. A single animal was treated first and as neither a corrosive nor a severe irritant effect was observed after 24 hours, the test was completed using the two remaining animals. The irritation effects were scored according to the scheme in Commission Directive 2004/73/EC, April 29, 2004 at approximately 1, 24, 48 and 72 hours, 7 and 10 days after instillation.

The instillation of CGA219417 300 g/l EC formulation (A14325E) into the eye resulted in mild to moderate, early onset and transient ocular changes, such as reddening of the conjunctivae and sclerae, discharge and chemosis. These effects were reversible and were no longer evident 10 days after treatment. No abnormal findings were observed in the cornea or iris of any animal, there were no signs of corrosion.

Based on the degree of eye reactions, CGA219417 300 g/l EC formulation (A14325E) is non-irritating to eyes.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) No. 1272/2008. Therefore no classification is required for eye irritating properties of A14325E.

MATERIALS AND METHODS

Test Material:	CGA219417 (cyprodinil) 300 g/l EC formulation (A14325E)
Description:	Formulation, yellow liquid
Lot/Batch #:	SMU5BP002
Purity:	303 g/l corresponding to 29.9 % w/w
Stability of test compound:	Stable at <30ºC, light protected

Vehicle and/or positive control: None

Test Animals:

Species	Rabbit
Strain	New Zealand White (SPF)
Age/weight at dosing	Male 11-12 weeks, females 10-11 weeks / male 2407g, females 2135g, 2242g
Source	Charles River Laboratories France, BP 0109, F-69592 L'Arbresle
Housing	Individually in stainless steel cages equipped with feed hoppers and drinking water bowls.
Acclimatisation period	At least 5 days
Diet	Pelleted standard Provimi Kliba 3418 rabbit maintenance diet *ad libitum*
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 17-23°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

In-life dates: Start: 18 April 2005 End: 29 April 2005

Animal assignment and treatment: 0.1 ml of undiluted CGA219417 300 g/l EC formulation (A14325E) was instilled into the conjunctival sac of the left eye of each of a group of three, young adult (one male and two female) New Zealand White rabbits. The right eye was untreated and served as a control. A single animal was treated first and as neither a corrosive nor a severe irritant effect was observed after 24 hours, the test was completed using the two remaining animals. The irritation effects were scored according to the scheme in Commission Directive 2004/73/EC, April 29, 2004 at approximately 1, 24, 48 and 72 hours, 7 and 10 days after instillation. The animals were observed daily for viability/mortality and clinical signs and were weighed at the start of acclimatisation, on the day of instillation and at the end of the observation period.

RESULTS AND DISCUSSION

There were no mortalities and no clinical signs of systemic toxicity. No abnormal findings were seen in the cornea or iris. Slight to moderate reddening of the conjunctivae was noted in all animals from the 1 hour to the 72 hour reading and persisted as slight reddening in two animals until day 7. Obvious chemosis with partial eversion of the lids was observed in all animals one hour after instillation and persisted as slight chemosis in two animals up to the 72 hour examination. Slight to moderate reddening of the sclerae was present in all animals from the 1 hour to the 72 hour reading and persisted as slight reddening in one animal until day 7. Slight to moderate ocular discharge was observed in all animals 1 hour after instillation and persisted as slight ocular discharge in 2 animals until the 24 or 48 hour readings. No abnormal findings were observed in any animal after 10 days. There were no signs of corrosion.

Table 7.1.5-1: Eye irritation scores of CGA219417 300 g/l EC formulation (A14325E) according to the Draize scheme

Time	Cornea			Iris			Conjunctiva					
							Redness			Chemosis		
Animal number	1	2	3	1	2	3	1	2	3	1	2	3
after 1 hour	0eds	0eds	0eds	0	0	0	2	2	2	2	2	2
after 24 hours	0ds	0s	0ds	0	0	0	2	2	2	1	0	1
after 48 hours	0ds	0s	0s	0	0	0	2	2	2	1	0	1
after 72 hours	0s	0s	0s	0	0	0	1	1	1	1	0	1
mean scores 24-72h	0	0	0	0	0	0	1.67	1.67	1.67	1.0	0	1.0
after 7 days	0	0	0s	0	0	0	1	0	1	0	0	0
after 10 days	0	0	0	0	0	0	0	0	0	0	0	0

e partial eversion of the lids, d discharge, s sclerae reddened

CONCLUSIONS

The instillation of CGA219417 300 g/l EC formulation (A14325E) into the rabbit eye resulted in mild to moderate, early-onset and transient ocular changes which were reversible and no longer evident 10 days after treatment.

The mean irritation scores 24 to 72 hours after application were less than the thresholds defined in Regulation (EC) No. 1272/2008. Therefore no classification is required for eye irritating properties of A14325E.

(Straube E, 2005c)

CP 7.1.6 Skin sensitization

Report:	K-CP 7.1.6/01 Straube E (2005d) CGA219417 300 g/l EC formulation (A14325E): Contact Hypersensitivity in Albino Guinea Pigs, Bühler Test (9-induction). RCC Ltd., Toxicology, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland. Laboratory Report No. 859447, 18 August 2005. Unpublished. Syngenta File No. CGA219417/1379.

GUIDELINES: OECD 406 (1992): OPPTS 870.2600 (2003): 96/54/EC B.6 (1996). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

The sensitisation potential of the test substance was assessed using a method based on that described by ***Ritz and Buehler (1980).*** Groups of 20 test and 10 control young adult male Albino Dunkin Hartley CRL:(HA)BR, SPF guinea pigs were used for the main study. Two main procedures were involved; (a) the potential induction of an immune response; (b) a challenge of that response.

In test animals, the induction phase involved a total of 9 topical applications of 0.5 ml of a 10% preparation of the formulation in purified water. Controls were treated in the same way except that purified water was applied for the induction applications.

In the challenge phase, 5% and 1% preparations of the formulation, in purified water, were applied to test and control animals.

A positive control study was conducted using essentially the same methodology and using alpha-hexylcinnamaldehyde (HCA) as the test substance. The test substance was applied as a 50% preparation in PEG 300 in the induction phase (once per week for 3 weeks) and as a 5% preparation in PEG 300 for the challenge phase.

Sixteen (at the 24 hour reading) and five (at the 48 hour reading) out of 20 main study test animals were observed with discrete/patchy to moderate/confluent erythema after the challenge with CGA219417 300 g/l EC formulation (A14325E) at the concentration of 5% in purified water. Discrete/patchy erythema was noted in seven (at the 24 hour reading) and five (at the 48 hour reading) out of 20 test animals when treated with the formulation at 1% in purified water. No skin reactions were seen in the control animals following challenge.

Based on the incidence of skin reactions, CGA219417 300 g/l EC formulation (A14325E) is considered to be a skin sensitiser in the guinea pig.

The sensitisation rate is more than the threshold of significance (15%) set in Regulation (EC) No. 1272/2008. Therefore, H317 classification is required for the skin sensitising properties of A14325E.

MATERIALS AND METHODS

Test Material:	CGA219417 (cyprodinil) 300 g/l EC formulation (A14325E)
Description:	Formulation, yellow liquid
Lot/Batch #:	SMU5BP002
Purity:	303 g/l corresponding to 29.9 % w/w
Stability of test compound:	Stable at <30ºC, light protected

Vehicle and/or positive control: Deionised water

Test Animals:

Species	Guinea Pig
Strain	Albino Dunkin Hartley Guinea Pig, CRL:(HA)BR,SPF
Age/weight at dosing	6-9 weeks / 369-500 g
Source	Charles River Deutschland GmbH, Stolzenseeweg 32-36, D-88353 Kisslegg / Germany
Housing	Individually in Makrolon type-4 cages with standard softwood bedding
Acclimatisation period	19 days
Diet	Pelleted standard Provimi Kliba 3418 guinea pig breeding / maintenance diet *ad libitum*
Water	Community tap water *ad libitum*
Environmental conditions	Temperature: 22±3°C Humidity: 30-70% Air changes: 10-15 per hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

In-life dates: Start: 30 May 2005 End: 30 June 2005

Animal assignment and treatment: Groups of 20 test and 10 control young adult male Albino Dunkin Hartley CRL:(HA)BR, SPF guinea pigs were used for the main study. Two main procedures were involved; (a) the potential induction of an immune response; (b) a challenge of that response.

Induction: In test animals, the induction phase involved the topical application of 0.5 ml of a 10% preparation of the formulation in purified water, in a 25mm Hill Top Chamber, under an occlusive dressing to a shorn area of the scapular region. Dressings were left in place for 6 hours. The induction process was repeated at the same site during the next two weeks giving a total of nine 6-hour exposures, three per week. Skin sites were examined approximately 24 hours following removal of the dressings. The animals were left untreated for nine days after the final induction exposure, prior to challenge. Controls were treated in the same way except that purified water was applied for the induction applications.

Challenge: In the challenge phase, 5% and 1% preparations of the formulation, in purified water, were applied for approximately 6 hours to naïve skin sites of both test and control animals. The preparations (0.5 ml) were applied using Hill Top Chambers as for the induction phase.

Skin sites were examined 1 and 2 days after removal of the dressings.

Positive control study: A positive control study was conducted using essentially the same methodology and using alpha-hexylcinnamaldehyde (HCA) as the test substance. The test substance was applied as a 50% preparation in PEG 300 in the induction phase to the test animals (3 induction applications only, 7 days apart), controls were untreated during the induction phase. Test and control animals were challenged with a 5% preparation in PEG 300.

RESULTS AND DISCUSSION

One control animal showed deep laboured respiration on days 11 and 12 and was removed from the study prior to the sixth induction application.

Induction reactions and duration: Discrete or patchy to moderate and confluent erythema was seen in all the test animals at some point during the induction phase, and in some cases was accompanied by scale formation. No erythema or other skin effects were seen in the control animals.

Challenge reactions and duration: Following challenge at 5%, discrete/patchy to moderate/confluent erythema was observed in sixteen (at the 24 hour reading) and five (at the 48 hour reading) out of twenty test animals. Following challenge at 1%, discrete/patchy erythema was noted in seven (at the 24 hour reading) and five (at the 48 hour reading) out of twenty test animals. There were no skin reactions in the control animals following challenge.

Positive control: Following challenge with 5% HCA, eleven out of twenty test animals had discrete/patchy erythema at the 24 hour reading and four test animals had discrete/patchy to moderate/confluent erythema at the 48 hour reading. No skin reactions were seen in the vehicle controls. The sensitivity of the test system was, therefore, confirmed.

Table 7.1.6-1: Buehler test: Number of animals with signs of allergic skin reactions

			Scored after:	
		Challenge concentration	24 hours	48 hours
Main study	Test item group	5%	16/20	5/20
		1%	7/20	5/20
	Vehicle control	5%	0/9	0/9
		1%	0/9	0/9
Positive control study	Test item group	5%	11/20	4/20
	Vehicle control	5%	0/10	0/10

CONCLUSIONS

Based on the results of this study, CGA219417 300 g/l EC formulation (A14325E) is considered to be a skin sensitiser in the guinea pig.

The sensitisation rate is more than the threshold of significance (15%) set in Regulation (EC) No. 1272/2008. Therefore, H317 classification is required for the skin sensitising properties of A14325E.

