Bayer CropScience

Document Title

Summary of the toxicological studies fluoxastrobin + prothioconazole EC 200 (100+100 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013

Document MCP

Section 7: Toxicological studies

According to the guidance document, SANCO 10181/2013, for preparing dossiers for the approval of a chemical active substance

Date

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Bayer CropScience

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[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 PRODUCT

CP 7.1 Acute toxicity

FXA+PTZ EC 200 (100+100 g/L) is a fungicide formulation containing 100 g/L fluoxastrobin and 100 g/L prothioconazole.
The acute toxicity of FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000008127) has been fully assessed earlier by CRD when the product was first approved under COP 2003/00189.

In this submission, the bridging options were explored in order to assess the toxicological properties of and to classify the improved recipe of the successor formulation FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000025822). This is based on an already available toxicological data package established with the predecessor formulation FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000008127) which is regarded as closely related to this successor formulation. The applicant believes to comply with animal welfare policies (avoidance of unnecessary testing in additional animals) when bridging the existing toxicological data from the predecessor to the successor recipe.

Based on this evaluation the acute oral and dermal toxicity studies as well as skin sensitisation and skin irritation studies performed with FXA + PTZ EC 200 (100+100 g/L) Specification No.: 102000008127 are considered still valid for the current formulation FXA+ PTZ EC 200 (100+100 g/L) (Specification No.: 102000025822) and no changes in toxicity are expected when moving from the predecessor to the successor recipe. However, two new studies (acute inhalation, eye irritation) were conducted with the improved recipe FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000025822).

Full details on the comparison of the formulation compositions and specifications of both the predecessor and the successor formulation and the related bridging argument(s) can be found in the confidential part of this submission (Document JCP 1.4.1)).

At the time of study conduct the test substances were named as follows:

- FXA+PTZ EC 200 (100+100 g/L)
- HEC 5725 & JAU 6476 EC 200
- HEC 5725 100 EC & JAU 6476 100

Table 7-1: Summary of acute toxicity studies conducted with FXA + PTZ EC 200 (100+100 g/L)

Type of study	Results	References
Specification No.: 102000008127		
Acute oral rat	LD_{50}: >2000 mg/kg bw	CP 7.1.1/01; [redacted].; [redacted]; 2002; M-088922-02-1 [1]
Acute dermal rat	LD_{50}: >4000 mg/kg bw	CP 7.1.2/01; [redacted].; [redacted]; 2002; M-087231-02-1 [2]
Skin irritation rabbit	Slightly irritating classification not triggered	CP 7.1.4/01; [redacted]s; 2001; M-085049-01-1 [3]
Skin sensitisation guinea pig (maximisation test)	Not sensitising	CP 7.1.6/01; [redacted].; 2002; M-064940-01-1 [4]
Specification No.: 102000025822		
Acute inhalation rat	0.91 mg/L < LC_{50} < 5.03 mg/L	CP 7.1.3/01 [redacted].; [redacted]; 2015; M-533854-01-1
Eye irritation rabbit	Severely irritating	CP 7.1.5/01 [redacted].; 2012; M-437242-01-1

Based on the study results, the new formulation FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000025822) is assessed to be slightly toxic after acute oral, non-toxic after acute dermal administration and moderately toxic after acute inhalation. It shows no skin irritating but a severely eye irritating potential. FXA + PTZ EC 200 (100+100 g/L) (Specification No. 102000025822) is not a skin sensitiser in the maximisation test on guinea pigs.

The study results trigger the following classification/labelling:

Regulation (EC) No 1272/2008 (CLP): Acute Tox. Cat. 4; H332 (Harmful if inhaled)

Eye irritation Cat. 1; H318 (Causes serious eye damage)

The applicant Bayer CropScience noted that in the past Member States have requested formulations containing prothioconazole at or above 3% to be labeled as reproductive toxic Repro. Cat. 2 (H361d; suspected of damaging the unborn child). This is based on the EFSA proposal to classify prothioconazole as reproductive toxic Repro. Cat. 2 (H361d) (EFSA Scientific Report (2007). However, Bayer CropScience is convinced that prothioconazole should not be classified for reproductive toxicity. Hence, in the absence of a harmonized EU classification (ECHA) for prothioconazole, the applicant wishes to self-classifiy his products. Scientifc arguments for non-classification are provided in a separately submitted position paper ([redacted]; 2006; M-266455-01-1).

[1] This study was already submitted in the UK for COP 2003/00189 under Doc.No. MO-02-003572; However, MO-02-003572 and M-088922-02-1 are identical reports; they only differ from each other as M-088922-02-1 is the revised version of MO-02-003572 in which formal corrections were made.
[2] This study was already submitted in the UK for COP 2003/00189 under Doc.No. MO-02-003579; However, MO-02-003579 and M-087231-02-1 are identical reports; they only differ from each other as M-087231-02-1 is the revised version of MO-02-003579 in which formal corrections were made.
[3] This study was already submitted in the UK for COP 2003/00189 under Doc.No. MO-01-020975.
[4] This study was already submitted in the UK for COP 2003/00189 under Doc.No. MO-02-007594.

CP 7.1.1 Oral toxicity

Report:	KCP 7.1.1/01 [redacted] <; [redacted]; 2002; M-088922-02-1
Title:	HEC 5725 100 EC + JAU 6476 100 - Study for acute oral toxicity in rats - 1st revised version of report no. 31606 of December 14, 2001
Report No.:	31819
Document No.:	M-088922-02-1
Guideline(s):	OECD 423; Directive 67/548/EEC, Annex IV, Part B, B.1 tris; US-EPA 712-C-98-190, OPPTS 870.1100
Guideline deviation(s):	The test substance is a commercial product known to be stable and homogenous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of stability and homogeneity of the formulations for administration were not performed. This deviation did not limit the assessment of the results.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: HEC 5725 100 EC + JAU 6476 100

- Development no.: 30-00280022
- Description: clear yellow liquid
- Lot/Batch no: 06899/0391(0390)
- Content: fluoxastrobin: 100.32 g/L; prothioconazole: 98.04 g/L
- Stability of test compound: guaranteed for study duration, expiry date: 2002-02-08

2. Vehicle: deionised water

3. Test animals

- Species: Wistar rat
- Strain: HsdCpb:WU (SPF-bred)
- Age: males: ≥ 8 weeks, females: ≥ 7 weeks
- Weight at dosing: males: 255 g – 266 g, females: 171 g – 177 g
- Source: [redacted] Germany
- Acclimatisation period: at least 5 days
- Diet: [redacted] No. 9441 Long Life W10 pellets ([redacted], Switzerland)
- Water: tap water
- Housing: group caged in polycarbonate cages; bedding: low-dust wood granules type BK 8/15 ([redacted] Germany)

B. Study design and methods

1. Animal assignment and treatment

- Dose: 2000 mg/kg bw
- Application route: oral
- Application volume: 10 mL/kg bw
- Fasting time: before administration: approx. 17 hours ± 1 hour
  after administration: approx. 2 hours

Group size:	3 rats/sex/group
Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological result*			Occurrence of signs	Time of death	Mortality (%)
Male rats						
2000	0	3	3	5’ - 3h	-	0
Female rats						
2000	0	3	3	5’ - 3h	-	0
LD50: >2500 mg/kg bw						

* 1st number = number of dead animals, 2nd number = number of animals with toxic signs, 3rd number = number of animals used

B. Clinical observations

Piloerection, decreased motility, decreased reactivity, laboured breathing, abdominal position, narrowed palpebral fissure, uncoordinated gait

C. Body weight

Body weight and body-weight gain were not affected by treatment.

