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Document Title

Summary of the toxicological studies Prothioconazole FS 100 (100 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013

Document MCB

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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Author(s)

[redacted]

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

INTRODUCTION

This document summarises the information related to…

1) …the toxicological studies for the representative formulation PTZ FS 100 specification number 102000030977.
2) …non-dietary exposure calculations and assessments to prothioconazole and its main metabolite prothioconazole-desthio during the seed treatment using the representative formulation PTZFS 100 and during sowing of treated seeds.

CP 7.1 Acute toxicity

Prothioconazole FS 100 is a fungicide formulation containing the active substance prothioconazole at 100 g/L.

The acute oral, dermal and inhalative toxicity studies as well as skin and eye irritation and sensitization studies have been performed in 2001 with batch 06528/0058(0054) of development no. 3000267751.

At the time of study conduct the formulation was named JAU 6476 100 FS

The specification of the product has not changed significantly and therefore all the studies are considered to be valid for this submission.

Full details of the formulation specification and the related Bridging Statement can be found in the confidential part of this submission (Document J).

The table below summarises the results from the acute toxicological studies conducted with the formulated product.

Type of study	Results	Report / document no.
Acute oral rat	LD_{50}: >2000 mg/kg bw	[redacted], P. (2001) CP 7.1.1 Report 31404 [M-137432-01-1]
Acute dermal rat	LD_{50}: >4000 mg/kg bw	[redacted], P. (2001) CP 7.1.2 Report 31403 [M-076832-01-1]
Acute inhalation rat	LC_{50}: > 2735 mg/m³ air [max. tech. attainable concentration]	[redacted], J. (2001) CP 7.1.3 Report 31313 [M-070287-01-1]
Acute skin irritation rabbit	not irritating	[redacted], J. (2001) CP 7.1.4 Report R8051 [M-075238-01-1]
Acute eye irritation rabbit	not irritating	[redacted], J. (2001) CP 7.1.5 Report R8052 [M-075102-01-1]
Skin sensitisation (maximization test on guinea pigs)	sensitising	[redacted], H. W. (2001) CP 7.1.6 Report 31575 [M-087838-01-1]

The formulation prothioconazole FS 100 is is non-toxic after acute oral, dermal and inhalative administration. It is not irritating to the skin and eyes of rabbits. Prothioconazole FS 100 shows a sensitising potential in the maximisation test on guinea pigs.

The following classification/labelling is triggered:

- Regulation (EC) No 1272/2008 (CLP): Skin sensitisation Cat. 1;
  H317 (may cause an allergic skin reaction)

CP 7.1.1 Oral toxicity

Report:	KCP 7.1.1/01 [redacted],; 2001; M-137432-01-1
Title:	JAU 6476 100 FS - Study for acute oral toxicity in rats
Report No.:	31404
Document No.:	M-137432-01-1
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 aqueous formulations for administration were not performed.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: JAU 6476 100 FS

Development no.:	300026775I
Description:	red suspension
Lot/Batch no:	06528/0058(0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: distilled water

3. Test animals

Species:	Wistar rat
Strain:	Hsd Cpb: WU
Age:	≥9 weeks
Weight at dosing:	males: 263 g - 277 g; females: 185 g - 194 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	NAFAG No. 9441/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: 2 hours
Group size:	3 rats/sex
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	0#	3	d2	--	0
female rats						
2000	0	0#	3	d2	--	0
LD_{50} > 2000 mg/kg bw						

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

\# refer to B. Clinical observations

B. Clinical observations

Red colored feces were observed on the day after administration. This is obviously related to the red colour of the test substance.

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 is non-toxic after acute oral administration

The study result triggers the following classification/labelling:
- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.2 Dermal toxicity

Report:	KCP 7.1.2/01 [redacted],; 2001; M-076832-01-1
Title:	JAU 6476 100 FS - Study for acute dermal toxicity in rats
Report No.:	31403
Document No.:	M-076832-01-1
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):	none
GLP/GEP:	**yes**

I. Materials and methods

1. Test material: JAU 6476 100 FS

Development no.:	3000267751
Description:	red suspension
Lot/Batch no:	06528/0058(0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: none

3. Test animals

Species:	Wistar rat
Strain:	Hsd Cpb: WU
Age:	males: 237 g - 248 g; females: 200 g - 214 g
Weight at dosing:	males: ≥8; females: ≥10 weeks
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	NAFAG No. 9441/W10 pellets ([redacted] Switzerland)
Water:	tap water
Housing:	individually; 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	22.50	42.1 – 44.1
females	4000	20.25	39.5 – 42.3

Application route:	dermal, semi-occlusive dressing
Exposure:	24 hours
Group size:	5 rats/sex
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	d2 - d10	-	0
Females rats						
4000	0	0#	5	d2 - d14	-	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

\# referto B. Clinical observations

B. Clinical observations

No systemic clinical signs were observed after treatment with 4000 mg/kg body weight.

The application site was discolored red during the experimental period. This is obviously related to the red colour of the test substance.

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 is non-toxic after acute dermal administration.

The study result triggers the following classification/labelling:

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

CP 7.1.3 Inhalation toxicity

Report:	KCP 7.1.3/01 [redacted]; 2001; M-070287-01-1
Title:	JAU 6476 100 FS (c.n.: --) - Study on acute inhalation toxicity in rats according to OECD no. 403
Report No.:	31313
Document No.:	M-070287-01-1
Guideline(s):	OECD 403; Directive 92/69/EEC, Method B.2.; US-EPA 712C-98-193, OPPTS 870.1300
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: JAU 6476 100 FS

Development no.:	3000267751
Description:	red suspension
Lot/Batch no:	06528/0058(-0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: aqueous solution

3. Test animals

Species:	Wistar rat
Strain:	Hsd Cpb:WU
Age:	approx. 2 months
Weight at dosing:	males: 186g - 202 g; females: 161 g - 187 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard fixed-formula diet (NAFAG No. 9439 pellets maintenance diet for rats and mice)
Water:	tap water
Housing:	individually in conventional Makrolon® Type II cages; bedding: type BK8/15 low-dust wood granulate (Ssniff, Soest, , Germany)

B. Study design and methods

1. Animal assignment and treatment

Dose:	0-2735 mg/m³ (max. tech. attainable concentration)
Application route:	inhalation, nose-only
Exposure:	4 hours
Group size:	5 rats/sex/group
Post-treatment observation period:	2 weeks

Observations: mortality, clinical signs, rectal temperature, reflex tests, body weight, gross necropsy

2. Generation of the test atmosphere / chamber description

Generation and characterization of chamber atmosphere

	Group 1	Group 2
Target concentration (mg/m³)	control (water)	5000
Actual concentration (mg/m³)	--	2735
Gravimetric concentration (mg/m³)	--	1395
Temperature (mean, °C)	21	23
Relative humidity (mean, %)	>95	92
MMAD (µm) GSD Aerosol mass < 3 µm (%) Mass recovered (mg/m³)	-- -- -- --	3.31 2.03 44.7 1339.4

MMAD = Mass Median Aerodynamic Diameter, GSD = Geometric Standard Deviation; -- = not applicable

II. Results and discussion

A. Mortality

Table 7.1.3-1 Doses, mortality / animals treated

Actual concentration (mg/m³)	Toxicological result*			Occurrence of signs	Time of death	Rectal temperature (°C)
Male rats						
0	0	0	5	--	--	37.9
2735	0	0	5	--	--	37.5 *
Female rats						
0	0	0	5	--	--	38.2
2735	0	0	5	--	--	37.1 *
LC_{50}: >2735 mg/m³ (max. tech. attainable concentration)						

* 1st number = number of dead animals; 2nd number = number of animals with signs after cessation of exposure, 3rd number = number of animals exposed

* = p<0.05

B. Clinical observations

Mortality did not occur at an exposure level considered to represent the maximum technically attainable concentration of 2735 mg/m³.