REFERENCES

Ritz HL and Buehler EV. Current Concepts Cutaneous Toxicity, ed. Drill VA and Lazar T (Academic Press, 1980) pp. 25-40: Planning, Conduct and Interpretation of Guinea Pig Sensitization Patch Tests.

(Straube E, 2005d)

CP 7.1.7 Supplementary studies on the plant protection product

No additional studies have been conducted. A14325E is a cyprodinil solo formulation and its potential acute toxicity has been fully addressed as presented in Sections 7.1.1-7.1.6. Additional studies to address potential health effects are considered to be unnecessary.

CP 7.1.8 Supplementary studies for combinations of plant protection product

This product does not contain recommendations for combinations of plant protection products therefore supplementary studies are not required.

CP 7.2 Data on Exposure

CP 7.2.1 Operator exposure

Cyprodinil

The potential dermal absorption of cyprodinil from A14325E through human skin has been evaluated in *in vitro* studies using human and rat epidermal membranes and an *in vivo* study in the rat (refer to CP 7.3). The dermal absorption figures from this study are included in Table 7.2.1-1.

Table 7.2.1-1: EU Conclusions - Toxicological endpoints of cyprodinil required for evaluation of operator, re-entry worker, bystander and residential risk

Endpoint	EU agreed endpoint (Cyprodinil: EFSA Scientific Report (2005) 51, 1-78)	Proposed endpoint
AOEL (mg/kg bw/day)	0.03 mg/kg bw/day	-
Dermal absorption of concentrate (300g/L)	-	0.9 %
Dermal absorption of in-use dilution 1 (1.5g/L)	-	6 %
Oral absorption	>80 %	-

The formulation A14325E is an emulsifiable concentrate (EC) containing 300 g/L cyprodinil which is intended to be used on barley as a fungicide (Table 7.2.1-2).

Table 7.2.1-2: Summary of critical use patterns (i.e. worst case) for use of A14325E

Representative Crop (field)	Application equipment	Application rate (g a.s./ha)	Spray dilution (L/ha)	Number applications	Application Interval (days)
Barley	Tractor-mounted boom sprayer	450	150-400	2	14

Risk assessment for operator

Operator exposure was assessed against the AOEL of cyprodinil. Operator exposure was modelled using the ***German BBA[1] and the UK POEM[2] model.*** An additional assessment according to the EFSA guidance[3] is presented, as requested by the RMS during their review, although this guidance was not in force at the time of this submission.

Estimations of operator exposure have been undertaken for A14325E using the critical uses (Table 7.2.1-2).

[1] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ("German Model").

[2] Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992, 2007 version. ("UK POEM").

[3] EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products[EFSA Journal 2014;12(10):3874 [55 pp.]

A summary of the estimated operator exposure to cyprodinil is presented in Table 7.2.1-3.

Table 7.2.1-3: Summary of estimated operator exposure to cyprodinil

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of AOEL (0.03 mg/kg bw/day)
Tractor-mounted boom sprayer application outdoors to low crops Application rate: 1.5 L A14325E/ha (450 g cyprodinil/ha)			
German Model • 20 ha/day • 70 kg operator	no PPE	0.01872	**62.4**
	Gloves during mixing/loading and application, coverall and sturdy footwear during application	0.001343	**4.5**
UK POEM • 50 ha/day, 6 h/day • 150 L/ha • 60 kg operator	no PPE	0.1457	**485.7**
	Gloves during mixing/loading and application	0.02415	**80.5**
EFSA model • 50 ha/day • 150 L/ha • 60 kg operator	no PPE	0.0120	**40**
	Gloves during mixing/loading and application	0.0009	**3**

No PPE German Model: Operator wearing T-shirt and shorts
UK POEM: Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves
EFSA model: Operator wearing coveralls or long-sleeved jackets and trousers

CONCLUSION

According to the German and EFSA model calculations, it can be concluded that the risk for the operator using A14325E for proposed uses is acceptable even if no PPE is worn.

According to the UK POEM model calculations, it can be concluded that the risk for the operator using A14325E for proposed uses is acceptable with the use of personal protective equipment, i.e. chemical resistant gloves during mixing/loading and application.

CP 7.2.1.1 Estimation of operator exposure

The following parameters were used in the operator exposure assessment:

UK POEM:

Application method:	Tractor-mounted boom sprayer, low target
Treated area:	50 ha/day
Pack sizes:	10 L 63 mm opening
Max. dose rate:	450 g cyprodinil/ha (1.5 L product/ha)
Operator body weight:	60 kg
No PPE:	Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves
PPE:	Gloves are worn during mixing/loading and application

German Model:

Application method:	Tractor-mounted boom sprayer, low target
Treated area:	20 ha/day
Max. dose rate:	450 g cyprodinil/ha (1.5 L product/ha)
Operator body weight:	70 kg
No PPE:	Operator wearing T-shirt and shorts
PPE:	Gloves are worn during mixing/loading and application, coverall and sturdy footwear during application

EFSA Model:

Application method:	Tractor-mounted boom sprayer, low target
Treated area:	50 ha/day
Max. dose rate:	450 g cyprodinil/ha (1.5L product/ha)
Operator body weight:	60 kg
No PPE:	Operator wearing coveralls or long-sleeved jackets and trousers
PPE:	Gloves are worn during mixing/loading and application

The detailed estimation of exposure is provided in Appendix 1. A summary is provided in Section CP 7.2.1.

CP 7.2.1.2 Measurement of operator exposure

Not required since model calculations predict the systemic exposure to cyprodinil to be within the AOEL with the use of personal protective equipment.

CP 7.2.2 Bystander and resident exposure

Risk assessment for bystander and resident

Estimations of bystander and residential exposure have been undertaken for A14325E using the critical uses (Table 7.2.1-2) and the German guidance paper[4]. An additional assessment according to the EFSA guidance[3] is presented, as requested by the RMS during their review, although this guidance was not in force at the time of this submission and according to the EFSA guidance. All assumptions made in the following are quoted in this guidance paper. Tractor-mounted boom sprayer application has been presented as a worst case scenario.

The EFSA guidance for bystander assessment compares exposure to an acute endpoint. As guidance on the derivation of acute endpoints for non-dietary human exposure has not yet been published, it is not possible to carry out an acute risk assessment for bystanders at this time. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission[5]. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by

[4] Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application; S. Martin et al.; J. Verbr. Lebensm. 3 (2008): 272 – 281, 1661-5751/08/030272-10 DOI 10.1007/s00003-008-0361-5, ©Birkhäuser Verlag, Basel, 2008.

[5] Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013

- the European Food Safety Authority[6], and
- the European Commission Standing Committee[7].

Therefore, this waiver is presented in line with the Guidance of the European Commission.

A risk assessment for residents according to EFSA guidance is provided.

A summary of the estimated bystander/resident exposure to cyprodinil is presented in Table 7.2.2-1.

Table 7.2.2-1: Estimated bystander/residential exposure to cyprodinil and % of the AOEL

	cyprodinil (AOEL = 0.03 mg/kg bw/day)	
Bystander exposure – German model	Adult	Child
Dermal exposure (mg/kg bw/day)	0.0001305	0.0001018
Inhalation exposure (mg/kg bw/day)	0.0000021	0.0000044
Total systemic exposure (mg/kg bw/day)	**0.0001362**	**0.0001063**
% of AOEL	**0.44**	**0.35**
Residential exposure – German model		
Dermal exposure (mg/kg bw/day)	0.0000158	0.0000209
Inhalation exposure (mg/kg bw/day)	0.0002762	0.0005146
Hand to mouth transfer (mg/kg bw/day)		0.0000267
Object to mouth transfer (mg/kg bw/day)		0.0000067
Total systemic exposure (mg/kg bw/day)	**0.0002919**	**0.0005689**
% of AOEL	**0.97**	**1.90**
Residential exposure – EFSA model		
Spray drift (75th %ile) (mg/kg bw/day)	0.0049	0.0012
Vapour (75th %ile) (mg/kg bw/day)	0.0011	0.0002
Surface deposits (75th %ile) (mg/kg bw/day)	0.0013	0.0003
Entry into treated crops (75th %ile) (mg/kg bw/day)	0.0079	0.0044
All Pathways (mean) (mg/kg bw/day)	**0.0110**	**0.0045**
% of AOEL	**37**	**15**

CONCLUSION

It is concluded that there is no undue risk to any bystander or resident from cyprodinil during and following local application of A14325E.

[6] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874)
[7] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015

CP 7.2.2.1 Estimation of bystander and resident exposure

Bystander Assessment

The following parameters were used in the bystander assessment (German approach):

- Application method: Tractor-mounted boom sprayer
- Application rate: 450 g cyprodinil/ha (1.5 L product/ha)
- Drift deposition: 0.29% at 10 m
- Exposure duration: 5 minutes
- Exposed body surface: 1 m² for an adult and 0.21 m² for children
- Dermal absorption: 6% for cyprodinil
- Body weights: 60 kg for adults and 16.15 kg for children.

Resident Assessment

The following parameters were used in the resident assessment (German approach):

- Application rate: 450 g cyprodinil/ha (1.5 L product/ha) – 2 application
- Drift deposition: 0.29% at 10 m
- The vapour pressure: 4.7 – 5.1 x 10^{-4} Pa @ 25°C, therefore cyprodinil is considered as semi-volatile
- Exposure duration: 2 hours for dermal exposure
- In the case of semi-volatile or volatile active substances, the inhalation exposure duration is 24 hours
- Dermal absorption: 6% for cyprodinil
- Body weights: 60 kg for adults and 16.15 kg for children.

According to EFSA guidance:

- Application rate: 450 g cyprodinil/ha (1.5 L product/ha) – 2 applications, interval14 days
- Drift deposition on surfaces: 5.6% (75^{th} %ile) or 4.1% (mean) at 2 m
- The vapour pressure: 4.7 – 5.1 x 10^{-4} Pa @ 25°C, therefore cyprodinil is considered as low-volatile in EFSA approach.
- Exposure duration: 2 hours for dermal exposure, 24 hours for inhalation exposure, 0.25 hours for re-entry into treated crops
- Dermal absorption: 6% for cyprodinil
- Body weights: 60 kg for adults and 10 kg for children

The detailed estimation of exposure is provided in Appendix 1. A summary is provided in Section CP 7.2.2.

CP 7.2.2.2 Measurement of bystander and resident exposure

Measurement of bystander exposure is not required since model estimations predict the systemic exposure to cyprodinil to be within the AOEL.

CP 7.2.3 Worker exposure

Risk assessment for worker

Estimations of worker exposure have been undertaken for A14325E using the critical uses (Table 7.2.1-2) and the generic re-entry exposure approach approved for use in Germany[8] and default parameters from the EUROPOEM II re-entry report[9]. An additional assessment according to the EFSA guidance[3] is presented, as requested by the RMS during their review, although this guidance was not in force at the time of this submission. Inspection has been presented as a worst case scenario.

A summary of the estimated worker exposure to cyprodinil is presented in Table 7.2.3-1.