D. Necropsy

No gross pathologic changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

The test item was slightly toxic to fasted male and female rats after acute oral application.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.2 Dermal toxicity

Report:	KCP 7.1.2/01 [redacted],; [redacted]; 2002; M-087231-02-1
Title:	HEC 5725 100 EC + JAU 6476 100 - Study for acute dermal toxicity in rats - 1st revised version of report no. 31543 of November 27, 2001
Report No.:	31818
Document No.:	M-087231-02-1
Guideline(s):	OECD 402; Directive 67/548/EEC, Annex V, Part B.3.; US-EPA 712-C-98-192, OPPTS 870.1200
Guideline deviation(s):	The liquid test substance is a commercial product known to be stable and homogenous in undiluted form. For the application, the liquid test substance was applied neat. Therefore, analytical determinations of stability and homogeneity of the formulations for administration were not performed.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: HEC 5725 100 EC + JAU 6476 100

Development no.:	30-00280022
Description:	clear yellow liquid
Lot/Batch no:	06899/0391(0390)
Content:	fluoxastrobin: 100.32 g/L; prothioconazole: 98.04 g/L
Stability of test compound:	guaranteed for study duration, expiry date 2002-02-08

2. Vehicle: none

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:WU (SPF-bred)
Age:	males: ~ 8 weeks, females: ~ 10 weeks
Weight at dosing:	males: 246 g – 259 g, females: 216 g – 219 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	[redacted] No. 9441 Long Life W10 pellets ([redacted] Switzerland)
Water:	tap water
Housing:	individually in polycarbonate cages; bedding: low-dust wood granules type BK 8/15 ([redacted], Germany

B. Study design and methods

1. Animal assignment and treatment

Dose:

Dose (mg/kg bw)		Surface area (cm²)	Range (mg/cm²)
males	4000	20.25	48.6 - 51.2
females	4000	20.25	42.7 - 43.3

Application route: dermal, semi-occlusive dressing

Exposure: 24 hours

Group size:	5 rats/sex/group
Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, skin effects, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality [%]
Male rats						
4000	0	0	5	--	--	0
Females rats						
4000	0	1#	5	--	--	0
LD_{50}: > 4000 mg/kg bw						

* 1st number = number of dead animals, 2nd number = number of animals with signs,
3rd number = number of animals in the group

\# animal showed only local skin reactions

B. Clinical observations

At dermal doses of 4000 mg/kg bw no clinical signs were observed. Local skin reactions developed within 3 - 5 days. They were as follows: partial scale formation, thickening and partial reddening. Effects were reversible by study day 8.

C. Body weight

Mean body weight and mean body weight gain was not affected by treatment.

D. Necropsy

No gross pathologic changes were observed in animals sacrificed at the end of the study period.

III. Conclusion

The test item was non-toxic to male and female rats after acute dermal application.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.3 Inhalation toxicity

Report:	KCP 7.1.3/01 [redacted] F; [redacted]; 2015; M-533854-01-1
Title:	Acute inhalation toxicity study (nose-only) in the rat with fluoxastrobin + prothioconazole EC 200 (100+100 g/L)
Report No.:	15/057-004P
Document No.:	M-533854-01-1
Guideline(s):	OECD 403; US-EPA OPPTS 870.1300; Commission Regulation (EC) No 440/2008, Annex Part B, B.2:
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material:	fluoxastrobin + prothioconazole EC 200 (100+100 g/L)
Short Name:	FXA+PTZ EC 200 (100+100) G
Description:	Yellow brown, light turbid liquid
Lot/Batch no.:	2013-000457
Specification no.:	102000025822
Content:	fluoxastrobin (HEC 5725 E-iso): 9.12 %w/w, 100.2 g/L; prothioconazole (JAU 6476): 8.98 %w/w, 98.74 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2016-05-03
2. Vehicle:	none
3. Test animals	
Species:	rat
Strain:	CRL:(WI)
Sex:	males and females (females were nulliparous and non-pregnant)
Age at dosing:	8-11 weeks
Weight at dosing:	232-384 g (males: 327-384 g, females: 232-253 g)
Source:	[redacted] Germany)
Acclimatisation period:	at least 12 days
Diet:	ssniff SM R/M „Autoclavable Complete Feed for Rates and Mice – Breeding and Maintenance" ([redacted], Germany) *ad libitum*
Water:	tap water *ad libitum*
Housing:	exposure: individually in tapered, polycarbonate restraining tube before and after exposure period: grouped by sex (up to 5 animals per cage) in polycarbonate type III solid floor cages with stainless steel mesh lids on Lignocel and Grade 5 Beddings for laboratory animals.

B. Study design and methods

1. Animal assignment and treatment

Dose (Target concentrations):	Sighting exposure:	5 mg/L
	Main study:	1 and 5 mg/L
Application route:	inhalation (nose-only)	
Exposure:	4 hours	

Group size:	Sighting exposure:	1 rat/sex/group
	Main study:	5 rats/sex/group
Post-treatment observation period:	2 weeks	
Observations:	Mortality, clinical signs, body weight, necropsy	

2. Generation of the test atmosphere / chamber description

Table 7.1.3-1 Test atmosphere and chamber description

	Sighting exposure: Group 0.1	Main study: Group 1	Main study: Group 2
Target concentration (mg/L)	5	5	1
Mean Achieved Concentration (mg/L)	5.00	5.03	0.91
Standard Deviation of Achieved Concentration (mg/L)	0.22	0.08	0.08
Nominal Concentration (mg/L)	25.47	25.96	3.46
Temperature (mean, °C)[#]	21.1	26.3	25.6
Relative humidity (mean, %)*	--	--	--
Mean Mass Median Aerodynamic Diameter (MMAD, µm)	1.98	1.90	1.71
Geometric Standard Deviation (GSD)	2.03	1.95	1.83
Inhalable Fraction (% <4µm)	83.9	86.6	91.9

-- = not applicable.
[#] The temperature in the inhalation chamber was higher than the required range during the exposure of Group 1 (Tmax=27.4°C) and 2 (Tmax=26.0°C) due to technical reason. These deviations had no effect on the purpose and integrity of the study.
* The relative humidity in the inhalation chamber was not evaluated due to the evidently false values caused by sensor interference generated by the aqueous formulation.