0, 2735 mg/m³: All rats tolerated the exposure without clinical signs.

In a battery of reflex measurements made on the first postexposure day, rats of the 2735 mg/m³ group did not experience changes in reflexes.

Statistical comparisons of the rectal temperature between control animals and the 2735 mg/m³ group revealed that the difference to the control group was statistically significant, however, the magnitude of change is not considered to be of any toxicological significance.

C. Body weight

Comparisons between control animals and the group exposed to the test substance did not reveal changes considered to be of any toxicological significance.

D. Necropsy

In animals sacrificed at the end of the observation period no consistent changes were observed that could be attributed to the exposure to the test item.

III. Conclusion

The aerosolized test substance (liquid aerosol) proved to have essentially no acute inhalation toxicity to rats.

The study result triggers the following classification/labelling:

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

CP 7.1.4 Skin irritation

Report:	KCP 7.1.4/01 [redacted]s; 2001; M-075238-01-1
Title:	Acute skin irritation test (patch test) of JAU 6476 100 FS in rabbits
Report No.:	R8051
Document No.:	M-075238-01-1
Guideline(s):	EC guideline B.4.; OECD 404
Guideline deviation(s):	none
GLP/GEP:	**yes**

A. Materials

1. Test material: JAU 6476 100 FS

Development no.:	300026775
Description:	red suspension
Lot/Batch no:	06528-0058 (0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	Himalayan
Age:	approx. 4.5 months
Weight at dosing:	2.2 kg - 2.3 kg
Source:	[redacted] Germany
Acclimatisation period:	at least 20 days
Diet:	Altromin 2023 ([redacted] Germany
Water:	tap water
Housing:	exposure period: singly in special restrainers which allowed free movement of the head but prevented a complete body turn; before/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
Exposure:	4 hours
Group size:	3 males
Observations:	clinical signs, skin effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

The study report describes for all three rabbits exposed for 4 hours to 0.5 mL JAU 6476 100 FS per animal (semi-occlusive condition) an "erythema (grade 1)"; animal no. one 24 hours to 7 days, animal no. two 60 minutes to 4 days and animal no. three 60 minutes to 7 days after patch removal.

As the tested formulation is a red suspension and taking into account the findings of the acute oral and dermal studies and the negative result of the eye irritation study, the "erythema" is obviously a discoloration of the skin by the test item.

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	1	1	1.0	--	8
	Oedema formation	0	0	0	0.0		na
2	Erythema (redness) and eschar formation	1	1	1	1.0	--	5
	Oedema formation	0	0	0	0.0		na
3	Erythema (redness) and eschar formation	1	1	1	1.0	--	8
	Oedema formation	0	0	0	0.0		na

na = not applicable

Response: -- = negative for mean scores <1.5 (GHS)
<2.3 (Regulation (EC) No 1272/2008)
(+) = mild irritant for mean scores ≥1.5 - <2.3 (GHS category 3)
\+ = irritant for mean scores ≥2.3 (Regulation (EC) No 1272/2008 and GHS category 2)

III. Conclusion

The reported "erythema" is obviously a discoloration of the skin by the test item.

In any case, classification is not triggered.

The study result triggers the following classification/labelling:

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

CP 7.1.5 Eye irritation

Report:	KCP 7.1.5/01 [redacted]; 2001; M-075102-01-1
Title:	Acute eye irritation study of JAU 6476 100 FS by instillation into the conjunctival sac of rabbits
Report No.:	R8052
Document No.:	M-075102-01-1
Guideline(s):	EC guideline B.5.; OECD 405
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: JAU 6476 100 FS

Development no.:	3000267751
Description:	red suspension
Lot/Batch no:	00528/0058(0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	Himalayan
Age:	approx. 3.5 months
Weight at dosing:	2.2 kg - 2.3 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 20 days
Diet:	Altromin 2023 ([redacted] Germany)
Water:	tap water
Housing:	for 8 hours following test substance application: singly in special restrainers which allowed free movement of the head but prevented a complete body turn and wiping of the eyes; before/after the 8-hour exposure period: separately in cages with dimensions of 425 mm x 600 mm x380 mm ([redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.1 mL/animal
Application route:	instillation into the conjunctival sac of one eye
Rinsing:	no
Group size:	3 males

Observations: clinical signs, eye effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

A single application of 0.1 mL JAU 6476 100 FS per animal into the conjunctival sac of the right eye, did not cause any changes.

The cornea, iris and conjunctivae were not affected by instillation of the test compound.

There were no systemic intolerance reactions.

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	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na
2	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na
3	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na

Response for mean scores:		Cornea opacity	Iritis	Conjunctival redness	Conjunctival oedema	
--	= negative	<1	<1	<2	<2	(Regulation (EC) No. 1272/2008 and GHS)
(+)	= mild irritant	≥1 - <3	≥1 - <2	≥2	≥2	(GHS category 2B (effects reversible within 7 days))
+	= irritant	≥1 - ≤3	≥1 - ≤2	≥2	≥2	(Regulation (EC) No. 1272/2008 (GHS) category 2)
++	= irreversible effects/ serious damage	>3	>1.5			(Regulation (EC) No. 1272/2008 and GHS category 1)

na : not applicable, *: in respect of the result 1 h post application

III. Conclusion

The test item is not irritating to the eyes of rabbits.

The following classification/labelling is triggered:

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

CP 7.1.6 Skin sensitization

Report:	KCP 7.1.6/01 [redacted]; 2001; M-087838-01-1
Title:	JAU 6476 100 FS - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman)
Report No.:	31575
Document No.:	M-087838-01-1
Guideline(s):	OECD 406; EC Guideline 96/54/EC, Method B.6.; US- 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. The documentation for the application of the control and dose finding animals during the second induction is missing. These deviations do not limit the assessment of the results.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: JAU 6476 100 FS

Development no.:	3000267751
Description:	red suspension
Lot/Batch no:	06528/0058(0054)
Content:	101.6 g/L
Stability of test compound:	guaranteed for study duration, expiry date: 2001-10-26

2. Vehicle: physiological saline solution

3. Test animals

Species:	guinea pig
Strain:	Hsd Poc:DH
Age:	3 - 5 weeks
Weight at dosing:	300 g - 399 g
Source:	[redacted] Germany
Acclimatisation period:	at least 5 days
Diet:	NAFAG 845 W4 - Maintenance Diet for Guinea Pigs ([redacted] Switzerland)
Water:	tap water
Housing:	type IV Makrolon® cages; adaptation: in groups of 5/cage, study period: in groups 2-3/cage; bedding: low-dust wood shavings ([redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment

Dose

Intradermal induction:	1% (= 4 mg test item/animal)
Topical induction:	25% (= 125 mg test item/animal)
Challenge:	6% (= 30 mg test item/animal)

Application route:	intradermal, dermal
Application volume:	0.1 mL/injection (intradermal induction) 0.5 mL/patch (topical induction, challenge)
Exposure:	topical induction: 48 hours, challenge: 24 hours
Group size:	41 females (test item group: 20, control: 10. range-finding: 11)
Observations:	skin effects, clinical signs, body weight (beginning/termination of study)

II. Results and discussion

A. Findings

48 hours after the intradermal induction (1st induction) the animals in the control group showed wheal.

The animals of the test item group showed 48 hours after the 1st induction wheal, red coloured wheal.