Table 7.2.3-1: Estimated worker exposure to cyprodinil

	Exposure parameter		
Exposure scenario	**AOEL [mg/kg bw/day]**	**Absorbed dose [mg/kg bw/day]**	**% of AOEL**
		unprotected worker[1]	
Inspection – according to German approach	0.03	0.0138	46.1
Inspection – according to EFSA guidance	0.03	0.0065	22
		protected worker[2]	
Inspection – according to German approach	0.03	0.00254	8.46

1) Worker wearing shoes, socks, long-sleeved shirt, and long trousers
2) Worker wearing shoes, socks, long-sleeved shirt, long trousers and gloves

CONCLUSION

It is concluded that there is no unacceptable risk anticipated from cyprodinil for the worker wearing adequate work clothing, when re-entering crops treated with A14325E.

CP 7.2.3.1 Estimation of worker exposure

Since the product A14325E is a fungicide in cereals where manual activities are not performed by re-entry workers during the growth stage of the intended application, mainly visual inspections will be carried out by a professional worker. Additionally, since the worker is expected to be aware what was applied, the use of protective gloves can be considered acceptable for crop inspection activities.

It has to be noted that no specific TC for re-entry activities performed in cereals is available from EUROPOEM II. Therefore, as surrogate value it is proposed with this evaluation to use the TC of 2500 cm^2/h established for harvesting vegetables (reach and pick scenario). This can be regarded as a conservative approach.

The following parameters were used in the re-entry worker assessment:

- Application rate: 450 g cyprodinil/ha (1.5 L product/ha) – 2 applications

[8] Krebs B. *et al*., (1998) Uniform Principles for Safeguarding the Health of Worker Re-entering Crop Growing Areas after Application of Plant Protection Products. (Bulletin of the German Plant Protection Service) Nachrichtenblatt des Deutschen Pflanzenschutzdienstes.10/98;Vol 50, Verlag Eugen Ulmer , Stuttgart, Germany
[9] Post-Application Exposure of Workers to Pesticides in Agriculture – Report of the Re-entry Working Group. EUROPOEM II Project, FAIR3-CT96-1406. December 2002.

- Dermal absorption: 6% for cyprodinil
- Body weight: 60 kg

The following parameters from the EUROPOEM II re-entry report were used in the assessment:

- DFR: 3 µg a.s./cm²/kg a.s. applied
- TC: 2560 cm^2/hr for scouting (to account for body actual exposure + hands potential exposure with no gloves)
- Working time: A daily working time of 2 hours is assumed for scouting.

The detailed estimation of exposure is provided in Appendix 1. A summary is provided in Section CP 7.2.3.

CP 7.2.3.2 Measurement of worker exposure

Measurement of worker exposure is not required since model estimations predict the systemic exposure to cyprodinil to be within the AOEL.

CP 7.3 Dermal Absorption

The dermal absorption of cyprodinil from A14325E has been investigated in an *in vitro* studies using human and rat skin, and an *in vivo* study in the rat.

Cyprodinil

Table 7.3-1: Summary of dermal absorption studies for cyprodinil in product A14325E

Test	% of applied dose		Reference
	Concentrate	Spray dilution 1 (1.5 g/L)	
***In vivo* (rat)**	21	28	(Smith A, 2005)
***In vitro* (human)**	0.8	17	(Johnson I, 2005)
***In vitro* (rat)**	20	84	(Johnson I, 2005a)

Following initial review the RMS questioned the dermal absorption values being proposed by Syngenta for cyprodinil (see below):-

"The dermal absorption values selected by the applicant are not clearly indicated. In the in vivo dermal absorption study, rats were exposed during 6 hours whereas in the in vitro dermal absorption studies, skin samples were exposed during 24 hours.

According to the EFSA guideline on dermal absorption, exposure durations should be comparable. Exposure durations are too different between in vivo and in vitro studies, so only the in vitro dermal absorption study on human skin will be used to establish dermal absorption of Cyprodinil in the preparation A14325E."

Syngenta acknowledge that the exposure duration between the *in vitro* dermal absorption studies and the *in vivo* study are different, a 24 hour exposure versus a 6 hour exposure, respectively. However, the EFSA guidance on dermal absorption (EFSA, 2012) states that if the *in vitro* studies are not well matched then the possibility of a comparison of the relative dermal absorptions should be very carefully evaluated, as oppose to basing the risk assessment solely on the human *in vitro* dermal absorption study.

The EFSA guidance on dermal absorption (EFSA, 2012) advocates that the exposure should mimic a working day (e.g. 6-10 hours) with sampling for up to 24 hours *in vitro* and a minimum of 96 hours *in vivo*. Although the proposed dermal absorption values are based a triple pack calculation, the *in vitro* studies used as part of this calculation have an exposure period which is 4 times greater than the EFSA recommendation. Therefore, the proposed values of 0.9% and 6% for the concentrate and spray dilution, respectively, already have a degree of conservatism built in.

For clarity Syngenta has supplied additional tables (Tables 7.3-8, 7.3-12 and 7.3-18) within the respective study summaries (K-CP 7.3/01, K-CP 7.3/02 and K-CP 7.3/03) to clearly indicate the values used to calculate the below triple pack dermal absorption position:

The dermal absorption values used in the evaluation of operator, worker, bystander and residential risk (CP 7.2) have been evaluated in accordance with the EFSA dermal absorption guidance (EFSA, 2012); although, these studies were conducted prior to the introduction of this guidance document. The human *in vivo* dermal absorption values were calculated based on the values in Table 7.3-1 using the equation below:

Human *in vivo* = (Human *in vitro*% × Rat *in vivo*%) / Rat *in vitro*%

To derive a final rounded position of:

Concentrate = 0.9 %
Spray dilution 1 (1.5 g/L) = 6 %

Report:	K-CP 7.3/01 Smith A (2005) CGA219417 300 g/l EC formulation (A14325E): *In Vivo* Dermal Penetration Study In The Rat. Syngenta CTL, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK. Report No. CTL/UR0863/Regulatory/Report, issue date 31 August 2005. Unpublished. Syngenta File No. CGA219417/1380.

Guidelines: OECD 427 (2004). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

In an *in vivo* dermal absorption study, [^{14}C]-CGA219417 (purity 99.2%), formulated as a 300 g/L EC concentrate (A14325E) and a nominal 1/200 aqueous dilution thereof, was administered to 2 groups of 16 male rats (Han Wistar (HsdBrlHan:WIST)). Measured amounts (100 µl) of the formulation concentrate and 1/200 aqueous dilution were applied to 10 cm^2 of skin, corresponding to nominal doses of 30 mg/rat and 0.15 mg/rat respectively. After a 6 hour exposure interval, the application sites of all rats were washed and groups of 4 rats were terminated at 6, 24, 72 and 120 hours after dosing.

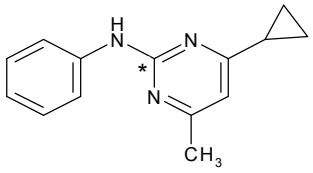
In the experiment with the formulation concentrate, following a 6 hour exposure period, 83% of the applied radioactivity was removed from the skin surface by a mild aqueous wash. The percentage of CGA219417 absorbed amounted to 3.2% of dose after 6 hours, 4.0% after 24 hours, 8.9% after 72 hours and 8.4% after 120 hours.

In the experiment with the 1/200 spray strength dilution, 65% of the applied radioactivity was removed by a mild aqueous wash following a 6 hour exposure period. Approximately 11% of the dose remained bound to the *stratum corneum*, which declined to *circa* 1.4% after 120 hours. The percentage of CGA219417 absorbed from this spray strength dilution accounted for 11.2% of dose after 6 hours, 14.6% after 24 hours, 19.5% after 72 hours and 18.1% after 120 hours.

Dermal absorption from the formulation concentrate over an interval of 6 hours is most relevant to mixer/loaders. However, the exposure over 120 hours is taken as this represents the longest exposure. The absorption figure of 8.9% is therefore the appropriate value for use in risk assessments for short-term exposure.

Dermal absorption from the spray strength dilution over an interval of 6 hours is most relevant to spray operators, but again the exposure over 120 hours is taken as this represents the longest exposure. Therefore an absorption figure of 19.5% is the appropriate value for use in risk assessments for the 1/200 aqueous dilution, corresponding to an application rate of 150 g a.i./hL.

MATERIALS AND METHODS

Test Material:	CGA219417
Description:	Technical
Lot/Batch #:	P.012011
Purity:	99.2%
CAS#:	121552-61-2
Stability of test compound:	Expiry date April 2008
Radiolabelled Test Material:	[^{14}C]-CGA219417
Specific activity:	3.75 MBq/mg
Radiochemical purity:	>98%
Source:	Syngenta Crop Protection AG, Basel, Switzerland
Lot/Batch number:	Not reported
Structure:	

* position of label

Vehicle/Solvent Used:	
Representative formulation:	A14325E
Formulation type:	300 g/l EC (emulsion concentrate)
Blank formulation:	A14325E blank formulation containing all the components of formulation A14325E, except for the active ingredient.
Dose vehicle for spray dilutions:	Water

Relevance of Test material to Proposed Formulation: The doses were prepared to simulate the formulation concentrate and a nominal 1/200 aqueous dilution. The doses were therefore identical to the proposed formulation and a representative in-use spray strength dilution.

Test Animals:

Species:	Rat
Strain:	Han Wistar (HsdBrlHan:WIST)
Age/weight at dosing:	Weight range 200-250g. Age 6-8 weeks
Source:	Harlan UK, Shaw's Farm, Blackthorn, Bicester, Oxon, OX6 0TP
Housing:	In groups in stock cages during the acclimatisation period. Individually in metabolism cages for duration of study.
Acclimatisation period:	8 days
Diet:	Rat and Mouse No.1 maintenance diet, Special Diet Services, Stepfield, Witham, Essex, UK *ad libitum*
Water:	Tap water *ad libitum*
Environmental conditions:	Temperature: 22 ± 3°C Humidity: 30 - 70% Air changes: At least 15 changes/hour Photoperiod: 12 hours light / 12 hours dark

Study Design and Methods

Study dates: Start: 07 June 2005 End: 06 July 2005

Dose rationale: The doses and intervals of exposure were selected to represent typical exposures to the formulation concentrate and a representative in-use aqueous spray strength dilution of 1/200, corresponding to an application rate of 150 g a.i./hL.

Nominal doses: 30 and 0.15 mg a.i./10 cm^2 skin.

Achieved doses: 29.059 and 0.141 mg a.i./10 cm^2 skin. The achieved doses are the group means of the calculated dose for each rat at each dose level.

Dose volume: 10 µl/cm^2 skin.

Duration of exposures (time from dose to skin wash): 6 hours.

Termination periods (time from dose to death): 6, 24, 72 and 120 hours. For each dose level, one sub-group of 4 rats was skin washed and killed immediately following a 6-hour exposure interval. The remaining rats were skin washed after 6 hours and sub-groups of 4 rats killed after 24, 72 and 120 hours.

Number of animals/group: 16 rats per dose level.