II. Results and discussion

A. Mortality

Table 7.1.3-2 Doses, mortality, animals treated

Achieved Concentration mean (mg/L)	Toxicological results*			Occurrence of signs	Time of death	Mortality [%]
Male rats						
0.91	1	5	5	1h - 6d	1d	20%
5.03	3	5	5	1h - 10d	2h - 1d	60%
Females rats						
0.91	0	5	5	1h - 6d	--	0%
5.03	5	5	5	1h - 2d	1d - 2d	100%
LC_{50}: >0.91 mg/L <5.03 mg/L						

* 1st number = number of dead animals, 2nd number = number of animals with signs, 3rd number = number of animals in the group

B. Clinical observations

Wet fur and/or ruffled fur, fur staining by the test item were recorded in all animals from Day 0 up to Day 3. These findings were considered to be related to the restraint and exposure procedures and not of toxicologically significance.

Clinical signs observed after inhalation exposure as extreme laboured, gasping and noisy respiration, sneezing as well as necropsy data are suggestive of a local irritating effect rather than systemic toxicity.

Sighting Exposure – Group 0.1 (5.00 mg/L)

Slight to extreme laboured, gasping and noisy respiration and decreased activity were recorded in animals on the day of exposure and the days following exposure. The male animal was found dead on Day 1. In the surviving female, sneezing also was observed until Day 11, however all clinical signs ceased from Day 12.

Main Study – Group 1 (5.03 mg/L)

Similar clinical signs as in the sighting exposure group were recorded in animals from the main study at the same dose: slight to extreme laboured, gasping and noisy respiration, decreased activity and sneezing. One male died in the second hour of exposure, 4 animals were found dead on Day 1, and additional 3 animals on Day 2. Both survivors recovered and were symptom free on Day 10 or 11.

Main Study – Group 2 (0.91 mg/L)

Slight to extreme laboured, gasping and noisy respiration, decreased activity, sneezing were recorded in the animals on the day of exposure and/or on the days following exposure. One male was found dead on the day following exposure, however all animals recovered and were symptom free from Day 6 until the end of the observation period.

C. Body weight

Slight body weight loss was recorded in survivors from Group 0.1 (sighting exposure, 5.00 mg/L) and group 1 (5.03 mg/L). Body weights of surviving animals of both groups were back to normal by Day 7. Normal body weight gain was noted for the survivors from Group 2 exposed to 0.91 mg/L during whole observation period.

D. Necropsy

Diffuse dark/red discoloration of the non-collapsed lungs and red dry/liquid material at the perinasal fur, were considered to be test item-related.

In surviving animals, no macroscopic changes were noted at terminal sacrifice on Day 14.

III. Conclusion

The acute inhalation median lethal concentration (LC50) in rats was considered to be between 0.91 mg/L and 5.03 mg/L.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): Category 4, H332 (harmful if inhaled)

CP 7.1.4 Skin irritation

Report:	KCP 7.1.4/01 [redacted]; 2001; M-085049-01-1
Title:	Acute skin irritation test (patch test) of HEC 5725 100 EC & JAU 6476 100 in rabbits
Report No.:	R8097
Document No.:	M-085049-01-1
Guideline(s):	EC guideline B.4.; OECD 404
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: HEC 5725 100 EC & JAU 6476 100

Development no.:	30-00280022
Description:	clear yellow liquid
Lot/Batch no.:	06899/0391(0390)
Content:	fluoxastrobin: 100.32 g/L; prothioconazole: 98.04 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2002-02-08

2. Vehicle: none

3. Test animals

Species:	rabbit
Strain:	Himalayan
Age:	approx. 3.5 months
Weight at dosing:	2.6 kg – 3.0 kg
Source:	[redacted] Germany
Acclimatisation period:	at least 20 days
Diet:	Altromin 2023 ([redacted], Germany)
Water:	tap water
Housing:	exposure: singly in special restrainers which allowed free movement of the head but prevented a complete body turn before and after exposure period: separately in cages with dimensions of 425 mm x 600 mm x 380 mm ([redacted] Germany)

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.5 mL/patch
Application route:	dermal (semi-occlusive procedure)
Exposure:	4 hours
Group size:	3 males
Observations:	clinical signs, skin effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

There were no systemic intolerance reactions.

Table 7.1.4-1 Summary of irritant effects (Score)

Animal	Observation (after patch removal)	24h	48h	72h	Mean scores	Response	Reversible (days)
1	Erythema (redness) and eschar formation	1	0	0	0.3	--	na
	Oedema formation	0	0	0	0.0	--	na
2	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na
3	Erythema (redness) and eschar formation	1	0	0	0.3	--	na
	Oedema formation	0	0	0	0.0	--	na

na = not applicable

Response:			Regulation (EC) No 1272/2008
	--	= negative for mean scores	<2.3 none
	+	= irritant for mean scores	≥2.3 Category 2

III. Conclusion

The test item was slightly irritating to the skin of rabbits.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.5 Eye irritation

Report:	KCP 7.1.5/01 [redacted], 2012; M-437242-01-1
Title:	Fluoxastrobin+prothioconazole EC 200 (100+100) G - Acute eye irritation study in rabbits
Report No.:	12/102-005N
Document No.:	M-437242-01-1
Guideline(s):	OECD 405; US-EPA 12-C-98-195, OPPTS 870.2400; Commission Regulation (EC) No 440/2008, B.5
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: FXA+PTZ EC 100+100A G

Specification no.:	102000025822-01
Description:	yellow-brown clear liquid
Lot/Batch no:	2012-001071
Content:	fluoxastrobin: 101.3 g/L; prothioconazole: 100.4 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2014-03-07

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	New Zealand White
Age:	~15 weeks
Weight at dosing:	3784 g – 3898 g
Source:	[redacted], Hungary
Acclimatisation period:	14 days
Diet:	UNI diet for rabbits ([redacted], Hungary)
Water:	tap water
Housing:	individually in AAALAC approved metal wire rabbit cages

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.1 mL/animal
Application route:	instillation into the conjunctival sac
Rinsing:	no
Group size:	3 males
Observations:	clinical signs, eye effects, body weight (at beginning and termination of study)

II. Results and discussion

A. Findings

There was no mortality observed during the study.

The general state and behaviour of animals were normal throughout the study period. The body weight and body weight changes were considered to be normal with no indication of any treatment related effect.

The eyes were examined at 1, 24, 48, 72 hours and at 1, 2 and 3 weeks after application. Fluorescein staining was performed 24 hours before administration, 24, 48, 72 hours and 1, 2 and 3 weeks after application.

Initial Pain Reaction (IPR) (score 2) was observed in all animals. One hour after application conjunctival redness (score 2), chemosis (score 2) and conjunctival discharge (score 3) were observed in all animals.

After three weeks the study was terminated in accordance with OECD 405 and in agreement with the Sponsor.

During the study, the control eye of each animal was symptom-free.