After 7 days the following effects were recorded at the injection sites in the control group and in the test item group: wheals and encrustation.

From day 11-14 encrustations on the treatment area of the 2nd (topical) induction in places appeared in the test item group after the second induction.

The challenge with the 6% test item formulation led to skin effects (grade 1 - 3) in 20 of 20 animals (100%) in the test item group. No skin effects were seen in the control group animals.

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.

	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 6%	20	20	20	0	0	0	0	0	0	0

The reliability of the Guinea Pig Maximization Test methodology was checked using alpha-Hexylzimtaldehyd formulated in sterile physiological saline solution at concentrations of 5% (intradermal induction), 25 (topical induction), 12% (challenge) [[redacted], [redacted]. (2000, 2001), 30207 [M-021611-01-1], 31458 [M-082311-01-1])

III. Conclusion

Under the conditions of the maximization test and with respect to the evaluation criteria the test item therefore exhibits a skin-sensitization potential.

The following classification/labelling is triggered:

- Regulation (EC) No 1272/2008 (CLP): Skin sensitisation Cat. 1;
  H317 (may cause an allergic skin reaction)

CP 7.1.7 Supplementary studies on the plant protection product

No supplementary studies have been performed

CP 7.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies have been performed.

CP 7.2 Data on exposure

The non-dietary risk assessment is presented for prothioconazole using the representative formulation 'Prothioconazole FS 100', for the use as fungicide for the treatment of cereal seed. The formulation contains the active substance prothioconazole (100 g/L). Exposure is estimated using the Seed TROPEX model.

In addition to the risk assessment for the active substance prothioconazole exposure is also assessed to prothioconazole-desthio.

This is done by means of higher tier studies.

Endpoints relevant for risk assessment:

<u>AOEL:</u>
For **prothioconazole**, based on a NOAEL of 25 mg/kg bw/day established in a subchronic oral toxicity study in the mouse, and also in a subchronic oral toxicity study in the dog, and an assessment factor of 100 a systemic **AOEL of 0.25 mg/kg bw/day** is proposed.

For **prothioconazole-desthio** the systemic **AOEL** is based on the results of the rat gavage developmental toxicity study as described in the EFSA Scientific Report (on prothioconazole)[1] and amounts to **0.01 mg/kg bw/day** including an assessment factor of 100.

For details please refer to Appendix I of the Document MCA: Section 5.

Dermal absorption:
Dermal absorption for **prothioconazole** was not evaluated with FS 100 formulation. The default dermal absorption values are used for the risk assessment based on the critical GAP uses:

- 25% for the concentrate (100 g a.s./L)

To obtain also data for **prothioconazole-desthio** the active substance prothioconazole was replaced by prothioconazole-desthio and diluted with water to a concentration of 5 g prothioconazole-desthio/L). As a result of the dermal absorption study the following dermal absorption value is used for the risk assessment:

- 6% obtained with a concentration of 5 g/L

For details see CP 7.3.

CP 7.2.1 Operator exposure

Operator exposure to prothioconazole during treatment of seeds and sowing of the treated seeds is estimated with the Seed TrOpEx Model. Detailed calculations are presented in CP 7.2.1.1.

In addition, operator exposure to prothioconazole as well as to its conversion product prothioconazole-desthio was estimated using results of compound and application specific exposure studies. The results of the studies are considered to represent higher tier data for the given application scenario.

One study was conducted during treatment of cereal seeds in professional seed treatment facilities in Germany with a formulation containing the active substance prothioconazole. Furthermore, results of two operator exposure studies conducted during loading and sowing of cereal seeds treated with a prothioconazole containing formulation are applied to estimate the operator exposure during loading and sowing.

The critical GAP (cGAP) for operator risk assessment is presented in Table CP 7.2.1-1.

Table CP 7.2.1-1 Critical GAP for operator exposure evaluations for prothioconazole

Crop (grouping)	Application method	Max. application rate (g a.s./100 kg seed)	Max. application rate (g a.s./ha)	Dermal absorption (%)
Barley, Oats, Rye, Triticale, Spelt, Wheat	Seed Treatment	10	18	PTZ: 25% PTZ-desthio: 6%

F = field; G = greenhouse

A comparison of the corresponding exposure estimates with the proposed AOEL (in terms of percentage of the respective AOEL) is presented in table CP 7.2.1-2.

[1] EFSA (European Food Safety Authority), 2007: Conclusion regarding the peer review of the pesticide risk assessment of the active substance prothioconazole. EFSA Scientific Report (2007) 106, 1-98, doi:10.2903/j.efsa.2007.106r

Table CP 7.2.1-2: Predicted operator exposure to prothioconazole and prothioconazole desthio

	Substance	PPE	Total systemic exposure (mg/kg bw/day)	% of AOEL#
	Seed TROPEX			
Seed Treatment	Prothioconazole	With PPE[1)]	0.0750	**30**
Loading /sowing	Prothioconazole	With PPE[2)]	0.0071	**3**
	Measurement of exposure			
Seed Treatment	Prothioconazole	With PPE[1)]	0.00071	**0.3**
	Prothioconazole-desthio	With PPE[1)]	0.00013	**1.3**
Loading /sowing (Not normalized study results)	Prothioconazole	With PPE[2)]	0.00065	**0.3**
	Prothioconazole-desthio	With PPE[2)]	0.00009	**0.9**
Loading /sowing (Normalized study results)	Prothioconazole	With PPE2)	0.00108	**0.4**
	Prothioconazole-desthio	With PPE2)	0.00017	**1.7**

1)Standard protective garment; protective gloves are worn during calibration, mixing and loading, cleaning.
2) Standard protective garment; protective gloves are worn when direct contact to treated seeds is given.
AOELprothioconazole: 0.25mg/kg bw/day; AOEL prothioconazole-desthio: 0.01 mg/kg bw/day

Assessment

The results of the calculations reveal that the situation is favourable for the intended use of 'Prothioconazole FS 100'.

Predicted systemic operator exposure according to the Seed TROPEX model

The estimated systemic exposures prothioconazole are always well below the respective systemic AOEL if PPE is worn by the operators.

During seed treatment predicted systemic operator exposure accounts for 30% of the systemic AOEL (0.25 mg/kg bw/day).

The model predicted systemic operator exposure during loading and sowing amounts to 3% of the systemic AOEL (0.25 mg/kg bw/day).

Estimated systemic operator exposure according to measurements

Compound and crop specific studies were evaluated to assess systemic operator exposure to prothioconazole and prothioconazole-desthio.

In both scenarios, seed treatment and loading/sowing of treated seeds, the exposure reveal that systemic exposure to prothioconazole accounts for <1% of the AOEL. Exposure to prothioconazole-desthio amounts to 1% of the AOEL during seed treatment and 2% of the AOEL during seed sowing.

Based on these results an unacceptable risk is not anticipated for the operator with the intended use of 'Prothioconazole FS 100'. Operators are supposed to wear normal work wear (e.g. a coverall), protective gloves when handling the undiluted or diluted product as well as when handling treated seeds or contaminated surfaces.

CP 7.2.1.1 Estimation of operator exposure

A) Estimation of operator exposure during seed treatment

SeedTROPEX differentiates four work tasks during seed treatment: calibration, mixing/loading, bagging, and cleaning. All tasks are considered individually, however, it is assumed that one single operator performs all tasks during a working shift.

It is assumed that operators are exposed to the seed dressing liquid (neat or diluted) during all tasks except during bagging. Therefore, the generic exposure figures for these tasks are expressed in mL/operation (taking into account the concentrations of active substances in different seed dressing liquids) whereas for bagging a constant generic figure – expressed as mg/h – is proposed in the model.