Animal Preparation: On the day before dosing, the fur from behind both shoulders of each rat was clipped and the exposed skin swabbed with acetone to remove sebum. To define each application site, an acetal plastic O-ring with screw thread cover was attached to the clipped skin behind each shoulder using cyanoacrylate glue. The screw thread cover held in place a nylon gauze (100 µm mesh) cover. Care was taken to avoid the inclusion of any damaged skin within each defined application site. A strip of non-occlusive elasticated bandage was placed around the rat and over the application devices to hold them in place. The total area of skin defined for dose application to each rat was 10 cm^2 per rat, comprising two sites each of nominally 5 cm^2.

Dose Preparation, Administration and Quantification:

Preparation: Doses were prepared on the day prior to dosing. The stability of the active ingredient in the formulation was confirmed after dosing.

The formulation concentrate was prepared by mixing the required amount of unlabelled technical grade CGA219417 and [^{14}C]-CGA219417 with an appropriate volume of the blank formulation.

The 1/200 aqueous dilution was prepared by mixing the required amount of [^{14}C]-CGA219417 with appropriate volumes of the blank formulation and water.

Application: The required volume of the dose preparation was applied and spread evenly across the surface each defined skin site using a positive displacement pipette. For each dose preparation, 50 µl was applied to each 5 cm^2 application site, equivalent to 100 µl per rat. Each application site was covered for the duration of the exposure interval by a charcoal filter and a nylon gauze cover. A strip of non-occlusive bandage was placed around the rat and over the application devices to hold them in place.

Quantification: The radiochemical purity of the [^{14}C]-CGA219417 was determined by TLC prior to dose preparation and in each dose preparation after dosing. The specific activity and homogeneity of the [^{14}C]-CGA219417 in each dose preparation was determined by LSC prior to dosing.

For each dose preparation, duplicate aliquots of the dose preparation were taken for analysis prior to, during and after dosing and the pair of pipette tips used to dispense each dose sample retained for extraction and analysis. Similarly, the pair of pipette tips used to administer the dose to each rat was also retained for extraction and analysis. The dose for each individual rat was calculated from the mean of the bracketing dose samples plus the radioactivity on the dose sample pipette tips, minus the radioactivity on the pipette tips used to dose that rat. Dose preparation details are summarised in the table below.

Table 7.3-42: Dose preparation details

Dose Level	Amount of compound in dose preparation		Specific Activity (MBq/mg)	Nominal Dose (mg/10 cm^2)	Achieved Dose (mg/10 cm^2)
	Radiolabelled	Non-labelled			
Formulation concentrate	8.0818 mg (30.3 MBq)	1803.9 mg	0.017	30	29.059
1/200 dilution	13.924 mg (52.2 MBq)	0.0 mg	3.75	0.15	0.141

Skin Wash (Pre-Sacrifice): For each dose level, sub-groups of 4 rats were skin-washed and terminated (i) immediately after a 6 hour exposure interval, (ii) 24 hours after dosing, following an interim skin-wash after 6 hours, (iii) 72 hours after dosing, following interim skin-washes after 6 hours and 48 hours and (iv) 120 hours after dosing, following interim skin-washes after 6 hours and 48 hours.

Interim skin-washes were conducted with the rat un-anaesthetised. Terminal skin-washes were conducted with the rat lightly anaesthetised using halothane Ph Eur vapour.

Each rat was removed from its cage and anaesthetised if appropriate. The bandage was removed and retained for analysis. The gauze covers and charcoal filters were removed and retained and each application site was washed using nominally 6 pieces of natural sponges pre-wetted with a 3% aqueous solution of Dove dishwashing liquid (Lever Brother Co.) and 6 with water, followed by two dry sponges to remove any residual water. Care was taken to avoid the transfer of test substance from the skin surface to the O-rings. All of the sponges used for each subject were retained for analysis.

Following interim skin-washing, the gauze covers were re-attached, a new elasticated bandage was fitted and the animal was returned to the same metabolism cage. Any urine and faeces excreted during the washing procedure were collected with the respective excreta collection.

Sample Collection: Following terminal skin washing, rats were exsanguinated by cardiac puncture under terminal anaesthesia. Each blood sample was divided between two pre-weighed heparinised tubes, which

were weighed as a pair before one was centrifuged to separate plasma. The skin beneath each application site, together with the O-rings and a surrounding annular ring of untreated skin, was excised and pinned out on a board. The O-rings were then detached and retained with the protective covers for each rat. The skin beneath each O-ring, together with a surrounding annular ring of untreated skin, was washed and dried with additional sponges, and these sponges were retained with the sponges used previously for washing each rat. Using adhesive, tape the application skin site was tape-stripped to remove successive layers of the *stratum corneum* until the epidermis was visible. The adhesive tape with attached *stratum corneum* from both application sites and the residual skin were retained for analysis. Any urine present in the bladder was collected and added to the corresponding excreted sample. The gastrointestinal tract and contents was removed from each rat and retained for analysis. The residual carcass was retained for analysis.

For the duration of each experiment, urine and faeces were collected from each cage at approximately 6, 24, 48, 72, 96 and 120 hours. Urine and faeces were frozen upon excretion by collection over solid carbon dioxide. An ethanol: water (1:1 v/v) cage wash was collected at the termination of each experiment.

Sample Preparation and Analysis: Urine and faeces samples were stored at approximately -20°C and cage washes were refrigerated prior to analysis. Blood samples were refrigerated prior to analysis, and tissue samples were stored with the residual carcasses at approximately
-20°C.

Details of sample preparation are provided in the table below.

Table 7.3-~~2~~3: Sample Preparation Details

Sample type	Preparation method
Diluted solutions of the dose preparation, urine, cage wash, plasma and other solutions, including solvent extracts and tissue digests.	Aliquots analysed directly by liquid scintillation counting (LSC).
Faeces	Samples were mixed with water to give a homogenous paste and aliquots analysed by sample oxidation.
Dose pipette tips, O-rings and gauze covers, charcoal covers and bandages.	Samples were extracted with ethanol and aliquots of the extracts analysed by liquid scintillation counting.
Sponges used to wash application sites, *stratum corneum* on tape strips, whole blood and skin.	Solubilised in Soluene tissue digestant and aliquots analysed by liquid scintillation counting.
Gastrointestinal tract and contents	Samples were homogenised and aliquots analysed by sample oxidation.
Residual carcasses	Solubilised in tissue digestant at 40°C and aliquots analysed by liquid scintillation counting.

Radioactivity in samples was analysed by liquid scintillation counting (LSC). LSC results were corrected for background activity and counting efficiency using [^{133}Ba] as the external source. Disintegration per minute (dpm) values were calculated using the appropriate instrument-stored quench correction data. Typical limit of detection (LOD) values are summarised in the table below for sample types counted using two different quench correction curves.

Table 7.3-34: Typical limit of detection values

Dose level	Typical limit of detection (LOD) values	
	Direct LSC (µg equiv CGA219417)	Oxidised samples (µg equiv CGA219417)
Formulation concentrate	0.01999 µg	0.04455 µg
1/200 aqueous dilution	0.00009 µg	0.00016 µg

Total amounts of radioactivity in samples were reported as a percentage of the total dose and as µg CGA219417 equivalents.

RESULTS AND DISCUSSION

Signs and Symptoms of Toxicity: For both dose levels, no clinical signs were observed over the duration of the experiment.

Summary Tables: Group mean results showing the distribution of radioactivity after 6, 24, 72 and 120 hours are presented as percentages of the applied dose in the tables below for the formulation concentrate and the 1/200 aqueous dilution.

Table 7.3-45: Mean distribution of [^{14}C]-CGA219417 residues following the application of the A14325E formulation concentrate to skin at a dose level of 29.059 mg/10 cm^2.

	Recovery (% of applied dose)			
	6 hours (n=4)	24 hour (n=2)	72 hours (n=4)	120 hours (n=4)
6 hour skin wash		83.00	72.66	84.12
48 hour interim skin wash			0.37	0.21
Terminal skin wash	83.50	1.56	0.31	0.05
O-rings	4.36	2.16	1.39	0.45
Covers	0.06	0.04	0.05	0.03
Bandages	<1.13	2.58	11.18	3.83
Total unabsorbed	**89.04**	**89.33**	**85.96**	**88.69**
Stratum corneum	1.00	0.93	0.49	0.21
Application site skin	3.86	0.95	2.62	0.11
Total potentially absorbable	**4.86**	**1.88**	**3.10**	**0.33**
Urine	0.31	0.93	4.07	4.47
Faeces	<0.02	0.84	<3.09	2.72
Cage wash		0.03	0.28	0.33
Terminal cage wash	0.03	0.27	0.16	<0.24
Carcass + blood	<2.38	<1.31	<1.13	<0.51
Gastrointestinal tract + contents	0.42	0.64	0.19	0.13
Total absorbed dose	**3.16**	**4.02**	**8.92**	**8.40**
Total recovered	**97.06**	**92.23**	**97.98**	**97.40**

Table 7.3-~~56~~: Mean distribution of [^{14}C]-CGA219417 residues following the application of a 1/200 aqueous dilution of the A14325E formulation concentrate to skin at a dose level of 0.141 mg/10 cm^2.

	Recovery (% of applied dose)			
	6 hours (n=4)	**24 hour (n=4)**	**72 hours (n=4)**	**120 hours (n=4)**
6 hour skin wash		75.57	72.01	73.64
48 hour interim skin wash			0.68	0.68
Terminal skin wash	65.33	2.01	0.27	0.19
O-rings	1.69	0.70	0.36	0.30
Covers	0.35	0.29	1.25	0.45
Bandages	0.02	0.12	0.32	0.28
Total unabsorbed	**67.39**	**78.69**	**74.90**	**75.54**
Stratum corneum	10.92	2.75	1.34	1.41
Application site skin	3.76	0.41	0.16	0.07
Total potentially absorbable	**14.68**	**3.16**	**1.50**	**1.49**
Urine	2.90	7.47	9.28	9.37
Faeces	0.14	4.65	8.14	7.75
Cage wash		0.24	1.63	0.72
Terminal cage wash	0.26	0.64	0.12	0.06
Carcass + blood	4.02	<0.62	<0.17	<0.13
Gastrointestinal tract + contents	3.84	0.96	0.10	0.04
Total absorbed dose	**11.16**	**14.59**	**19.45**	**18.08**
Total recovered	**93.23**	**96.44**	**95.84**	**95.10**

Table 7.3-~~67~~: Concentration of [^{14}C]-CGA219417 residues in whole blood and plasma following the application of the A14325E formulation concentrate and a 1/200 aqueous dilution to skin.

Exposure time	**Concentration (µg equiv CGA219417/g)**			
	Formulation concentrate		**1/200 dilution**	
	Whole blood	**Plasma**	**Whole blood**	**Plasma**
6 hours	<0.359	0.760	0.018	0.032
24 hours	<0.310	0.542	<0.002	0.003
72 hours	<0.282	<0.128	<0.003	<0.001
120 hours	<0.273	<0.100	<0.003	<0.001

Total Absorbed Dose: The absorbed dose included the radioactivity in urine, faeces, cage wash, gastrointestinal tract including contents and in the residual carcass. The reported carcass values include measurements of radioactivity in the blood samples collected at termination. Radioactivity recovered from the application site skin washes, the O-rings, covers and bandages was considered to be unabsorbed. Radioactivity present in the application site skin and *stratum corneum* was considered to be potentially absorbable as it is recognised that some of this material may be absorbed beyond the duration of exposure investigated, however these values have not been included in the calculation of total absorbed dose values.