Table 7.1.5-1 Summary of Irritant Effects (Score)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	0	0	0	0.00	--	na
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	2	2	2	2.00	++	not reversible
	Chemosis conjunctivae	2	1	1	1.33	+	21
	Discharge	3	2	1	2.00		21
2	Corneal opacity	1	1	1	1.00	++	not reversible
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	2	2	2	2.00	++	not reversible
	Chemosis conjunctivae	2	2	2	2.00	++	not reversible
	Discharge	3	3	3	3.00		not reversible
3	Corneal opacity	1	1	1	1.00	+	7
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	2	2	2	2.00	++	not reversible
	Chemosis conjunctivae	1	1	1	1.00	--	7
	Discharge	3	2	1	1.67		7

Response for mean scores	Corneal opacity	Iritis	Conjunctival redness	oedema	Regulation (EC) No. 1272/2008
-- = negative	< 1	< 1	< 2	< 2	none
+ = irritant	≥ 1 - < 3	≥ 1 - < 2	≥ 2	≥ 2	Category 2
++ = irreversible effects / serious damage	≥ 3	≥ 1.5			Category 1

III. Conclusion

The test item caused conjunctival effects and opacity of cornea which were not reversible within the 21 days observation period.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): Eye irritation Cat. 1; H318 (causes serious eye damage)

CP 7.1.6 Skin sensitization

Report:	KCP 7.1.6/01 [redacted],; 2002; M-064940-01-1
Title:	HEC 5725 100 EC & JAU 6476 100 - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman)
Report No.:	32024
Document No.:	M-064940-01-1
Guideline(s):	OECD 406; Guideline 96/54/EC, Method B.6.; EPA 712-C-98-197, OPPTS 870.2600
Guideline deviation(s):	The test item contains commercial products known to be stable and homogenous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of the stability and homogeneity of the formulations in physiological saline solution for administration were not performed. This deviation did not limit the assessment of the results.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: HEC 5725 100 EC & JAU 6476 100

Development no.:	30-00280022
Description:	clear yellow liquid
Lot/Batch no:	06899/039l (0390)
Content:	fluoxastrobin: 99.27 g/L; prothioconazole: 95.84 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2002-07-30

2. Vehicle: physiological saline solution

3. Test animals

Species:	guinea pig
Strain:	Hsd Poc:DH (SPF-bred)
Age:	4 – 5 weeks
Weight at dosing:	300 g – 416 g
Source:	[redacted] Germany
Acclimatisation period:	at least five days
Diet:	"PROVIMI KLIBA 3420 - Maintenance Diet for Guinea Pigs" (PROVIMI KLIBA AG)
Water:	tap water
Housing:	conventionally in type IV Makrolon® cages, adaptation: 5 animals/cage, study period: 2 or 3 animals/cage; bedding: low-dust wood shavings ([redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment

Dose

Intradermal induction:	5% (= 20 mg test item/animal)
Topical induction:	100% (= 500 mg test item/animal)
Challenge:	100% (= 500 mg test item/animal)
Application route:	intradermal, dermal

Application volume:	intradermal: 0.1 mL/injection topical induction, challenge: 0.5 mL/patch
Exposure:	topical induction: 48 hours, challenge:24 hours
Group size:	37 females (test item: 20; control: 10, dose-range finding: 7)
Observations:	mortality, clinical signs, skin effects, body weight (at beginning and termination of study)

II. Results and discussion

A. Findings

48 hours after the intradermal induction (1st induction) the animals of the control group showed red wheals and the animals of the test item group showed white or red wheals, white or red injection sites, partly with red surrounding. After 7 days wheals were recorded at the injection sites of the control group and in the test item group in addition encrustations.

Appearance and behaviour of the test item group were not different from the control group.

At the end of the study, the mean body weight of the treatment group animals was in the same range than that of the control group animals.

Table 7.1.6-1 Number of animals exhibiting skin effects

	Test item group (20 animals)					Control group (10 animals)				
	Test item patch			Control patch		Test item patch			Control patch	
Hours	48	72	Total	48	72	48	72	Total	48	72
Challenge 100%	0	0	0	0	0	0	0	0	0	0

The Guinea Pig Maximization Test methodology was checked for reliability in a test on female guinea pigs using alpha-Hexylzimtaldehyd formulated in sterile physiological saline solution at the following concentrations: intradermal induction: 5 %, topical induction: 25 %, challenge: 12 %. After challenge, 100 % of the test animals exhibited dermal reactions in the challenge treatment. There was no reddening of the skin to be observed on control group animals. The sensitivity as well as the reliability of the experimental technique is thus confirmed by this study ([redacted]; 2001; M-082311-01-1).

III. Conclusion

Under the conditions of the maximization test and with respect to the evaluation criteria the test item exhibits no skin-sensitization potential.

The study results trigger the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.7 Supplementary studies on the plant protection product

Not applicable according to Commission Regulation (EU) No 284/2013.

CP 7.1.8 Supplementary studies for combinations of plant protection products

As stipulated by Part A of Commission Regulation (EU) No 284/2013 (data requirements for plant protection products) this point shall be considered on a case by case basis. Whether or not FXA+PTZ EC 200 is recommended for tank mixing may differ from country to country within the European Union. Hence, this point will be addressed in national addenda post EU re-approval of Fluoxastrobin.

CP 7.2 Data on exposure

The non-dietary risk assessment is presented for fluoxastrobin using the representative formulation 'Fluoxastrobin + Prothioconazole EC 200', for use as a fungicide in cereals and onions. The formulation contains the active substance fluoxastrobin (100 g/L). Exposure is estimated using the EFSA guidance on assessment of non-dietary exposure:

> *EFSA, 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014, 2(10):3874, 55pp., doi:10.2903/j.efsa.2014.3874.*

The Standing Committee noted at their meeting in May 2015 that for the acute risk assessment the derivation of the corresponding toxicological reference value (AAOEL) is still outstanding.

Following the noting at the Standing Committee meeting in May, the Commission have published a guidance[5] on the implementation of EFSA's non-dietary exposure guidance document which notes that the EFSA guidance will apply to applications submitted from 1 January 2016. However, for the approval of active substances under Regulation (EC) No 1107/2009, an acute risk assessment is currently not required.

Endpoints relevant for risk assessment:

AOEL:

The Review Report for Fluoxastrobin (SANCO/3921/07- 22 January 2007) is considered to provide the relevant scientific information for the review of the product. An AOEL of 0.03 mg/kg bw/d was established using a SF of 100.

Dermal absorption:

Dermal absorption was evaluated with the representative formulation (EC 200) *in vitro* using human skin. As a result of the study conducted with the representative formulation (EC 200), the following dermal absorption values are used for the risk assessment based on the critical GAP uses:

- 2% for the concentrate (100 g a.s./L)
- 2% for the intermediate dose (1.25 g a.s./L
- 5% for the low dose (0.15 g a.s./L)

For details see CP 7.3.

[5] http://ec.europa.eu/food/plant/pesticides/approval_active_substances/guidance_documents/docs/pesticides_approval-active_guidance_2015-10832.pdf

CP 7.2.1 Operator exposure

The EFSA guidance on assessment of non-dietary exposure is used. The critical GAP (cGAP) for operator risk assessment is presented in the table below.