Since the delivery, some of the generic exposure values have been revised and the values currently being used are presented in Table CP 7.2.1.1-1.

Table CP 7.2.1.1-1: Task related generic exposures of seed treatment plant operatives

TASK		Total Potential Dermal Exposure (ml/op)*	Estimated Actual Dermal Exposure (ml/op)*	Inhalation Exposure (ml/op)*
Calibration		0.0330	0.014	0.0010
Mixing / Loading	Fast-Couple	0.0052	0.005	0.0001
	Pre-mix	0.0047	0.001	0.0001
Bagging (mg/hr)	all data	1.8400	0.698	0.0054
	worst case			0.0540
Cleaning		0.8720	0.083	0.0160

* exposure during bagging in mg/hour

It is assumed that the daily work of operators will involve one calibration and one cleaning operation, eight hours of bagging and the required number of mixing/loading operations. These assumptions are relevant for a static treatment plant with a low level of automation resulting in a throughput of about 75 tonnes of cereal seeds per day. It is generally accepted that although plants with higher levels of automation would achieve higher throughputs (resulting in higher daily product uses) exposure in these plants would be lower because of the less intensive involvement of operators during bagging which contributes most to the overall exposure in less automated plants.

It is noted that the type of normalisation used for bagging (mg a.s./hour) does not reflect all possible scenarios correctly. Exposure in this case is only time dependant and calculations will result in the same exposure value independent of the seed loading rate. It is considered that dust is the main source of contamination during bagging. The contamination of the dust depends on the dose of a.s. loaded to the seed. Thus, the high loading rates in the model (370 - 500 g a.s./tonne) would likely overestimate exposure to products with lower dose rates. Therefore, it is proposed that exposure during bagging should be normalised to mg a.s./kg a.s. handled. This kind of normalisation reflects at best the relation between exposure and the amount of active substance(s) loaded to the seed.

Exposure values for bagging normalised to mg/kg a.s. handled are available in the original study reports of SeedTROPEX and presented in the following table (it is noted that report values representing combined tasks e.g. bagging + loading or bagging + calibration are not included).

Table CP 7.2.1.1-2: Data on exposure for "pure" bagging determined in the UK

Potential Dermal Exposure in mg a.s./kg a.s.(only bagging) SeedTROPEX UK-data	**Actual Dermal Exposure** in mg a.s./kg a.s. (only bagging) SeedTROPEX UK-data	**Potential Inhalation Exposure** in mg a.s./kg a.s.(only bagging) SeedTROPEX UK-data
0.073	0.025	0.0023
0.188	0.074	0.0100
0.225	0.095	0.0115
0.278	0.120	0.0094

The corresponding geometric mean values are:

Potential dermal exposure:	0.1710 mg/kg a.s.
Actual dermal exposure:	0.0678 mg/kg a.s.
Potential inhalation exposure:	0.00710 mg/kg a.s.

These values are used in the following calculations to make predictions of exposure during bagging.

The following assumptions and requirements were taken into account for the estimate of operator exposure during seed treatment:

Crop:	Cereals
No. of cleaning operations:	1
No. of mixing/loading operations:	1
No. of calibration operations:	1
Seed treatment rate:	75 tonnes per day
Application rate:	1 L FS 100/tonne seed containing 0.1kg prothioconazole/ tonne seed
Active substance handled (kg/day):	7.5 kg prothioconazole/day
Dilution factor:	1 (undiluted)
Dermal absorption:	25%
Body weight:	60 kg
Clothing scenario:	Coverall and gloves during all operations except bagging

The detailed spread sheet calculations are presented in Table CP 7.2.1.1-3.

Table CP 7.2.1.1-3: Calculation of operator exposure to prothioconazole during seed treatment

TASK	Total Potential Dermal Exposure (mg/op)	Estimated Actual Dermal Exposure (mg/op)	Inhalation Exposure (mg/op)	PPE* RPE	Frequency (operations/ day)	Total Potential Dermal Exposure (mg/day)	Estimated Actual Dermal Exposure (mg/day)	Inhalation Exposure (mg/day)
Calibration	3.2557	1.4228	0.1381	no	***1***	3.2557	1.4228	0.1381
Mixing / Loading	0.5192	0.5192	0.0102	no	***1***	0.5192	0.5192	0.0102
Bagging (mg/kg a.s.)**	0.1712	0.0678	0.0071	no	***7.5***	1.2838	0.5083	0.0530
Cleaning	87.1757	8.3364	1.6000	no	***1***	87.1757	8.3364	1.6000
	Absorbed dose (mg/kg bw/day):				**Calibration**		0.0059	0.0023
					Mixing/loading		0.0022	0.0002
					Bagging		0.0021	0.0009
					Cleaning		0.0347	0.0267
					Total		0.0750	
	% of AOEL	**30**						
	MoS:	**333**						

* standard clothing of the operators is one layer of work clothing during all tasks and in addition protective gloves except for bagging

** exposure during bagging mg/kg a.s. handled

B) Estimation of operator exposure during loading and sowing of the treated seed

Exposure during seed sowing is calculated with SeedTROPEX.

Exposure estimates include dermal and inhalation exposure. The normalisation used in the model (mg a.s./hour) does not take into account varying amounts of active substance applied to the seed. Dust is regarded to be the main source of exposure during loading and sowing and the contamination of dust is proportional to the loading of active substances on the seed. Thus, calculations would result in a significant overestimation for substances applied with lower dose rates compared to those used in the SeedTROPEX studies (375 and 500 g a.s./tonne of seed) and an underestimation for substances applied with higher dose rates. Exposure normalized to the amount of a.s. handled reflects at best the relation between exposure and the amount of active substance loaded to the seed. Individual actual and dermal exposure values using this normalization are available in the SeedTROPEX, study reports and presented in the following table.

Table CP 7.2.1.1-4: Actual dermal and potential inhalation exposure figures of the study report of Seed-TROPEX (UK-data) for the tasks loading and sowing of the treated seed normalised to mg a.s./kg a.s. handled

Operator ID	Actual Dermal Exposure [mg a.s./kg a.s]	Potential Inhalation Exposure [mg a.s./kg a.s]
1	8.200	0.069
2	0.784	0.086
3	8.49	0.149
4	11.500	0.017
5	7.440	0.143
6	3.810	0.790
11	0.912	0.049
12	8.260	0.228
13	4.220	0.008
14	3.660	0.031
15	20.100	0.388
16	38.200	0.692
17	6.180	0.280
geo. mean	**5.870**	**0.110**

In total, 13 operators (UK data) were monitored for dermal and inhalation exposure during loading and sowing. The geometric mean of actual dermal exposure is 5.87 mg a.s./kg a.s. and of potential inhalation exposure is 0.11 mg a.s./kg a.s. It has to be mentioned that 8 operators handled treated seed without wearing protective gloves (e.g. to evenly spread the seed within the hopper). This is not in accordance with good agricultural practice. Therefore, the allowance of this data in the model represents the worst case when calculating dermal exposure.

The exposure calculation for 'Prothioconazole FS 100' is performed with the normalization as presented above.

The following assumptions and requirements are taken into account for the estimate of operator exposure during seed loading and sowing:

Crop:	Cereals
Drilling rate:	180 kg/ha
Work rate:	15 ha/day
Application rate:	10 g a.s./100 kg seed

Amount of a.s. handled:	270 g a.s./day
Body weight:	60 kg
Clothing scenario:	Coverall; gloves partly worn (only few operators with gloves considered in the model)

The detailed spreadsheet calculations are presented in Table CP 7.2.1.1-5.