Recovery of the applied dose was acceptable, with mean percentage recoveries of 92-98% for the formulation concentrate and 93-96% for the 1/200 aqueous dilution. Results were not adjusted for incomplete recovery of the applied dose. Values at or below the limit of detection were included in the calculations as being equal to the limit of detection.

Absorption of [^{14}C]-CGA219417 following dermal exposure to the formulation concentrate or the 1/200 aqueous dilution was limited.

Following dermal exposure to the formulation concentrate for 6 hours, 72-85% of the applied dose was readily removed from the skin surface by mild skin washing. Subsequent daily skin washes, including the terminal wash, continued to remove further residues from the skin surface, amounting to an additional 0.3-1.6% of the dose. By the end of the experiment, the potentially absorbable dose had declined to 0.33%, of which 0.2% was present in the *stratum corneum* and only 0.1% in the skin. Following dermal exposure to the formulation concentrate, the amount of dose absorbed after 6 hours was 3.2%, increasing to 4.0% after 24 hours, 8.9% after 72 hours and 8.4% after 120 hours.

Following dermal exposure for 6 hours to the 1/200 aqueous dilution, 65-76% of the applied dose was readily removed from the skin surface by mild skin washing. The potentially absorbable dose remaining in the application site skin after 6 hours accounted for a mean of 14.7% of the dose, of which the majority (11%) was present in the *stratum corneum*. After 5 days, this had declined to 1.5%, of which 1.4% was present in the *stratum corneum*. The amount of dose present in the skin beneath the *stratum corneum* declined steadily over the time course investigated, representing only 0.07% after 5 days. Following dermal exposure to the 1/200 aqueous dilution, the amount of dose absorbed after 6 hours was 11.2%, increasing to 14.6% after 24 hours, 19.5% after 72 hours and 18.1% after 120 hours.

The low levels of radioactivity in blood and plasma were consistent with the limited dermal absorption of CGA219417 from the formulation concentrate and the 1/200 aqueous dilution.

At both dose levels, elimination of the absorbed dose in urine and faeces was fairly slow, with the greater proportion excreted *via* the urine. Very low residues remained in the carcass after 5 days.

Dermal absorption from the formulation concentrate is most relevant to mixer/loaders over an interval of 6 hours. The absorption figure of 8.9% is the most appropriate value for use in risk assessments for short-term exposure.

Dermal absorption from the spray strength dilution is most relevant to spray operators over an interval of 6 hours, and therefore an absorption figure of 19.5% is the most appropriate value for use in risk assessments for the 1/200 aqueous dilution, corresponding to an application rate of 150 g a.i./hL.

Limitations of the study: The study was designed to investigate the dermal absorption of CGA219417 from the A14325E formulation concentrate and representative spray strength aqueous dilution of that formulation. The study has met those aims.

Table 7.3-~~7~~8: EFSA Derivation of Dermal Absorption Based on the Rat *In Vivo* for Cyprodinil in A14325E

Active Substance	**Cyprodinil**	
Cyprodinil EC (A14325E) Dose Concentration (g/L)	Concentrate 300	Spray Dilution 1.50
Time point leading to highest absorption (hrs)	24*	6*
Mean Standard Deviation (SD) Mean + SD	12.06 8.95 21.01	27.79 n/a n/a
Dermal Penetration (%) **to be used in risk assessment** **(ESFA Rounding)**	**21**	**28**

*based on data normalization, due to recovery

CONCLUSIONS

Following an *in vivo* dermal exposure interval of 6 hours to CGA219417 EC (300) formulation concentrate (A14325E), the applied dose was readily removed by mild skin washing. After 5 days, absorption accounted for less than 9% of the dose, including epidermal residues.

Following a 6 hour dermal exposure to a 1/200 spray strength dilution, absorption represented 18% of the dose after 5 days, with an additional 1.5% present in the epidermis.

(Smith A, 2005)

Report:	K-CP 7.3/02 Johnson I (2005) CGA219417 300g/l EC formulation (A14325E): In Vitro Dermal Absorption of Cyprodinil Through Human Epidermis. Syngenta Central Toxicology Laboratory, UK. Report No.CTL/JV1862/Regulatory/Report, 24 August 2005. Unpublished. (Syngenta File No. CGA219417/1377).

Guidelines: OECD 428 (2004). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

The absorption of cyprodinil from a nominal 300g/l EC formulation was measured *in vitro* through human epidermis. The formulation was applied as the concentrate formulation and as a 1:200 v/v (1.5g/l) spray strength dilution of the formulation in water. The absorption process was followed using [^{14}C]-labelled cyprodinil, which was added to the formulations prior to application. The concentrate formulation and the spray strength dilution were applied to the epidermal membranes at a rate of 10µl/cm^2; all applications were left unoccluded for an exposure period of 24h. These applications were designed to simulate potential human dermal exposure to the formulation during normal use. At the end of the exposure period, the distribution in the test system was measured.

The results obtained in this study indicate that the absorption of cyprodinil through human epidermis is slow when compared with the absorption rates of other penetrants measured using this *in vitro* technique. The vast majority of the test substance is likely to be removed from the surface

of, human skin by normal washing procedures. The small residual amount found in human skin is most likely to be lost by desquamation *in vivo*. These data predict that the human dermal absorption of cyprodinil from potential exposure to the spray strength dilution of CGA219417 300g/l EC would be minimal.

MATERIALS AND METHODS

Test Material:	CGA219417
Description:	Technical, light beige crumbs
Lot/Batch #:	P.012011
Purity:	99.2% a.i
Stability of test compound:	Confirmed
Radiolabelled Test Material:	[^{14}C]-CGA219417
Radiochemical number:	7008
Purity:	>98 %
Stability of test compound:	Confirmed

Blank Formulation:	A-14807B
Batch number:	J4551/112
Reference number:	Y13326/001
Stability of formulation:	Confirmed

Experimental dates: The study was initiated on 7th June 2005. The experimental phase started on 8th June 2005 and was completed on 1st July 2005.

Diffusion cell: Diffusion of cyprodinil into and across the skin to a receptor fluid was measured using glass diffusion cells in which the human epidermis formed a horizontal membrane and provided an application area of 2.54cm^2.

Receptor fluid: The receptor fluid (50% ethanol in deionised water) was chosen to ensure that the a.i would freely partition into this from the skin membrane and never reach a concentration that would limit its diffusion.

Skin preparations: Epidermal membranes were prepared from human whole skin by heat separation.

Skin preparation integrity: The integrity of the membranes was checked by measurement of the electrical resistance across the skin. Only membranes with a resistance greater than 10kΩ were considered to be intact and used on the study.

Test substance: The two doses were prepared to mimic the commercial 300g/l formulation and its aqueous 1/200v/v spray dilution (1.5g/l) using the technical material, [^{14}C]-labelled test material and formulation blank. The doses were prepared as close to the time of application as was practicable and were analysed to confirm their suitability for use in the study.

Application to the skin: Each application was represented by six replicates from at least two subjects at a dose of 10µl/cm² and left unoccluded for the exposure period.

Temperature: Throughout the experiment the receptor fluid was stirred and the epidermal membranes were maintained at a normal skin temperature of 32 ± 1^{o}C in a water bath.

Duration of exposure and sampling: The skin was exposed to the test preparations for 24 hours during which time samples of receptor fluid (0.1ml) were taken at suitable intervals (pre, 1, 2. 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours) to allow adequate characterisation of the absorption profile.

Terminal procedures: The donor chamber was carefully removed and washed with methanol. The epidermal surface of the skin was decontaminated by gently swabbing the application site with natural sponges pre-wetted with 3% Teepol® and with further sponges pre-wetted with water. Decontamination was shown to be complete following assessment of residual radioactivity levels on the skin surface with a Geiger counter. The sponges were digested in Soluene 350® and made up to a recorded volume. The surface of the skin was allowed to dry naturally and to assess penetration through the *stratum corneum*, successive layers of the *stratum corneum* were removed by the repeated application of adhesive tape to a maximum of 5 strips. Each individual adhesive strip was sequentially numbered and extracted in ethanol. The remaining epidermal tissue was carefully removed from the receptor chamber and digested in Soluene 350® and the whole digest analysed.

Analysis: All components of the test system (e.g. receptor fluid, skin wash, donor chamber, tape strips and epidermis) were analysed by LSC and the recovery determined.

Data: Results of the analysis of the samples of receptor fluid collected in the study were expressed as amounts of cyprodinil in the receptor solution in terms of µg/cm^2. The amounts absorbed, rates of absorption (µg/cm^2/h) and 'percentage of dose absorbed' were determined. The results of the mass balance and distribution determinations are expressed in terms of 'percentage of applied dose' (see Tables below).

Definition of absorbed test material: The absorbed (systemically available) dose is considered to be the test material detected in the receptor fluid. Material removed from the surface of the epidermis by the washing procedure is regarded as unabsorbed. The test material recovered from the epidermis at the end of the exposure is also considered to be unabsorbed, although it is recognised that a proportion of this material may be absorbed beyond the duration of the exposure investigated in this study. *In vivo*, the majority of the dose in the epidermis, especially that recovered from the *stratum corneum* (i.e. that found on the tape strips), would eventually be lost by desquamation.

RESULTS AND DISCUSSION

The mean mass balance recovery was 95.4 % to 100 % of the applied dose.

Concentrate - 10µl/cm² (3000µg/cm^2)

Absorption of cyprodinil from a 10µl/cm², unoccluded dose through human epidermis was slow, an absorption rate of 0.331µg/cm²/h during the 24 hour exposure period. The absorption rate was similar throughout the exposure period. In terms of amount and percentage of dose absorbed during periods typical of a working day (i.e. 6-10 hours), mean cyprodinil absorption was between 1.54µg/cm^2 (0.051% of dose) at 6 hours and 2.78µg/cm^2 (0.093%) at 10 hours, with a total of 8.23µg/cm^2 (0.275%) being absorbed by the end of the experiment at 24 hours.

The vast majority of the applied dose (mean 99.0%) was washed off the skin after 24 hours. A small proportion of the dose applied was recovered from the *stratum corneum* (0.155%) and 0.119% was found in the remaining epidermis.

1:200 v/v Spray strength dilution - 10µl/cm² (15µg/cm^2)

Absorption of cyprodinil from a 10µl/cm², unoccluded dose through human epidermis was very slow, an absorption rate of 0.056µg/cm²/h during the 24 hour exposure period. The absorption rate was similar throughout the exposure period. In terms of amount and percentage of dose absorbed during periods typical of a working day (i.e. 6-10 hours), mean cyprodinil absorption was between 0.356µg/cm^2 (2.56% of dose) at 6 hours and 0.581µg/cm^2 (4.17%) at 10 hours, with a total of 1.34µg/cm^2 (9.62%) being absorbed by the end of the experiment at 24 hours. The vast majority of the applied dose (mean 83.9%)

was washed off the skin after 24 hours. A small proportion of the dose applied was recovered from the *stratum corneum* (0.26%) and 1.2% was found in the remaining epidermis.