Table 7.2.1-1 Critical GAP for operator exposure evaluations

Crop	F/ G	Application method	Application rate (kg a.s./ha)	Spray volume (L/ha)	Dermal absorption (%)
Wheat, rye, triticale	F	Field crop sprayer	0.150	100-400	5%
Barley, oats	F	Field crop sprayer	0.125	100-400	5%
Onions	F	Field crop sprayer	0.125	300-800	5%

F = field; G = greenhouse

The product will be applied with tractor-mounted/-trailed field crop (boom) sprayers. The cGAP in wheat, rye and triticale results in the highest exposure due to the higher application rate. Separate calculations for the use in barley, oats and onions are therefore not presented in this dossier.

A summary of the exposure estimates resulting from the critical GAP is presented in the following table. Further information on input parameters and EFSA calculator output are presented in CP 7.2.1.1.

Summary

Table 7.2.1-2: Predicted operator exposure to fluoxastrobin

Crops	F/ G	Application method	PPE	Systemic exposure (mg/kg bw/day)	% of AOEL (0.03 mg/kg bw/day)
Wheat, rye, triticale	F	Vehicle mounted/ trailed boom sprayer	No[1]	0.0089	30
			With[2]	0.0005	2

[1] No PPE: Cotton/polyester working coverall, no gloves
[2] With PPE: In addition to the working coverall protective gloves are worn during mixing/loading and when getting into contact with contaminated surfaces

Assessment

Exposure of operators wearing a working coverall but working with bare hands is 30% of the AOEL. Exposure of operators wearing, in addition, protective gloves during mixing/loading and when getting into contact with contaminated surfaces is 2% of the AOEL.

Conclusion

Based on these favourable exposure estimates there is no unacceptable risk anticipated for operators with regard to exposure to fluoxastrobin.

CP 7.2.1.1 Estimation of operator exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of operators including the EFSA calculator[6] (version: 20 Mar 2015).

The product is applied using field crop sprayers in arable crops (cereals and onions). Exposure is calculated based on the cGAP for wheat, rye, triticale (see Table 7.2.1-1).

A summary of the input parameters and the exposure output resulting from the EFSA calculator is presented below.

Table 7.2.1.1-1: Summary of operator exposure to fluoxastrobin

No PPE: Work wear: arms, body and legs covered

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate = 0.15 kg a.s./ha	Spray dilution = 1.5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 2	Dermal for in use dilution = 1	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	0.0143	% of RVNAS	47.66%
	Acute systemic exposure mg/kg bw/day	0.0841	% 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	0.0089	% of RVNAS	29.80%
	Acute systemic exposure mg/kg bw/day	0.0387	% of RVAAS	

[6] http://www.efsa.europa.eu/en/efsajournal/pub/3874

With PPE: Gloves during mixing/loading and when getting in contact with contaminated surfaces, work wear: arms, body and legs covered

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.15 kg a.s. /ha	Spray dilution = 1.5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 2	Dermal for in use diluation = 5	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		0.0143	% of RVNAS	47.66%
	Acute systemic exposure mg/kg bw/day		0.0841	% 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		0.0005	% of RVNAS	1.74%
	Acute systemic exposure mg/kg bw/day		0.0059	% of RVAAS	

CP 7.2.1.2 Measurement of operator exposure

Since the exposure estimate carried out indicate that the AOEL will not be exceeded under practical conditions of use, a study to provide a measure of operator exposure was not necessary and was therefore not carried out.

CP 7.2.2 Bystander and resident exposure

The EFSA guidance on assessment of non-dietary exposure is used. Exposure estimations for the resident scenario which also covers the bystander scenario are provided using the EFSA calculator.

The critical GAP (cGAP) for resident/bystander risk assessment is presented in the table below.

Table 7.2.2-1: Summary of critical GAPs for residents (covers bystander)

Crop	Application technique	Max. dose rate (kg a.s./ha)	Spray volume (L/ha)	Max conc. of a.s. in spray (g/L)	Max no. of appl.	Min. spray interval (days)	Dermal absorption (%)
Wheat, rye, triticale	Field crop sprayer	0.15	100-400	1.5	2	14	2%
Onions	Field crop sprayer	0.125	300-800	0.42	2	10	5%

The critical resident and bystander exposure scenario for field crop spray application with off-target drift is the use in wheat, rye and triticale (2 x 0.150 kg a.s./ha in 100 L water). With this use the highest application rate is combined with the lowest water volume yielding the highest concentration of a.s. in the spray. Consequently also appropriate dermal absorption data are used.

Since due to the lower in-use concentration of fluoxastrobin during spray application in onions (2 x 0.125 kg a.s./ha in 300 L water) the higher dermal absorption value has to be considered for the exposure assessment in onions resident exposure is also calculated for the use in onions.

A summary of the exposure estimates resulting from the critical GAP is presented in the following table. Further information on input parameters and EFSA calculator output are presented in CP 7.2.2.1.

Summary

Table 7.2.2-2: Predicted systemic exposures to fluoxastrobin

Crop	Target group	Scenario	Total systemic exposure (mg/kg bw/day)*	% of AOEL (0.03 mg/kg bw/day)
Wheat, rye, triticale	Resident-child	Spray drift	0.0008	3
		Vapour	0.0011	4
		Surface deposits	0.0003	<1
		Entry into treated crops	0.0009	3
		All pathways	0.0024	8
	Resident-adult	Spray drift	0.0002	<1
		Vapour	0.0002	<1
		Surface deposits	0.00004	<1
		Entry into treated crops	0.0005	2
		All pathways	0.0007	2
Onions	Resident-child	Spray drift	0.0006	2
		Vapour	0.0011	4
		Surface deposits	0.0003	1
		Entry into treated crops	0.0019	6
		All pathways	0.0031	10
	Resident-adult	Spray drift	0.0001	<1
		Vapour	0.0002	<1
		Surface deposits	0.0001	<1
		Entry into treated crops	0.0011	4
		All pathways	0.0012	4

* Assumes a 60 kg body weight for an adult and 10 kg for a child

Assessment

Mean estimates over all pathways for adult and child resident exposure to fluoxastrobin are 2% and 8% of the AOEL, respectively, for cereals. For onions exposure to fluoxastrobin over all pathways amounts to 4% and 10% of the AOEL for adult and child residents, respectively.

Conclusion

Based on these favourable exposure estimates there is no unacceptable risk anticipated for residents/bystanders with regard to exposure to fluoxastrobin.

CP 7.2.2.1 Estimation of bystander and resident exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of residents including the EFSA calculator (version: 20 Mar 2015).

The product is applied using field crop sprayers in arable crops (cereals and onions). Exposure is calculated based on the cGAP for wheat, rye, triticale as well as for onions (see Table 7.2.2-1).

A summary of the input parameters and the exposure output resulting from the EFSA calculator is presented below.