Table CP 7.2.1.1-5: Calculation of operator exposure to prothioconazole during loading/sowing of treated seed

Route of exposure	Specific exposure [mg/person x kg a.s.]		Seed [kg/day] x use rate [kg a.s./kg seed]		**Route specific** [mg/person/day]	**Absorption** [%]	**Absorbed Dose** [mg/person/day]
$D_{L/S}$	5.87	x	0.27	=	**1.585**	25	**0.396**
$I_{L/S}$	0.11	x	0.27	=	**0.0297**	100	**0.0297**
Systemic exposure							**0.4257**
Total absorbed dose [mg/kg bw/day]:							**0.00710**

CP 7.2.1.2 Measurement of operator exposure

It has been found that prothioconazole in diluted solutions can convert to prothioconazole-desthio (other internal code: SXX 0665) during the drying process on clothing, skin or on certain plant surfaces. The conversion product, prothioconazole-desthio is known to have an embryotoxic potential in experimental animals.

Therefore, three operator exposure studies were conducted to determine exposure to prothioconazole and prothioconazole-desthio during seed treatment of cereal seeds under real use conditions as well as during loading/sowing of the treated seeds to get a better basis for a realistic risk assessment.

Subsequently, a risk assessment is performed for the seed treatment product 'Prothioconazole FS 100' based on the results of the operator exposure studies.

The exposure of operators to prothioconazole and its conversion product prothioconazole-desthio during seed treatment was experimentally determined in one operator exposure study. The study was performed in commercial seed treatment facilities in Germany during treatment of cereal seeds with EfA FS 76.25 (37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole). The study was already evaluated by CRD (COP 2014/001477).

In two further studies the exposure of operators to prothioconazole and its conversion product prothioconazole-desthio was experimentally determined during loading and sowing of cereal seeds treated with EfA FS 76.25 (37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole).

The substance and application type specific data will be applied to evaluate the exposure of operators to the active substance prothioconazole and its conversion product prothioconazole-desthio.

The studies are summarised in the following. The studies were conducted in compliance with the current OECD Principles of Good Laboratory Practice (GLP).

Report:	KCP 7.2.1.2/04 [redacted] =; [redacted] ; [redacted] ; 2011; M-418917-01-1
Title:	Determination of operator exposure to prothioconazole and prothioconazole-desthio during seed treatment of cereals with EfA in Germany
Report No.:	MR.-07/313
Document No.:	M-418917-01-1
Guideline(s):	OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Material and Methods:

Eight professional seed treatment plants in Germany which are regarded to be representative for a variety of technical standards for seed dressing were chosen. In these plants cereal seeds (winter wheat, winter and spring barley, winter rye, or triticale) were dressed with EfA FS 76.25 at application rates of 120 to 200 mL product per 100 kg seed (corresponding to 3 – 5 g prothioconazole per 100 kg seed). The seeds were treated in batch treaters or continious flow treaters representing the current technical standard used in Europe. The treated seeds were bagged into paper bags (30 – 50 kg/bag) or big bags (500 – 1000 kg/bag).

At each plant one to three operators who usually conduct all activities necessary for the treatment of seeds and the bagging of the treated seeds were monitored for two consecutive days performing their daily routine. In total 16 operators were monitored for full working shifts of about 5 to 9 hours. 15 operators were monitored for two consecutive days, 1 operator for one day resulting in 31 replicates monitored in the study.

The work in the seed treatment plants covered two main areas:

- Seed treatment: includes all activities in which the concentrated or diluted product is handled, i.e. mixing/loading, calibration, cleaning of the treatment chamber, maintenance in the treatment chamber, operation of the treater.
- Bagging: includes all activities in which the treated seeds are handled, i.e. bagging into paper bags or big bags, stacking of paper bags, forklift driving, maintenance at the bagging equipment, cleaning of the bagging area.

6 of the replicates were mainly performing activities connected to the seed treatment, 11 replicates mainly bagged the treated seeds and the other 14 replicates conducted a mixture of seed treatment and bagging activities during the monitoring period.

An overview of the work conditions and details of the operators work in the different plants is given in the following table.

Table CP 7.2.1.2-1: Operator details and working conditions

Plant	Operators'			Working time [min]	Amount seed handled [tonnes]	Units bagged [bb = big bags, pb = paper bag]	Amount prothioconazole handled [kg]
	ID	Function #	Body weight [kg]				
Plant 1	OA	T	85	395	68.0	68 bb	2.72
	OB	B	100	402	62.8	63 bb	2.50
	OC	B	65	393	62.8	63 bb	2.50
	OD	T	85	405	64.0	64 bb	2.57
	OE	B	100	382	64.0	64 bb	2.57
	OF	B	65	415	64.0	64 bb	2.57
Plant 2	OG	T	82	420	74.4	78 bb	2.98
	OH	B	83	424	73.0	77 bb	2.92
	OI	T	82	427	25.5	29 bb, 9 pb	1.15
	OK	B	83	405	25.5	29 bb, 9 pb	1.15
Plant 3	OL	T/B	85	372	41.3	1116 pb	1.80
	OM	T/B	70	367	41.3	1116 pb	1.80
	ON	T/B	85	356	42.5	14 bb, 862 pb	1.28
	OO	T/B	70	362	42.5	14 bb, 862 pb	1.28
Plant 4	OP	T/B	80	349	24.1	482 pb	1.01
	OR	B	90	335	24.1	482 pb	1.01
	OS	T/B	80	308	19.1	382 pb	0.67
	OT	B	90	297	19.1	382 pb	0.67
Plant 5	O8A	T/B	65	350	25.3	31 bb	1.01
	O8B	T	90	311	25.3	31 bb	1.01
	O8C	T/B	65	334	40.0	50 bb	1.60
	O8D	T	90	363	40.0	50 bb	1.60
Plant 6	O8E	T/B	75	441	66.4	65 bb, 28 pb	4.25
	O8F	T/B	75	420	68.0	69 bb	3.67
Plant 7	O8G	T/B	80	460	52.0	8 bb, 1515 pb	1.56
	O8H	T/B	80	440	67.8	2259 pb	2.03
Plant 8	O8I	T/B	68	536	30.0	600 pb	1.20
	O8K	B	88	536	30.0	600 pb	1.20
	O8L	B	65	536	30.0	600 pb	1.20
	O8M	T/B	68	376	27.4	29 bb	1.10
	O8N	B	88	379	27.4	29 bb	1.10

#: Main function of the operator in the seed treatment and bagging process: T = Treatment B = Bagging

Regarding the seed treatment phase several differences in the equipment and the work routines could be observed which may have had an influence on potential exposure of the operators.

Pre-mixture of the product is common practice in Germany. The product is diluted with water or combined with other products in mixing vessels prior to the application in the treatment chamber. Mixing/loading of the product was either performed by pouring the product directly out of 50 L containers into a mixing vessel (one plant) or via suction lances connected with pumps. Lances had to be transferred from empty to full containers by the operators.

Calibration of the metering pumps was performed in two plants by measuring with a measuring cup the amount of product delivered by the pump in a defined time. In all other plants no calibration was performed since the dosing equipment was regulated automatically by the computerized control unit of the treatment equipment.

Cleaning of the treatment chamber was performed routinely in most of the plants at least once per day to remove residues which may have influence on the treatment or to remove seeds out of the system to provide purity of the seed variety after change of variety.

During all activities in which the concentrate or the diluted product was handled (i.e. mixing/loading, calibration, cleaning) operators wore in accordance with their usual practice chemical resistant gloves to protect their hands. Furthermore a protective coverall was worn by two operators during cleaning of the treatment chamber.