Table 7.3-~~89~~: Summary of cyprodinil absorption through human epidermis

Details of test material application	Mean absorption rates		Mean amount and percentage of dose absorbed		
	Time period (h)	Absorption rate (µg/cm²/h ± SEM)	Time (h)	Amount (µg/cm²)	Percent absorbed
Concentrate formulation (300g cyprodinil/l) 10µl/cm² (3000µg ai/cm²) Unoccluded Exposure period 24h n = 5	0 - 6 6 - 24 0 – 24	0.232 ± 0.032 0.374 ± 0.093 0.331 ± 0.077	6 8 10 24	1.54 2.18 2.78 8.23	0.051 0.073 0.093 0.275
1:200 aqueous spray dilution (1.5g cyprodinil/l) 10µl/cm² (15µg ai/cm²) Unoccluded Exposure period 24h n = 5	0 - 6 6 - 24 0 – 24	0.059 ± 0.011 0.055 ± 0.011 0.056 ± 0.011	6 8 10 24	0.356 0.468 0.581 1.34	2.56 3.36 4.17 9.62

Table 7.3-~~910~~: Summary of cyprodinil distribution from the concentrate formulation – 24 hour exposure

Test Compartment	Percent of Dose Recovered (%)						Mean % Recovered	SEM
	Cell 2	Cell 3	Cell 4	Cell 5	Cell 12	Cell 13		
Donor Chamber	0.015	1.48	0.200	0.160	0.095	0.637	0.432	0.228
Skin Wash	92.1	95.2	105	98.1	99.1	105	99.0	2.07
Stratum Corneum	0.167	0.208	0.124	0.105	0.167	0.159	0.155	0.015
Remaining Epidermis	0.076	0.299	0.061	0.076	0.139	0.063	0.119	0.038
Absorbed	0.207	0.516	0.147	0.107	0.231	0.440	0.275	0.067
Total Recovered	92.6	97.7	105	98.5	99.8	106	100	2.05

Table 7.3-~~1011~~: Summary of cyprodinil distribution from the 1/200 v/v aqueous spray dilution – 24 hour exposure

Test Compartment	Percent of Dose Recovered (%)					Mean % Recovered	SEM
	Cell 31	Cell 32	Cell 35	Cell 37	Cell 38		
Donor Chamber	0.205	0.347	1.02	0.186	0.196	0.391	0.159
Skin Wash	94.4	88.9	68.5	83.9	83.9	83.9	4.31
Stratum Corneum	0.308	0.195	0.408	0.159	0.229	0.260	0.044
Remaining Epidermis	0.237	0.310	4.75	0.297	0.387	1.20	0.887
Absorbed	3.67	5.45	15.20	11.66	12.09	9.62	2.17
Total Recovered	98.8	95.2	89.8	96.2	96.8	95.4	1.50

Table 7.3-~~11~~12: EFSA Derivation of Dermal Absorption Based on the Human *In Vitro* for Cyprodinil in A14325E

Active Substance	**Cyprodinil**	
Cyprodinil EC (A14325E) Dose Concentration (g/L)	Concentrate 300	Spray Dilution 1.50
Meets EFSA criteria for exclusion of tape strips (% absorbed in first 12h)	No 44	No 51
Recovery (%) of applied dose	100.0	95.4
Stratum corneum (%) Remaining Epidermis (%) Absorbed (%)	0.155 0.119 0.275	0.260 1.200 9.620
Total (%) EFSA Rounded (%)	0.549 0.50	11.080 11
Should the standard deviation (SD) be added? (Standard deviation (%) of mean)	Yes 49	Yes 57
Mean Standard Deviation (SD) Mean + SD	0.549 0.269 0.82	11.08 6.39 17.46
Dermal Penetration (%) to be used in risk assessment (ESFA Rounding)	**0.8**	**17**

CONCLUSIONS

The results obtained in this study indicate that the absorption of cyprodinil through human epidermis is slow when compared with the absorption rates of other penetrants measured using this in vitro technique. The vast majority of the test substance is likely to be removed from the surface of, human skin by normal washing procedures. The small residual amount found in human skin is most likely to be lost by desquamation *in vivo.* These data predict that the human dermal absorption of cyprodinil from potential exposure to the spray strength dilution of CGA219417 300g/l EC would be minimal.

(Johnson I, 2005)

Report:	K-CP 7.3/03 Johnson I (2005a) CGA219417 300g/l EC formulation (A14325E): *In Vitro* Dermal Absorption of Cyprodinil Through Rat Epidermis. Syngenta Central Toxicology Laboratory, UK. Report No.CTL/JV1863/Regulatory/Report, 24 August 2005. Unpublished. (Syngenta File No. CGA219417/1376).

Guidelines: OECD 428 (2004). There were no deviations from the current regulatory guideline considered to compromise the scientific validity of the study.

GLP: Signed and dated GLP and Quality Assurance statements were provided.

EXECUTIVE SUMMARY

The absorption of cyprodinil from a nominal 300g/l EC formulation was measured *in vitro* through rat epidermis. The formulation was applied as the concentrate formulation and as a 1:200 v/v (1.5g/l) spray strength dilution of the formulation in water. The absorption process

was followed using [^{14}C]-labelled cyprodinil, which was added to the formulations prior to application. The concentrate formulation and the spray strength dilution were applied to the epidermal membranes at a rate of 10µl/cm^2; all applications were left unoccluded for an exposure period of 24h. These applications were designed to simulate potential rat dermal exposure to the formulation during normal use. At the end of the exposure period, the distribution in the test system was measured.

The results obtained in this study indicate that the absorption of cyprodinil through rat epidermis is slow when compared with the absorption rates of other penetrants measured using this *in vitro* technique. The vast majority of the test substance is likely to be removed from the surface of, rat skin by normal washing procedures. The small residual amount found in rat skin is most likely to be lost by desquamation *in vivo*. These data predict that the dermal absorption of cyprodinil from potential exposure to the spray strength dilution of CGA219417 300g/l EC would be minimal.

MATERIALS AND METHODS

Test Material:	CGA219417
Description:	Technical, light beige crumbs
Lot/Batch #:	P.012011
Purity:	99.2% a.i
Stability of test compound:	Confirmed
Radiolabelled Test Material:	[^{14}C]-CGA219417
Radiochemical number:	7008
Purity:	>98 %
Stability of test compound:	Confirmed
Blank Formulation:	A14807B
Batch number:	J4551/112
Reference number:	Y13326/001
Stability of formulation:	Confirmed

Experimental dates: The study was initiated on 7th June 2005. The experimental phase started on 8th June 2005 and was completed on 1st July 2005.

Diffusion cell: Diffusion of cyprodinil into and across the skin to a receptor fluid was measured using glass diffusion cells in which the rat epidermis formed a horizontal membrane and provided an application area of 2.54cm^2.

Receptor fluid: The receptor fluid (50% ethanol in deionised water) was chosen to ensure that the a.i would freely partition into this from the skin membrane and never reach a concentration that would limit its diffusion.

Skin preparations: Epidermal membranes were prepared from rat whole skin by heat separation.

Skin preparation integrity: The integrity of the membranes was checked by measurement of the electrical resistance across the skin. Only membranes with a resistance greater than 2.5kΩ were considered to be intact and used on the study.

Test substance: The two doses were prepared to mimic the commercial 300g/l formulation and its aqueous 1/200v/v spray dilution (1.5g/l) using the technical material, [^{14}C]-labelled test material and formulation blank. The doses were prepared as close to the time of application as was practicable and were analysed to confirm their suitability for use in the study.

Application to the skin: Each application was represented by six replicates from at least two subjects at a dose of 10µl/cm² and left unoccluded for the exposure period.

Temperature: Throughout the experiment the receptor fluid was stirred and the epidermal membranes were maintained at a normal skin temperature of 32 ± 1°C in a water bath.

Duration of exposure and sampling: The skin was exposed to the test preparations for 24 hours during which time samples of receptor fluid (0.1ml) were taken at suitable intervals (pre, 1, 2. 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours) to allow adequate characterisation of the absorption profile.

Terminal procedures: The donor chamber was carefully removed and washed with methanol. The epidermal surface of the skin was decontaminated by gently swabbing the application site with natural sponges pre-wetted with 3% Teepol® and with further sponges pre-wetted with water. Decontamination was shown to be complete following assessment of residual radioactivity levels on the skin surface with a Geiger counter. The sponges were digested in Soluene 350® and made up to a recorded volume. The surface of the skin was allowed to dry naturally and to assess penetration through the *stratum corneum*, successive layers of the *stratum corneum* were removed by the repeated application of adhesive tape to a maximum of 5 strips. Each individual adhesive strip was sequentially numbered and extracted in ethanol. The remaining epidermal tissue was carefully removed from the receptor chamber and digested in Soluene 350® and the whole digest analysed.

Analysis: All components of the test system (e.g. receptor fluid, skin wash, donor chamber, tape strips and epidermis) were analysed by LSC and the recovery determined.

Data: Results of the analysis of the samples of receptor fluid collected in the study were expressed as amounts of cyprodinil in the receptor solution in terms of µg/cm^2. The amounts absorbed, rates of absorption (µg/cm^2/h) and 'percentage of dose absorbed' were determined. The results of the mass balance and distribution determinations are expressed in terms of 'percentage of applied dose' (see Tables below).

Definition of absorbed test material: The absorbed (systemically available) dose is considered to be the test material detected in the receptor fluid. Material removed from the surface of the epidermis by the washing procedure is regarded as unabsorbed. The test material recovered from the epidermis at the end of the exposure is also considered to be unabsorbed, although it is recognised that a proportion of this material may be absorbed beyond the duration of the exposure investigated in this study. *In vivo*, the majority of the dose in the epidermis, especially that recovered from the *stratum corneum* (i.e. that found on the tape strips), would eventually be lost by desquamation.

RESULTS AND DISCUSSION

The mean mass balance recovery was 96.1 % to 96.2 % of the applied dose

Concentrate: Absorption of cyprodinil through rat epidermis was slow, an absorption rate of 15.2µg/cm²/h during the 24 hour exposure period. The absorption rate was slightly faster during the latter 18 hours. In terms of amount and percentage of dose absorbed during periods typical of a working day (i.e. 6-10 hours), mean cyprodinil absorption was between 56.2µg/cm^2 (1.88% of dose) at 6 hours and 119µg/cm^2 (3.96%) at 10 hours, with a total of 358µg/cm^2 (11.9%) being absorbed at 24 hours.

Approximately three quarters of the applied dose (mean 73.4%) was washed off the skin after 24 hours. A small proportion of the dose applied was recovered from the skin (4.23%).

1:200 v/v spray strength dilution: Absorption of cyprodinil through rat epidermis was slow, an absorption rate of 0.458µg/cm²/h during the 24 hour exposure period. The absorption rate was fastest during the first 6 hours. In terms of amount and percentage of dose absorbed during periods typical of a working day (i.e. 6-10 hours), mean cyprodinil absorption was between 5.64µg/cm^2 (40.5% of dose) at 6 hours and 7.71µg/cm^2 (55.3%) at 10 hours, with a total of 11.2µg/cm^2 (80.4%) being absorbed at 24 hours. A small proportion of the applied dose (mean 7.56%) was washed off the skin after 24 hours. A small proportion of the dose applied was recovered from the skin (3.35%).