Table 7.2.2.1-1: Summary of resident exposure to fluoxastrobin: cereals

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1 kg a.s. /ha	Spray dilution = 1.5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted,			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 2	Dermal for in use dilution = 2	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	0.0008	% of RVNAS	2.79%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	3.57%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	0.95%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0009	% of RVNAS	2.91%
	All pathways (mean) mg/kg bw/day	0.0024	% of RVNAS	8.14%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.65%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.77%
	Surface deposits (75th percentile) mg/kg bw/day	0.0000	% of RVNAS	0.12%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	1.62%
	All pathways (mean) mg/kg bw/day	0.0007	% of RVNAS	2.45%

Table 7.2.2.1-2: Summary of resident exposure to fluoxastrobin: onions

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.125 kg a.s. /ha	Spray dilution = 0.416666666666667 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Bulb vegetables / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 2	Dermal for in use diluation = 5	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	0.0006	% of RVNAS	1.89%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	3.57%
	Surface deposits (75th percentile) mg/kg bw/day	0.0003	% of RVNAS	1.15%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0019	% of RVNAS	6.31%
	All pathways (mean) mg/kg bw/day	0.0031	% of RVNAS	10.49%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.45%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.77%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.25%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	3.50%
	All pathways (mean) mg/kg bw/day	0.0012	% of RVNAS	3.96%

CP 7.2.2.2 Measurement of bystander and resident exposure

Since the exposure estimate carried out indicate that the AOEL will not be exceeded under practical conditions of use a study to provide a measure of resident and bystander exposure was not necessary and was therefore not carried out.

CP 7.2.3 Worker exposure

The EFSA guidance on assessment of non-dietary exposure is used including, in addition, results from dislodgeable foliar residues as higher tier. The critical GAP (cGAP) for worker risk assessment is presented in Table 7.2.3-1.

Table 7.2.3-1 Critical GAP for worker exposure evaluations

Crop	F/ G	Re-entry activity	Application rate (kg a.s./ha)	Number of applications	Min. spray interval (days)	Dermal absorption (%)
Wheat, rye, triticale	F	Crop inspection	0.150	2	14	5%
Onions	F	Crop inspection	0.125	2	10	5%

F = field; G = greenhouse

The product will be applied with tractor-mounted/-trailed field crop (boom) sprayers. The cGAP in cereals is wheat, rye and triticale resulting in the highest exposure due to the higher application rate. Separate calculations for the use in barley and oats are therefore not presented in this dossier. Additionally the GAP in onions is considered due to the shorter spray interval.

No manual activities are necessary for maintaining the crops. Harvesting of cereals and onions is performed by appropriate machines. Hence, there is in general no scenario for which worker exposure needs to be addressed. However, for field crops it is required to assess worker exposure due to crop inspection activities. The work duration is proposed to be 2 hours per day.

A summary of the exposure estimates resulting from the critical GAP is presented in the following table. Further information on input parameters and EFSA calculator output are presented in CP 7.2.3.1.

Summary

Table 7.2.3-2: Predicted worker exposure to fluoxastrobin

Crops	F/ G	Re-entry activity	Clothing scenario	Systemic exposure (mg/kg bw/day)	% of AOEL (0.03 mg/kg bw/day)
Wheat, rye, triticale	F	Crop inspection	No clothing	0.0162	54
			Arms, body, legs covered	0.0018	6
Onions	F	Crop inspection	No clothing	0.0140	47
			Arms, body, legs covered	0.0016	5
Predicted worker exposure to fluoxastrobin including DFR measurements					
Onions	F	Crop inspection	No clothing	0.0057	19
			Arms, body, legs covered	0.0006	2

Assessment

Exposure of naked workers is 54% of the AOEL in cereals and 47% of the AOEL in onions. Exposure of workers wearing one layer of work clothing is 6% of the AOEL in cereals and 5% of the AOEL in onions.

In addition, measurements of dislodgeable foliar residues are available for the scenario 're-entry in onions'. Integrating this data the exposure of a naked worker amounts to 19% of the AOEL and 2% of the AOEL for a worker wearing one layer of work clothing.

Conclusion

Based on these favourable exposure estimates no unacceptable risk is anticipated for workers with regard to exposure to fluoxastrobin.

CP 7.2.3.1 Estimation of worker exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of workers including the EFSA calculator (version: 20 Mar 2015).

The product is applied using field crop sprayers in arable crops (cereals and onions). Exposure is calculated based on the cGAP for wheat, rye, triticale as well as onions (see Table 7.2.3-1).

A summary of the input parameters and the exposure output resulting from the EFSA calculator is presented below.

Table 7.2.3.1-1: Summary of worker exposure to fluoxastrobin: cereals

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc	Application rate = 0.15 kg a.s. /ha	Spray dilution = 1.5 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 2	Dermal for in use dilution = 5	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	0.0162	% of RVNAS	53.86%
	Working clothing mg/kg bw/day	0.0018	% of RVNAS	6.03%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

Table 7.2.3.1-2: Summary of worker exposure to fluoxastrobin: onions

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.125 kg a.s. /ha	Spray dilution = 0.416666666666667 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2 Application interval = 10 days
Percentage Absoprtion	Dermal for product = 2 Dermal for in use diluation = 5		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	0.0140	% of RVNAS	46.71%
	Working clothing mg/kg bw/day	0.0016	% of RVNAS	5.23%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

In addition, dislodgeable foliar residues (DFR_M) were experimentally determined for leek after application of 'Fluoxastrobin + Prothioconazole EC 200'. A summary of the respective trials and its results are provided below. Leek can be regarded as a surrogate for onions since the habitus is similar and both species belonging to the same botanical genus.

With a very conservative approach highest DFR_M values observed in the course of the experiments are considered (Table 7.2.3.1-3) for the use in a refined risk assessment. A rapid dissipation of the foliar residues of fluoxastrobin was observed in the trials and accumulation of residues after repeated application did not occur within a spray interval of 10 days.

Table 7.2.3.1-3: Experimentally derived maximum DFR_M values

Crop	Trial	DFR_M [µg/cm²]	Observed on
Leek	Central zone	0.204	Day 0 after 2nd application
	Southern zone	0.272	Day 0 after 1st application

A refined calculation of worker exposure to fluoxastrobin during re-entry in onion fields for crop inspection is presented below.

For using this data in conjunction with the EFSA calculator the dislodgeable foliar residue has to be normalised and the highest residue is related to one application:

DFR_M: 0.272 µg/cm²
DFR_M normalised: 2.18 µg/cm² per kg a.s./ha (= 0.272 µg/cm² : 0.125 kg a.s./ha)

Table 7.2.3.1-3: Summary of worker exposure to fluoxastrobin: onions with DFR data

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.125 kg a.s. /ha	Spray dilution = 0.416666666666667 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 1, Application interval = 365 days
Percentage Absoprtion	Dermal for product = 2 Dermal for in use diluation = 5		Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	2.18 µg a.s./cm2 per kg a.s./ha		DT50	30 days	
Worker - Inspection, irrigation	Potential exposure mg/kg bw/day		0.0037	% of RVNAS	18.92%
	Working clothing mg/kg bw/day		0.0006	% of RVNAS	2.12%
	Working clothing and gloves mg/kg bw/day			% of RVNAS	

Report: KCP 7.2.3.1/01[redacted]; 2015; M-513058-01-1
Title: Determination of the dislodgeable foliar residues (DFR) of prothioconazole and fluoxastrobin in/on leek after spraying of fluoxastrobin & prothioconazole EC 200 in the field in Germany
Report No.: 14-2910
Document No.: M-513058-01-1
Guideline(s): US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation
Guideline deviation(s): none
GLP/GEP: **yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislodgeable foliar residues of fluoxastrobin, prothioconazole and its conversion product prothioconazole desthio on leek foliage after each of four spray applications performed in the field with Fluoxastrobin + Prothioconazole EC 200 (100 g fluoxastrobin/L and 100 g prothioconazole/L). The study trial was conducted in Central Europe (Gemany) during the 2014 season. The actual application data are presented in the following table.