Differences in the activities belonging to the bagging phase were due to the level of automation in the plants and the type of bags in which seeds were bagged (i.e. big bags or paper bags). Bagging into big bags was performed in two plants exclusively and in five plants during parts of the working shift. More or less the same manual activities were necessary in all plants to fill seeds into big bags. The bags had to be connected and disconnected manually from the filling head of the bagging station. Operators tied the big bag up and the full big bags were carried with a forklift to the storage place. Bagging into paper bags was performed in one plant exclusively and in five plants in combination with bagging into big bag. Dependent on the level of automation the operations performed by the workers varied between the plants. In the low automated plants all activities (i.e. attaching of empty bags at the filling head, stitching and labelling of the full bags, stacking of full bags on pallet) were performed manually. In these plants the bagging activities were performed by one or two baggers in cooperation with the operator who mainly performed the treatment activities. In the medium automated plants attaching of empty bags at the filling head was still performed manually whereas stacking of the full bags was automated. Two operators were performing these activities. In the highest automated plant the bagging and stacking was fully automated. In this plant the whole seed treatment and bagging process was performed by a single operator.

Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns), as well as by analysing a long sleeved shirt (cotton), a work jacket and a pair of trousers (both cotton/polyester) as outer garments. Two of the operators wore additionally an impermeable coverall (Tyvek) during cleaning. Exposure to the head was determined by face neck wipes and a cap. Exposure to the hands was determined via rinsing of protective gloves (nitrile gloves) and by hand washings.

The results of the outer garments, the glove rinsings, the face neck wipes, and the cap together with the results of the underwear and the hand washings correspond to potential dermal exposure whereas the results of the underwear plus the face neck wipes, cap and the hand washings are regarded as actual dermal exposure.

Inhalation exposure was measured via IOM samplers equipped with glass fiber filters which were fixed to the garments at the breathing zone of the operator and connected to a battery powered personal air pump. The pumps ran for the duration of the respective working task.

All samples (clothing samples, face-neck wipes, caps, gloves and hand wash bottles, IOM samplers) were transported to the test facility latest three days after sampling. The sample preparation was performed – if feasible – directly upon receipt of the samples or latest within 96 hrs after sampling. The extracted samples and sample extracts were stored in freezers and refrigerators, respectively, until analysis was performed.

For the determination of the exposure to prothioconazole and prothioconazole-desthio, the samples were extracted and analysed by liquid chromatography with MS/MS detection. The results of the measurement are given in the study report as determined (i.e. µg prothioconazole per sample and µg protioconazole-desthio per sample) and expressed as specific exposures (e.g. µg of exposure per kg of prothioconazole handled).

II. Findings:

The recoveries performed concurrently with the analysis of the samples were good and revealed that the method used for samples analysis was well suited for determining residues of prothioconazole and prothioconazole-desthio in or on the dosimeter matrices. Field recoveries that were set up during the study showed that the sample residues were stable during transport and storage.

The measured exposure results are summarised in the following table.

Table CP 7.2.1.2-2: Summary of the Measured Exposure Results

Operator ID	Function[#]	Prothioconazole [µg/day] PDE	ADE	IE	Prothioconazole-desthio [µg/day] PDE	ADE	IE
OA	T	1434	38.98	2.986	118.17	16.43	1.040*
OB	B	367.3	39.32	5.841	63.18	13.18	1.040*
OC	B	495.7	84.66	7.996	82.70	21.72	1.040*
OD	T	4624	116.0	1.040*	311.6	31.71	1.040*
OE	B	335.0*	35.00*	4.700	62.75	12.75	1.040*
OF	B	378.8	53.31	1.591	145.3	27.95	1.040*
OG	T	135.0*	35.00*	4.786	50.00*	10.00*	1.040*
OH	B	172.0	72.01	3.472	50.00*	10.00*	1.040*
OI	T	2332	50.51	2.988	130.6	10.00*	1.040*
OK	B	255.2	123.2	4.144	52.54	12.54	1.040*
OL	T/B	4567	32.50*	1.958	224.2	10.02	1.040*
OM	T/B	3674	32.50*	1.616	146.2	9.00*	1.040*
ON	T/B	2284	35.67	2.748	223.5	10.10	1.040*
OO	T/B	1095	36.79	3.404	97.56	9.00*	1.040*
OP	T/B	381.9	81.93	1.040*	64.01	14.01	1.040*
OR	B	137.6	37.57	1.040*	50.60	10.60	1.040*
OS	T/B	349.4	49.36	1.040*	61.00*	11.00*	1.040*
OT	B	361.7	61.70	1.040*	60.86	10.86	1.040*
O8A	T/B	2945	69.62	1.040*	85.26	11.00*	1.040*
O8B	T	335.0*	35.00*	1.040*	60.00*	10.00*	1.040*
O8C	T/B	1174	46.22	1.040*	102.9	11.44	1.040*
O8D	T	400.0	100.0	1.040*	67.24	17.24	1.040*
O8E	T/B	31682	46.15	1.040*	285.7	11.25	1.040*
O8F	T/B	23480	51.63	1.040*	357.7	11.68	1.040*
O8G	T/B	1626	42.90	2.784	212.3	12.38	1.040*
O8H	T/B	589.6	32.50*	4.190	145.7	12.73	1.040*
O8I	T/B	12775	40.70	2.188	220.9	15.79	1.040*
O8K	B	137.5*	37.50*	3.958	53.00	14.00	1.040*
O8L	B	137.5*	37.50*	1.689	51.00*	11.00*	1.040*
O8 M	T/B	20280	39.25	1.040*	236.7	13.27	1.040*
O8N	B	135.0*	35.00*	1.040*	50.00*	10.00*	1.040*
Geometric mean		936.0	48.39	1.988	102.4	12.63	1.040
75th percentile		2638	57.50	3.438	179.3	13.63	1.040
95th percentile		21880	108.0	5.313	298.7	24.83	1.040
Maximum value		31682	123.2	7.966	357.7	31.71	1.040

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)
[#]: Main function of the operator in the seed treatment and bagging process: T = Treatment B = Bagging
*: All samples < LOQ

In general the dermal and inhalation exposure to prothioconazole and prothioconazole-desthio was low for all monitored operators. On many samples the residue level was below the LOQ of the respective sampling matrix for prothioconazole as well as for prothioconazole-desthio.

The results in the table show that the replicates who were mainly involved in the bagging activities were less exposed dermally compared to operators who handled the pure or diluted product during mixing/loading, calibration or cleaning. Nevertheless, since potential exposure was mainly detected on

the hands which were effectively protected by chemical resistant gloves, actual dermal exposure was in a close range for all operators.

Overall, inhalation exposure was low. For 13 of the replicates prothioconazole residues measured on the IOM filters were below LOQ and all prothioconazole-desthio values were below the LOQ. Differences in the extend of inhalation exposure were identified between plants and within single plants between bagging procedures (big bags vs. 50 kg paper bags). In some plants during bagging of big bags higher inhalation exposure was detected in others during bagging of small paper bags. Reasons for this may be seen in the level of automation or the quality of air exhaustion in different parts of the plants.

III. Conclusions:

The study results reflect exposure encountered during typical activities necessary for cereal seed treatment in professional plants in Europe with standard seed treatment equipment. The level of PPE used in the plants (i.e. chemical resistant gloves when handling the concentrate and diluted product) was in accordance with good occupational practice and the common work practice in the plants.