Table 7.3-~~11~~13: Summary of cyprodinil absorption through rat epidermis

Details of test material application	Mean absorption rates		Mean amount and percentage of dose absorbed		
	Time period (h)	Absorption rate (µg/cm^2/h ± SEM)	Time (h)	Amount (µg/cm^2)	Percent absorbed
Concentrate formulation (300g cyprodinil/l) 10µl/cm^2 (3000µg ai/cm^2) Unoccluded Exposure period 24h n = 6	0 - 6 6 - 24 0 – 24	9.36 ± 1.26 16.8 ± 2.95 15.2 ± 2.60	6 8 10 24	56.2 85.0 119 358	1.88 2.84 3.96 11.9
1:200 aqueous spray dilution (1.5g cyprodinil/l) 10µl/cm^2 (15µg ai/cm^2) Unoccluded Exposure period 24h n = 5	0 - 6 6 - 24 0 – 24	0.941 ± 0.047 0.307 ± 0.008 0.458 ± 0.007	6 8 10 24	5.64 6.80 7.71 11.2	40.5 48.9 55.3 80.4

Table 7.3-~~12~~14: Summary of cyprodinil distribution from the concentrate formulation – 24 hour exposure

Test Compartment	Percent of Dose Recovered (%)						Mean % Recovered	SEM
	Cell 16	Cell 19	Cell 20	Cell 22	Cell 25	Cell 26		
Donor Chamber	1.37	2.19	2.05	0.943	8.17	0.845	2.59	1.14
Skin Wash	1.86	1.25	3.55	11.4	4.63	1.16	3.98	1.59
Stratum Corneum	72.9	67.8	72.3	72.3	73.1	82.1	73.4	1.91
Remaining Epidermis	1.92	2.87	3.87	5.97	7.37	3.41	4.23	0.833
Absorbed	13.4	17.9	16.1	5.68	5.40	13.2	12.0	2.15
Total Recovered	91.5	92.0	97.8	96.3	98.6	101	96.1	1.51

Table 7.3-~~1315~~: Summary of cyprodinil distribution from the 1/200 v/v aqueous spray dilution – 24 hour exposure

Test Compartment	Percent of Dose Recovered (%)					Mean % Recovered	SEM
	Cell 51	Cell 53	Cell 55	Cell 56	Cell 59		
Donor Chamber	0.614	0.639	0.083	0.480	1.89	0.741	0.304
Skin Wash	0.367	0.571	0.484	0.473	0.922	0.563	0.095
Stratum Corneum	5.29	11.36	5.26	6.96	8.93	7.56	1.16
Remaining Epidermis	2.41	4.13	3.25	3.03	3.94	3.35	0.308
Absorbed	83.3	75.4	83.6	81.9	78.0	80.4	1.61
Total Recovered	92.0	92.1	92.7	92.8	93.7	92.6	0.304

Table 7.3-~~1416~~: EFSA Derivation of Dermal Absorption Based on the Rat *In Vitro* for Cyprodinil in A14325E

Active Substance	**Cyprodinil**	
Cyprodinil EC (A14325E) Dose Concentration (g/L)	Concentrate 300	Spray Dilution 1.50
Meets EFSA criteria for exclusion of tape strips (% absorbed in first 12h)	No 43	No 72
Recovery (%) of applied dose	96.10	92.60
Receptor & Grids (%) Remaining Epidermis (%) Absorbed (%)	3.98 4.23 12.00	0.56 3.35 80.40
Total (%) EFSA Rounded (%)	20.21 20	84.31 84
Should the standard deviation (SD) be added? (Standard deviation (%) of mean)	No 14.93	No 3.41
Mean	20.16	84.31
Dermal Penetration (%) to be used in risk assessment (ESFA Rounding)	**20**	**84**

CONCLUSIONS

The results obtained in this study indicate that the absorption of cyprodinil through rat epidermis is slow when compared with the absorption rates of other penetrants measured using this *in vitro* technique. The vast majority of the test substance is likely to be removed from the surface of, rat skin by normal washing procedures. The small residual amount found in rat skin is most likely to be lost by desquamation *in vivo*. These data predict that the dermal absorption of cyprodinil from potential exposure to the spray strength dilution of CGA219417 300g/l EC would be minimal.

(Johnson I, 2005a)

CP 7.4 Available Toxicological Data Relating to Co-Formulants

CONFIDENTIAL information - data provided separately (Document J)

Appendix 1: Detailed Exposure Calculations

Table 7.2.1.1-1: UK POEM - Exposure to cyprodinil during tractor-mounted boom spraying; no PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**A14325E**	Active substance	**cyprodinil**
Formulation type	organic solvent-based	a.s. concentration	**300** mg/ml
Dermal absorption from product	**0.9** %	Dermal absorption from spray	**6** %
Container	10 litres 63 mm closure		
PPE during mix/loading	None	PPE during application	None
Dose	**1.5** l/ha	Work rate/day	**50** ha
Application volume	**150** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1.5	litres product/ha
Work rate	50	ha/day
Number of operations	8	/day
Hand contamination	0.4	ml/day
Protective clothing	None	
Transmission to skin	100	%
Dermal exposure to formulation	0.4	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	150	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	None	Permeable	Permeable	
Penetration	100%	5%	15%	
Dermal exposure	6.5	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.4	ml/day	41.55	ml/day
Concen. of a.s. product or spray	300	mg/ml	3	mg/ml
Dermal exposure to a.s.	120	mg/day	124.65	mg/day
Percent absorbed	0.9	%	6	%
Absorbed dose	1.08	mg/day	7.479	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	3	mg/ml
Inhalation exposure to a.s.	0.18	mg/day
Percent absorbed	100	%
Absorbed dose	0.18	mg/day

PREDICTED EXPOSURE

Total absorbed dose	8.739	mg/day
Operator body weight	60	kg
Operator exposure	0.14565	mg/kg bw/day

Table 7.2.1.1-2: UK POEM - Exposure to cyprodinil during tractor-mounted boom spraying; with PPE

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**A14325E**	Active substance	**cyprodinil**
Formulation type	organic solvent-based	a.s. concentration	**300** mg/ml
Dermal absorption from product	**0.9** %	Dermal absorption from spray	**6** %
Container	10 litres 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**1.5** l/ha	Work rate/day	**50** ha
Application volume	**150** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	10	litres
Hand contamination/operation	0.05	ml
Application dose	1.5	litres product/ha
Work rate	50	ha/day
Number of operations	8	/day
Hand contamination	0.4	ml/day
Protective clothing	Gloves	
Transmission to skin	10	%
Dermal exposure to formulation	0.04	ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	150	spray/ha		
Volume of surface contamination	10	ml/h		
Distribution	Hands	Trunk	Legs	
	65%	10%	25%	
Clothing	Gloves	Permeable	Permeable	
Penetration	10%	5%	15%	
Dermal exposure	0.65	0.05	0.375	ml/h
Duration of exposure	6	h		
Total dermal exposure to spray	6.45	ml/day		

ABSORBED DERMAL DOSE

	Mix/load		Application	
Dermal exposure	0.04	ml/day	6.45	ml/day
Concen. of a.s. product or spray	300	mg/ml	3	mg/ml
Dermal exposure to a.s.	12	mg/day	19.35	mg/day
Percent absorbed	0.9	%	6	%
Absorbed dose	0.108	mg/day	1.161	mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	3	mg/ml
Inhalation exposure to a.s.	0.18	mg/day
Percent absorbed	100	%
Absorbed dose	0.18	mg/day

PREDICTED EXPOSURE

Total absorbed dose	1.449	mg/day
Operator body weight	60	kg
Operator exposure	0.02415	mg/kg bw/day

Table 7.2.1.1-3: German model - Exposure to cyprodinil during tractor-mounted boom spraying; no PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles					
Product	**A14325E**			Active substance		**cyprodinil**
Formulation type	Liquid			a.s. concentration		**300** g/l
Dermal absorption from product		**0.9** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None			RPE during application		None
PPE during mix/loading	None					
PPE during application: Head	None		Hands	None	Body	None
Dose		**1.5** l product/ha		Work rate/day		**20** ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	21.6	mg/day
Protective clothing	none	
Transmission to skin	100	%
Dermal exposure to a.s.	21.6	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.0054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0054	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body	
Dermal contamination/kg a.s.	0.06	0.38	1.6	
Dermal contamination/day	0.54	3.42	14.4	
Protective clothing	none	none	none	
Transmission to skin	100	100	100	%
Total dermal exposure to a.s.	18.36	mg/day		

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.009	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.009	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	21.6	mg/day	18.36	mg/day
Percent absorbed	0.9	%	6	%
Absorbed dose (dermal route)	0.1944	mg/day	1.1016	mg/day
Inhalation exposure to a.s.	0.0054	mg/day	0.009	mg/day
Total systemic exposure	0.1998	mg/day	1.1106	mg/day

PREDICTED EXPOSURE

Total systemic exposure	1.3104	mg/day
Operator body weight	70	kg
Operator exposure	0.01872	mg/kg bw/day

Table 7.2.1.1-4: German model - Exposure to cyprodinil during tractor-mounted boom spraying; with PPE

THE GERMAN MODEL (GEOMETRIC MEAN VALUES)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles					
Product	**A14325E**			Active substance		**cyprodinil**
Formulation type	Liquid			a.s. concentration		**300** g/l
Dermal absorption from product		**0.9** %		Dermal absorption from spray		**6** %
RPE during mix/loading	None			RPE during application		None
PPE during mix/loading	Gloves					
PPE during application: Head	None		Hands	Gloves	Body	Coverall and sturdy footwear
Dose		**1.5** l product/ha		Work rate/day		**20** ha

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	2.4	mg/kg a.s.
Hand contamination/day	21.6	mg/day
Protective clothing	gloves	
Transmission to skin	1	%
Dermal exposure to a.s.	0.216	mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0006	mg/kg a.s.
Inhalation exposure/day	0.0054	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.0054	mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique Tractor-mounted/trailed boom sprayer: hydraulic nozzles

	Head	Hands	Rest of body
Dermal contamination/kg a.s.	0.06	0.38	1.6
Dermal contamination/day	0.54	3.42	14.4
Protective clothing	none	gloves	coverall and sturdy footwear
Transmission to skin	100	1	5 %
Total dermal exposure to a.s.	1.2942	mg/day	

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure/kg a.s.	0.001	mg/kg a.s.
Inhalation exposure/day	0.009	mg/day
RPE	none	
Transmission through RPE	100	%
Inhalation exposure to a.s.	0.009	mg/day

ABSORBED DOSE

	Mix/load		Application	
Dermal exposure to a.s.	0.216	mg/day	1.2942	mg/day
Percent absorbed	0.9	%	6	%
Absorbed dose (dermal route)	0.001944	mg/day	0.077652	mg/day
Inhalation exposure to a.s.	0.0054	mg/day	0.009	mg/day
Total systemic exposure	0.007344	mg/day	0.086652	mg/day