Table 7.2.3.1-4: Application parameters

Country	Appl. mode	Application						
		No. of appl.	Interval (days)	Growth stage (BBCH code)	Test item rate (L/ha)	Water rate (L/ha)	a.s.	Appl. rate (kg a.s./ha)
Germany	Field crop sprayer	1	-	45	1.25	300	fluoxastrobin	0.125
							prothioconazole	0.125
		2	6	46	1.25	300	fluoxastrobin	0.125
							prothioconazole	0.125
		3	4	47	1.25	300	fluoxastrobin	0.125
							prothioconazole	0.125
		4	4	48	1.25	300	fluoxastrobin	0.125
							prothioconazole	0.125

The test site consisted of a single plot which was divided into three sub-plots for sampling.

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler ([redacted] Co; El Monte, CA). Each sample consisted of 40 disks cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples as well as samples needed for the field recoveries were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept on wet ice for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but no longer than 4 hours after collection. The samples were dislodged by adding 100 mL of a 0.01 % Aerosol OT solution (i.e. docusate sodium salt), which corresponds to a surfactant. Each jar containing the leaf material and the 100 mL 0.01% Aerosol OT solution was capped securely and placed on a shaker operating at approximately 200 cycles per minute for a period of approximately 10 min. The dislodging solution was sampled and the dislodging was repeated with 100 mL fresh 0.01 % Aerosol OT solution. The second dislodging solution was combined with the first and 1 mL of a 250g/L cysteine-hydrochloride solution was added to stabilize the prothiconazole in the solution.

Field fortification samples were used to demonstrate the stability of the samples during storage period of the study and the ability of the analytical laboratory to recover an analyte fortified into a sample at the field test site. The solutions from dislodged control samples were separately fortified with a mixture of fluoxastrobin and prothioconazole-desthio or prothioconazole at the LOQ and at a level of 10 to 200 times of the LOQ. Field spikes were performed prior to the 1st application. The field recovery samples were treated in the same manner as the field residue samples until analysis.

II Results and discussion

The results with regard to fluoxastrobin are summarised in the following table.

Table 7.2.3.1-5: Amounts of fluoxastrobin dislodgeable foliar residues on leek in Germany [µg a.s./cm²], two sided. Figures in bold indicate day of treatment

Sampling				Dislodgeable foliar residues [µg a.s./cm²]
Day after 1st appl.	Day after 2nd appl.	Day after 3rd appl.	Day after 4th appl.	Fluoxastrobin
-0				0.005
0				0.103
2				0.0842
6	-0			0.0545
	0			0.204
	2			0.0815
	4	-0		0.0618
		0		0.167
		2		0.106
		4	-0	0.0405
			0	0.179
			1	0.183
			3	0.0850
			5	0.0725
			7	0.0437
			14	0.0219

" - " = before respective treatment

Subsequently to each treatment the trial shows a clear decline of DFR for fluoxastrobin. The decline of foliar residues of fluoxastrobin within the spray interval was >70% of the DFR_0. The highest DFR_0 value of 0.204 µg a.s./cm² was measured after the second application

III Conclusion

Under central European conditions in the field DFR of fluoxastrobin on leek shows a rapid decline. Hence, the results indicate that with four consecutive treatments and a spray interval of 5 days accumulation of DFR on leek does not occur.

Leek can be regarded as a surrogate for onions since the habitus is similar and both species belonging to the same botanical genus.

Report:	KCP 7.2.3.1/02 [redacted],; 2015; M-514393-01-1
Title:	Determination of the dislodgeable foliar residues (DFR) of prothioconazole and fluoxastrobin in/on leek after spraying of fluoxastrobin & prothioconazole EC 200 in the field in Italy
Report No.:	14-2909
Document No.:	M-514393-01-1
Guideline(s):	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation
Guideline deviation(s):	none
GLP/GEP:	**yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislodgeable foliar residues of fluoxastrobin, prothioconazole and its conversion product prothioconazole desthio on leek foliage after each of two spray applications performed in the field with Fluoxastrobin + Prothioconazole EC 200 (100 g fluoxastrobin/L and 100 g prothioconazole/L). The study trial was conducted in southern Europe (Italy) during the 2014 season. The actual application data are presented in the following table.

Table 7.2.3.1-6: Application parameters

Country	Appl. mode	Application						
		No. of appl.	Interval (days)	Growth stage (BBCH code)	Test item rate (L/ha)	Water rate (L/ha)	a.s.	Appl. rate (kg a.s./ha)
Italy	FCS	1	-	43	1.25	400	fluoxastrobin	0.125
							prothioconazole	0.125
		2	10	45	1.25	400	fluoxastrobin	0.125
							prothioconazole	0.125

FCS: Field crop sprayer

The test site consisted of a single plot which was divided into three sub-plots for sampling.

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler ([redacted] Co; El Monte, CA). Each sample consisted of 40 disks cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples as well as samples needed for the field recoveries were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept on wet ice for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but no longer than 4 hours after collection. The samples were dislodged by adding 100 mL of a 0.01 % Aerosol OT solution (i.e. docusate sodium salt), which corresponds to a surfactant. Each jar containing the leaf material and the 100 mL 0.01% Aerosol OT solution was capped securely and placed on a shaker operating at approximately 200 cycles per minute for a period of approximately 10 min. The dislodging solution was sampled and the dislodging was

repeated with 100 mL fresh 0.01 % Aerosol OT solution. The second dislodging solution was combined with the first and 1 mL of a 250g/L cysteine-hydrochloride solution was added to stabilize the prothiconazole in the solution.

Field fortification samples were used to demonstrate the stability of the samples during storage period of the study and the ability of the analytical laboratory to recover an analyte fortified into a sample at the field test site. The solutions from dislodged control samples were separately fortified with a mixture of fluoxastrobin and prothioconazole-desthio or prothioconazole at the LOQ and at a level of 10 to 200 times of the LOQ. Field spikes were performed prior to the 1st application. The field recovery samples were treated in the same manner as the field residue samples until analysis.

II Results and discussion

The results with regard to fluoxastrobin are summarised in the following table.