Thus, it can be concluded that the study conditions (i.e. selected plants, work tasks, work rate, work conditions, etc.) and subsequently the determined exposure figures are representative for cereal seed treatment in Europe.

Report:	KCP 7.2.1.2/05 [redacted].; [redacted]; 2014; M-481315-01-1
Title:	Determination of operator and resident / bystander exposure to prothioconazole and prothioconazole-desthio during loading and sowing of EfA treated cereal seed in Germany
Report No.:	M-481315-01-1
Document No.:	M-481315-01-1
Guideline(s):	OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Material and Methods

Nine operators were monitored on nine farms in Germany during loading and sowing of cereal seeds treated with EfA (FS containing 37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole) in order to determine the dermal and inhalation exposure to prothioconazole and its conversion product prothioconazole-desthio.

The seed was treated in different commercial seed treatment plants and farmers were supplied by their local warehouses. One farmer used self-grown seed which was cleaned and treated in a local warehouse. Samples of the sown seeds were taken each farm and the loading rate was determined. The measured loading rates ranged from 3.1 to 5.4 g prothioconazole per 100 kg seed.

The monitoring covered a whole working day and included all activities which are necessary to prepare the equipment for sowing and the sowing of the seeds, i.e. loading of treated seeds into the hopper, calibration of the sowing machine, sowing, checking of sowing quality on the field, maintenance if necessary.

All relevant methods of seed loading into the hopper were observed within the study, i.e. loading out of small paper bags, loading out of big bags and loading from a trailer via an auger. A wide range of sowing conditions and sowing equipment was covered. Mechanical or pneumatic sowing machines with

working width ranging from 3 m to 6 m were used. Dependent on the equipment used and the farm size the treaded area ranged from 6.2 ha to 49.5 ha. Duration of work ranged from 345 minutes to 664 minutes. Sowing density was determined by the farmers and varied in dependence of the seed variety and the sowing conditions between 90 kg and 170 kg seed per ha. The resulting amount of prothioconazole handled during the monitoring was between 50 g and 230 g per day. Details of the study conditions are summarized in Tables CP 7.2.1.2-7 and CP 7.2.1.2-8.

Dermal exposure was measured by passive dosimetry techniques. Beneath usual work clothing (shirt or jacket and trousers) the operators wore long cotton underwear; all clothing was used as sampling clothing. Exposure of the head was measured by a cap and face-neck wipes, exposure of the hands by hand washes (with detergent) and after the last working task in addition with isopropanol. Protective gloves worn during loading and sowing were rinsed with isopropanol.

Potential dermal exposure of the operator was calculated from the sum of the residues detected on the outer clothes, the underwear, the protective gloves, hand washes, face-neck wipes and cap.

Actual dermal exposure was calculated from the sum of the residues detected on the underwear, hand washes, face neck wipes and cap.

Inhalation exposure of operators and bystander/residents was determined by use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter, located in the breathing zone of the person.

All samples (clothing samples, face-neck wipes, caps, gloves and hand wash bottles, IOM samplers) were transported to the test facility latest three days after sampling. The sample preparation was performed – if feasible – directly upon receipt of the samples or latest within 96 hrs after sampling. The extracted samples and sample extracts were stored in freezers and refrigerators, respectively, until analysis was performed.

For the determination of the prothioconazole and prothioconazole-desthio exposure, the samples were extracted and analysed by liquid chromatography with MS/MS detection. The results of the measurement are given in the study report as determined (i.e. µg prothioconazole per sample and µg protioconazole-desthio per sample) and expressed as specific exposures (e.g. µg of exposure per kg of prothioconazole handled).

II. Results:

Field recoveries which were set up at one site showed that residues can be considered stable for most of the matrices. Only for inner garments and nitrile gloves recovery rates < 70 % were detected. The results of these matrices were corrected for the recovery rate.

The measured exposure values to prothioconazole and prothioconazole desthio are summarized in the table below.

Table CP 7.2.1.2-3: Exposure to prothioconazole

Operator ID	Prothioconazole [µg/person/day]			Prothioconazole [µg/kg bw]			Prothioconazole [µg/kg a.s.handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
OA	475.0*	35.00*	1.040*	5.163	0.380	0.0113	3146	231.8	6.89
OB	998.6	36.38	30.63	12.178	0.444	0.3735	18424	671.1	565.09
OC	475.0*	35.00*	3.353	3.654	0.269	0.0258	9814	723.1	69.28
OD	472.5*	32.50*	1.040*	4.295	0.295	0.0095	5363	368.9	11.80
OE	610.1	84.76	2.589	6.290	0.874	0.0267	10780	1497.5	45.73
OF	475.0*	35.00*	1.759	3.393	0.250	0.0126	2128	156.8	7.88
OG	777.4	70.59	3.635	8.637	0.784	0.0404	3415	310.1	15.97
OH	472.5*	32.50*	1.040*	6.750	0.464	0.0149	8607	592.0	18.94
OI	472.5*	32.50*	1.040*	5.081	0.349	0.0112	7383	507.8	16.25

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)
*: All samples < LOQ

Table CP 7.2.1.2-4: Exposure to prothioconazole-desthio

Operator ID	Prothioconazole-desthio [µg/person/day]			Prothioconazole-desthio [µg/kg bw]			Prothioconazole-desthio [µg/kg a.s.handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
OA	73.00*	13.00*	1.040*	0.793	0.141	0.0113	483.4	86.09	6.887
OB	148.23	12.00*	5.702	1.808	0.146	0.0695	2734.9	221.40	105.21
OC	73.00*	13.00*	1.040*	0.562	0.100	0.0080	1508.3	268.60	21.49
OD	72.00*	12.00*	1.040*	0.655	0.109	0.0095	817.3	136.21	11.80
OE	169.51	50.86	1.040*	1.748	0.524	0.0107	2994.9	898.62	18.37
OF	73.00*	13.00*	1.040*	0.521	0.093	0.0074	327.1	58.24	4.659
OG	135.26	18.58	1.040*	1.503	0.206	0.0116	594.3	81.64	4.569
OH	72.00*	12.00*	1.040*	1.029	0.171	0.0149	1311.5	218.58	18.94
OI	72.00*	12.00*	1.040*	0.774	0.129	0.0112	1125.0	187.50	16.25

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)
*: All samples < LOQ

Exposure values to prothioconazole and prothioconazole-desthio > LOQ were found on clothing and hand wash samples of 3 operators, however, at a very low level.

Two of the operators with measurable residues on clothing loaded bulked seed from a trailer via an auger into the hopper of the sowing machine. The third operator handled seed which was packaged in used bags which were visibly contaminated. This operator was the only one with measured residues on the hands. The highest residues of prothioconazole and prothioconazole desthio in a hand wash solution of this operator were measured after he had handled treated seeds leaking out of a broken bag with bare hands.

Inhalation exposure to prothioconazole was low. Five operators showed measurable amounts of prothioconazole on the filters. Only one operator had a significantly higher value than the LOQ. This operator also showed inhalation exposure to prothioconazole-desthio. Again, the reason for this is the type of loading via an auger and a certain proximity to the outlet hose of the auger. For all other operators inhalation exposure to prothioconazole-desthio was found to be negligible, i.e. to be below LOQ.

III. Conclusions:

The study results represent exposure from typical seed loading/sowing activities with modern standard seed sowing equipment. The level of PPE used by the farmers (i.e. chemical resistant gloves when direct contact with the treated seeds or contaminated surfaces is given) was in accordance with good occupational practice.

Thus, it can be concluded that the study conditions (i.e. selected farms, sowing equipment, work tasks, work rate, work conditions, etc.) and subsequently the determined exposure figures are representative for the cereal seed sowing in Europe.