PREDICTED EXPOSURE

Total systemic exposure	0.093996	mg/day
Operator body weight	70	kg
Operator exposure	0.0013428	mg/kg bw/day

Table 7.2.1.1-5: EFSA model - Exposure to cyprodinil during tractor-mounted boom spraying; no PPE

Substance	Cyprodinil	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.45 kg a.s. /ha	Spray dilution = 3 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 0.9	Dermal for in use diluation = 6	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0185	% of RVNAS	61.62%
	Acute systemic exposure mg/kg bw/day		0.0909	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0120	% of RVNAS	39.84%
	Acute systemic exposure mg/kg bw/day		0.0552	% of RVAAS	

Table 7.2.1.1-6: EFSA model - Exposure to cyprodinil during tractor-mounted boom spraying; with PPE

Substance	Cyprodinil	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.45 kg a.s. /ha	Spray dilution = 3 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 0.9	Dermal for in use diluation = 6	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0185	% of RVNAS	61.62%
	Acute systemic exposure mg/kg bw/day		0.0909	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0009	% of RVNAS	2.93%
	Acute systemic exposure mg/kg bw/day		0.0081	% of RVAAS	

Table 7.2.2.1-1: Estimated bystander exposure to cyprodinil – German approach

Estimation of bystander exposure during/after application in Field Crops, Tractor Mounted

Input parameters considered for the estimation of bystander exposure:

Intended use(s):	Barley		**Drift (D):**	0.29	% (FCTM, 10 m)
Application rate (AR):	0.45	kg a.s./ha	**Exposed Body Surface Area (BSA):**	1	m² (adults)
				0.21	m² (children)
Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I*A):**	0.001	mg/kg a.s. (6 hours, adults)
	16.15	kg/person (children)		0.00057	mg/kg a.s. (6 hours, children)
Dermal absorption (DA):	6.00	% ('worst case')	**Area Treated (A):**	20	ha/d (based on Field Crops, Tractor Mounted
Inhalation absorption (IA):	100	%	**Exposure duration (T):**	5	min
AOEL:	0.03	mg/kg bw/d			

Bystander exposure towards cyprodinil					
Adults			**Children**		
Bystander: Dermal exposure after application in Barley (via spray drift)					
SDE_B = (AR x D x BSA x DA) / BW			SDE_B = (AR x D x BSA x DA) / BW		
(45 x 0.29% x 1 x 6%) / 60			(45 x 0.29% x 0.21 x 6%) / 16.15		
External exposure	0.1305	mg/person	External exposure	0.027405	mg/person
External exposure	0.002175	mg/kg bw/d	External exposure	0.0016969	mg/kg bw/d
Absorbed dose:	**0.0001305**	**mg/kg bw/d**	**Absorbed dose:**	**0.0001018**	**mg/kg bw/d**
Bystander: Inhalation exposure after application in Barley					
SIE_B = (I^*_A x AR x A x T x IA) / BW			SIE_B = (I^*_A x AR x A x T x IA) / BW		
(0,000 / 360 x 0.45 x 20 x 5 x 100%) / 60			(0,000 / 360 x 0.45 x 20 x 5 x 100%) / 16.15		
External exposure	0.000125	mg/person	External exposure	7.1839E-05	mg/person
External exposure	2.0833E-06	mg/kg bw/d	External exposure	4.4482E-06	mg/kg bw/d
Absorbed dose:	**0.0000021**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000044**	**mg/kg bw/d**
Total systemic exposure: $SE_B = SDE_B + SIE_B$			Total systemic exposure: $SE_B = SDE_B + SIE_B$		
Total systemic exposure (absorbed dose)	0.007955	mg/person	Total systemic exposure (absorbed dose)	0.00171614	mg/person
Total systemic exposure (absorbed dose)	**0.0001326**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0001063**	**mg/kg bw/d**
% of AOEL:	**0.44**	**%**	**% of AOEL:**	**0.35**	**%**

Table 7.2.2.1-2: Estimated residential exposure to cyprodinil - German approach

Estimation of resident exposure after application in Field Crops, Tractor Mounted (FCTM)

Input parameters considered for the estimation of resident exposure:

Intended use(s):	Barley		**Drift (D):**	0.24	% (FCTM, 10 m)
Application rate (AR):	0.45	kg a.s./ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
				2600	cm^2/h (children)
Number of applications (NA):	2		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16.15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	0.001	mg/m3
Dermal absorption (DA):	6.00	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults),
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA)	100	%	**Saliva Extraction Factor (SE):**	50	%
AOEL	0.03	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Resident exposure towards cyprodinil					
Adults			**Children**		
Residents: Dermal exposure after application in Barley (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0.0045 x 2 x 0.24% x 5% x 7300 x 2 x 6%) / 60			(0.0045 x 2 x 0.24% x 5% x 2600 x 2 x 6%) / 16.15		
External exposure	0.015768	mg/person	External exposure	0.005616	mg/person
External exposure	0.0002628	mg/kg bw/d	External exposure	0.00034774	mg/kg bw/d
Absorbed dose:	**0.0000158**	**mg/kg bw/d**	**Absorbed dose:**	**0.0000209**	**mg/kg bw/d**
Residents: Inhalation exposure to vapour					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0.001 x 16.57 x 100%) / 60			(0.001 x 8.31 x 100%) / 16.15		
External exposure	0.01657	mg/person	External exposure	0.00831	mg/person
External exposure	0.00027617	mg/kg bw/d	External exposure	0.00051455	mg/kg bw/d
Absorbed dose:	**0.0002762**	**mg/kg bw/d**	**Absorbed dose:**	**0.0005146**	**mg/kg bw/d**
			Residents: Oral exposure (hand-to-mouth transfer)		
			SOE_H = (AR x NA x D x TTR x SE x SA x Freq x H x OA) /		
			(0.0045 x 2 x 0.24% x 5% x 50% x 20 x 20 x 2 x 100%) / 16.15		
			External exposure	0.000432	mg/person
			External exposure	2.6749E-05	mg/kg bw/d
			Absorbed dose	**0.0000267**	**mg/kg bw/d**
			Residents: Oral exposure (object-to-mouth transfer)		
			SOE_O = (AR x NA x D x DFR x IgR x OA) / BW		
			(0.0045 x 2 x 0.24% x 20% x 25 x 100%) / 16.15		
			External exposure	0.000108	mg/person
			External exposure	6.6873E-06	mg/kg bw/d
			Absorbed dose	**0.0000067**	**mg/kg bw/d**
Total systemic exposure: SE_R = SDE_R + SIE_R			Total systemic exposure: SE_R = SDE_R + SIE_R + SOE_H + SOE_O		
Total systemic exposure (absorbed dose)	0.01751608	mg/person	Total systemic exposure (absorbed dose)	0.00918696	mg/person
Total systemic exposure (absorbed dose)	**0.0002919**	**mg/kg bw/d**	**Total systemic exposure** (absorbed dose)	**0.0005689**	**mg/kg bw/d**
% of AOEL:	**0.97**	**%**	**% of AOEL:**	**1.90**	**%**

Table 7.2.2.1-3: Estimated residential exposure to cyprodinil – EFSA guidance

Substance	Cyprodinil	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.45 kg a.s. /ha	Spray dilution = 3 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 0.9	Dermal for in use diluation = 6	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0049	% of RVNAS	16.31%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	3.57%
	Surface deposits (75th percentile) mg/kg bw/day	0.0013	% of RVNAS	4.36%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0079	% of RVNAS	26.18%
	All pathways (mean) mg/kg bw/day	0.0110	% of RVNAS	36.66%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0012	% of RVNAS	3.87%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.77%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	1.06%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0044	% of RVNAS	14.54%
	All pathways (mean) mg/kg bw/day	0.0045	% of RVNAS	14.98%

Table 7.2.3.1-1: Estimated worker exposure to cyprodinil – German approach

Estimation of worker (re-entry) exposure

Input parameters considered for the estimation of worker exposure:

Intended use(s):	Barley		**Dislodgeable foliar residues (DFR):**	3	µg/cm²/kg a.s.
Application rate (AR):	0.45	kg a.s./ha	**Body potential (TC):**	3600	cm²/person/h
Number of applications (NA):	2		**Body actual (TC):**	360	cm²/person/h
Body weight (BW):	60	kg/person	**Hands potential (TC):**	2200	cm²/person/h
Dermal absorption (DA):	6	% ('worst case')			
			Work rate per day (WR):	2	h/d
AOEL	0.03	mg/kg bw/d	**PPE**	5	%

Worker (re-entry): Systemic dermal exposure after application in Barley					
Worker exposure towards cyprodinil					
Without PPE - Body - Potential			**Body - Actual**		
SDEw = (DFR x TC x WR x AR x NA x DA) / BW			SDEw = (DFR x TC x WR x AR x NA x DA) / BW		
(3 x 3600 x 2 x 0.45 x 2 x 6%) / 60			(3 x 360 x 2 x 0.45 x 2 x 6%) / 60		
External dermal exposure	19.44	mg/person	External dermal exposure	1.94	mg/person
External dermal exposure	0.32	mg/kg bw/d	External dermal exposure	0.03	mg/kg bw/d
Total systemic exposure	1.17	mg/person	Total systemic exposure	0.12	mg/person
Total systemic exposure	**0.019440**	**mg/kg bw/d**	**Total systemic exposure**	**0.001944**	**mg/kg bw/d**
% of AOEL	**64.8**	**%**	**% of AOEL**	**6.5**	**%**

Without PPE - Hands - Potential			**Hands - with PPE**		
SDEw = (DFR x TC x WR x AR x NA x DA) / BW			SDEw = (DFR x TC x WR x AR x NA x PPE x DA) / BW		
(3 x 2200 x 2 x 0.45 x 2 x 6%) / 60			(3 x 2200 x 2 x 0.45 x 2 x 5% x 6%) / 60		
External dermal exposure	11.88	mg/person	External dermal exposure	0.59	mg/person
External dermal exposure	0.20	mg/kg bw/d	External dermal exposure	0.01	mg/kg bw/d
Total systemic exposure	0.71	mg/person	Total systemic exposure	0.04	mg/person
Total systemic exposure	**0.011880**	**mg/kg bw/d**	**Total systemic exposure**	**0.000594**	**mg/kg bw/d**
% of AOEL	**39.6**	**%**	**% of AOEL**	**2.0**	**%**

Total potential exposure	**0.031**	**mg/kg bw/d**	**% of AOEL**	104.40	**%**
Total actual exposure	**0.014**	**mg/kg bw/d**	**% of AOEL**	46.08	**%**
Total exposure with PPE	**0.003**	**mg/kg bw/d**	**% of AOEL**	8.46	**%**

Table 7.2.3.1-1: Estimated worker exposure to cyprodinil – EFSA guidance

Substance	Cyprodinil	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.45 kg a.s. /ha	Spray dilution = 3 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 0.9	Dermal for in use diluation = 6	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0582	% of RVNAS	193.91%
	Working clothing mg/kg bw/day	0.0065	% of RVNAS	21.72%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	