Table 7.2.3.1-7: Amounts of fluoxastrobin dislodgeable foliar residues on leek in Italy [µg a.s./cm²], two sided. Figures in bold indicate day of treatment

Sampling		Dislodgeable foliar residues [µg a.s./cm²]
Day after 1st application	**Day after 2nd application**	**Fluoxastrobin**
-0		<0.005
0		0.272
1		0.184
4		0.0070
10	-0	<0.005
	0	0.254
	1	0.225
	4	0.150
	7	0.0972
	14	0.00768
	21	<0.005

" - " = before respective treatment

Subsequently to each treatment the trial shows a clear decline of DFR for fluoxastrobin. A decline of foliar residues of fluoxastrobin to values <LOQ within the spray interval was observed. The highest DFR_0 value of 0.272 µg a.s./cm² was measured after the first application.

III Conclusion

Under southern European conditions in the field DFR of fluoxastrobin on leek shows a rapid decline. Hence, the results indicate that with two consecutive treatments and a spray interval of 10 days accumulation of DFR on leek does not occur.

Leek can be regarded as a surrogate for onions since the habitus is similar and both species belonging to the same botanical genus.

CP 7.2.3.2 Measurement of worker exposure

Since the exposure estimate carried out indicate that the AOEL will not be exceeded under practical conditions of use, a study to provide a measure of worker exposure was not necessary and was therefore not carried out.

CP 7.3 Dermal adsorption

The extent of dermal absorption of fluoxastrobin formulated as an EC 200 formulation was investigated *in vitro* using human skin. A summary of the study is given in the following. A conclusion and recommendation regarding the dermal absorption of fluoxastrobin formulated as an EC 200 (fluoxastrobin + prothioconazole EC 100 + 100) is given below.

Report:	KCP 7.3/01 [redacted]; 2013; M-456865-01-1
Title:	Fluoxastrobin in Fandango New (FXA + PTZ EC 100 + 100) formulation: [14C]-fluoxastrobin in vitro dermal absorption study using human and skin
Report No.:	SA 13031
Document No.:	M-456865-01-1
Guideline(s):	OECD Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004). OECD Environmental Health and Safety Publication Series on testing and Assessment N° 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004). EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption, EFSA Journal 2012; 10(4): 2665.
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and methods

Human skin: Source: [redacted], France.
Number and sex: 9 donors, female.
Anatomical region: Abdomen.
Thickness: 332 to 535 µm.

Test Material:

Non-radiolabelled: Batch: EDCJ000205.
Purity = 99.5%.

Radiolabelled: [pyrimidine-2-^{14}C] HEC 5725 Isomer E (Fluoxastrobin)
Batch: KML 9464.
Specific activity: 4.18 MBq/mg.
Radiopurity of the formulation: >99% by HPLC.

Formulation: The formulation used in this experiment was the Fandango New, Fluoxastrobin+prothioconcazole EC 100+100, formulation (specification number 102000025822) It was used at three nominal concentrations of fluoxastrobin: neat, 100 g fluoxastrobin /L, 1.25 g fluoxastrobin /L and 0.15 g fluoxastrobin /L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50

mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment: The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm² exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffer saline) using natural sponge swabs, in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay: The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. Efficiency correlation curves were prepared for each scintillation cocktail and were regularly checked by the use of [^{14}C-n-hexadecane standards. The scintillation counter was recalibrated when a deviation of greater than 2% was observed when counting quality control standards. The limit of detection was taken to be twice the background values for blank samples in appropriate scintillation cocktails.

Findings:

Fluoxastrobin was demonstrated to be soluble in the receptor fluid at the concentration of 0.39 mg/mL of receptor fluid. During the study, the maximal concentration per hour of fluoxastrobin in the receptor fluid was 0.098 µg/mL. Therefore the solubility in the receptor fluid was deemed to be sufficient to avoid any risk of back diffusion.

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable.

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 96.99% to 103.9% of the applied dose.

These study results are presented in Table 7.3-1.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-fluoxastrobin in an EC 200 formulation at the rates of 100 g/L, 1.25 g/L and 0.15 g/L to human and rat skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)					
Dose Levels	Neat formulation: High dose (SYP13779, 100 g/L)		Dilution: Intermediate dose (SYP13781, 1.25 g/L)		Dilution: Low dose (SYP13785, 0.15 g/L)	
Species	Human (n=4)		Human (n=4)		Human (n=5)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (8h)	93.11	2.66	99.12	2.28	96.25	3.59
Skin swabs (24h)[a]	0.84	0.85	1.41	1.21	2.17	1.16
Total skin swabs	93.95	2.00	100.52	1.59	98.41	3.12
Surface Dose (1st two tape-strips)	0.54	0.47	1.37	1.07	1.32	1.14
Donor chamber	1.51	1.34	0.24	0.23	n.d.	n.a.
Total % non-absorbed	*96.00*	*0.33*	*102.1*	*1.41*	*99.73*	*2.37*
SKIN COMPARTMENT						
Skin[b]	0.44	0.27	0.42	0.18	0.59	0.26
Stratum corneum[c]	0.47	0.36	1.02	0.53	1.37	0.71
Total % at dose site	*0.92*	*0.60*	*1.45*	*0.62*	*1.96*	*0.87*
RECEPTOR COMPARTMENT						
Receptor fluid (0-24h)	0.06	0.09	0.30	0.17	0.33	0.15
Receptor fluid terminal	0.01	0.02	0.03	0.02	0.03	0.03
Receptor chamber	n.d.	n.a.	n.d.	n.a.	1.65	1.68
Total % directly absorbed[d]	*0.08*	*0.11*	*0.33*	*0.18*	*2.01*	*1.60*
Total % Potentially Absorbable	*0.99*	*0.70*	*1.78*	*0.60*	*3.97*	*1.39*
TOTAL % RECOVERY	96.99	0.43	103.9	1.44	103.7	2.11

[a]: sum of radioactivity found in swabs at termination and in surrounding swabs.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a. : not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:

The dermal penetration of [^{14}C]-fluoxastrobin through human dermatomed skin from the EC 200 formulation was investigated at three concentrations corresponding to the neat product (100 g/L) and to two representative dilutions (1.25 and 0.15 g/L), respectively.

Overall, the dermal penetration of [^{14}C]-fluoxastrobin in the FXA+PTZ EC 200 formulation through human skin was low at all concentrations used.

The mean percentage of fluoxastrobin in the EC 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site minus the first 2 tape strips)* over a period of 24 hours for the neat formulation was 1% for human skin.

The mean percentage of fluoxastrobin in the EC 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site minus the first 2 tape strips)* over a period of 24 hours for the intermediate dose rate was 1.8% for human skin.

The mean percentage of fluoxastrobin in the EC 200 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site minus the first 2 tape strips)* over a period of 24 hours for the low dose rate was 4% for human skin.

According to the new EFSA guidance[7] a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Albeit that the notifier considers that the value of 25% for the standard deviation limit to be too conservative, the application of the guidance results in the values of 1.7% (neat formulation), 2.4% (1.25 g/L) and 5.4% (0.15g/L) for fluoxastrobin in the EC 200 formulation (FXA+PTZ EC 100+100) which can be rounded to:

- 2% for the neat formulation (100 g/L)
- 2% for the intermediate dose (1.25 g/L)
- 5% for the low dose (0.15 g/L).

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document JCP for FXA+PTZ EC 200).

[7] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.