Report:	KCP 7.2.1.2/06 [redacted]; 2015; M-531731-01-1
Title:	First amendment to report - Determination of operator exposure to prothioconazole and prothioconazole-desthio during loading and sowing of EfA treated cereal seed in Germany
Report No.:	20130166
Document No.:	M-531731-01-1
Guideline(s):	OECD Series on Testing and Assessment No. 9 "Guidance document on the conduct of studies of occupational exposure to pesticides during agricultural application", Paris 1997. OCDE/GD(97)148
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Material and Methods

Five operators were monitored on five farms in Germany during loading and sowing of cereal seeds treated with EfA (FS containing 37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole) in order to determine the dermal and inhalation exposure to prothioconazole and its conversion product prothioconazole-desthio.

The seed was treated in different commercial seed treatment plants and farmers were supplied by their local warehouses. One farmer used self-grown seed which was cleaned and treated in a local warehouse. Samples of the sown seeds were taken each farm and the loading rate was determined. The measured loading rates ranged from 3.5 to 4.4 g prothioconazole per 100 kg seed.

The monitoring covered a whole working day and included all activities which are necessary to prepare the equipment for sowing and the sowing of the seeds, i.e. loading of treated seeds into the hopper, calibration of the sowing machine, sowing, checking of sowing quality on the field, maintenance if necessary.

Filling the hopper of the planter was conducted by loading out of big bags (500 to 1000 kg/big bag) or loading from a trailer via an auger. A wide range of sowing conditions and sowing equipment was covered. Mechanical or pneumatic sowing machines with a working width of 3 m were used. Dependent on the equipment used and the farm size the treaded area ranged from 6.6 ha to 20.5 ha. Duration of work ranged from 331 minutes to 585 minutes. Sowing density was determined by the farmers and varied in dependence of the seed variety and the sowing conditions between 134 kg and 188 kg seed per ha. The resulting amount of prothioconazole handled during the monitoring was between 38 g and 139 g per day. Details of the study conditions are summarized in Tables CP 7.2.1.2-7 and CP 7.2.1.2-8.

Dermal exposure was measured by passive dosimetry techniques. Beneath usual work clothing (jacket and trousers) the operators wore long cotton underwear; all clothing was used as sampling clothing. Exposure of the head was measured by a cap and face-neck wipes, exposure of the hands by hand washes (with detergent) and after the last working task in addition with isopropanol. Protective gloves worn during loading and sowing were rinsed with isopropanol.

Potential dermal exposure of the operator was calculated from the sum of the residues detected on the outer clothes, the underwear, the protective gloves, hand washes, face-neck wipes and cap.

Actual dermal exposure was calculated from the sum of the residues detected on the underwear, hand washes, face neck wipes and cap.

Inhalation exposure of operators and bystander/residents was determined by use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter, located in the breathing zone of the person.

All samples (clothing samples, face-neck wipes, caps, gloves and hand wash bottles, IOM samplers) were transported to the test facility latest two days after sampling. The sample preparation was performed – if feasible – directly upon receipt of the samples or latest within 48 hrs after sampling. The extracted samples and sample extracts were stored in freezers and refrigerators, respectively, until analysis was performed.

Residues of Prothioconazole and prothioconazole-desthio were determined by HPLC-MS/MS in the multiple-reaction-monitoring mode (MRM) using an electrospray interface (ESI). The results of the measurement are given in the study report as determined (i.e. µg prothioconazole per sample and µg protioconazole-desthio per sample) and expressed as specific exposures (e.g. µg of exposure per kg of prothioconazole handled).

II. Results:

Field recoveries which were set up at two sites showed that residues can be considered stable for most of the matrices. Only for inner garments recovery rates of prothioconazole < 70 % were detected. The results of these matrices were corrected for the recovery rate.

The measured exposure values to prothioconazole and prothioconazole desthio are summarized in the table below.

Table CP 7.2.1.2-5: Exposure to prothioconazole

Operator ID	Prothioconazole [µg/person/day]			Prothioconazole [µg/kg bw]			Prothioconazole [µg/kg a.s.handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
OA	239.8	7.00*	0.520*	2.960	0.0864	0.0064	6396	186.7	13.87
OB	159.5	13.54	6.560	1.595	0.135	0.0656	1149	97.56	47.27
OC	779.0	7.00*	5.940	9.274	0.083	0.0707	9578	86.07	73.04
OD	1305.6	52.98	13.650	12.675	0.514	0.1325	16822	682.6	175.88
OE	276.4	35.46	5.830	3.005	0.385	0.0634	2798	358.9	59.01

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20 l/min)
*: All samples < LOQ

Table CP 7.2.1.2-6: Exposure to prothioconazole-desthio

Operator ID	Prothioconazole-desthio [µg/person/day]			Prothioconazole-desthio [µg/kg bw]			Prothioconazole-desthio [µg/kg a.s.handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
OA	87.00*	7.00*	0.520*	1.074	0.0864	0.0064	2321	186.72	13.87
OB	87.00*	7.00*	1.670	0.870	0.0700	0.0167	626.9	50.44	12.03
OC	120.68	7.00*	0.520*	1.437	0.0833	0.0062	1484	86.07	6.39
OD	139.90	8.20	2.500	1.358	0.0796	0.0243	1803	106.66	32.21
OE	99.88	7.00*	0.520*	1.086	0.0761	0.0057	1012	70.85	5.26

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)
*: All samples < LOQ

Exposure values to prothioconazole > LOQ were found on clothing and hand wash samples of four operators, however, at a very low level. Exposure values to prothioconazole-desthio > LOQ were found on clothing and hand wash samples of two operators, however, at a very low level.

The operator (Operator OD) with the highest measurable residues of prothioconazole and prothioconazole-desthio on clothing and in hand washes loaded bulked seed from a trailer via an auger into the hopper of the sowing machine. He also cleaned the empty trailer with a broom from dust and remaining seeds. Operator OE emptied the seed bags while standing in the hopper. As a result contamination on the legs of the inner and outer clothing was observed. Potential dermal exposure of operator OC was mainly attributed to the contamination of the nitrile gloves. The operator leveled the seed in the hopper several times with his hands after loading the seeds and during the sowing process. Since he was always wearing gloves while doing this the actual hand exposure was <LOQ.

Inhalation exposure to prothioconazole was low. Four operators showed measurable amounts of prothioconazole on the filters. The two operators with the highest exposure to prothioconazole also showed inhalation exposure to prothioconazole-desthio. For all other operators inhalation exposure to prothioconazole-desthio was found to be negligible, i.e. to be below LOQ.

III. Conclusions:

The study results represent exposure from typical seed loading/sowing activities with modern standard seed sowing equipment. The level of PPE used by the farmers (i.e. chemical resistant gloves when direct contact with the treated seeds or contaminated surfaces is given) was in accordance with good occupational practice.

Thus, it can be concluded that the study conditions (i.e. selected farms, sowing equipment, work tasks, work rate, work conditions, etc.) and subsequently the determined exposure figures are representative for the cereal seed sowing in Europe.

Overall Conclusion

Both studies were designed as loading/sowing-studies as this type of study reflects best the real work situation of farmers in Europe when handling treated seeds. In total, 14 operators were monitored.

The first study was conducted in 2009 with nine professional farmers in their fields. To increase the number of replicates the second study was conducted in 2013 with five professional farmers loading and sowing prothioconazole treated cereal seeds in their fields.

In Table CP 7.2.1.2-7 and Table CP 7.2.1.2-8 study parameters are shown in a detailed as well as in a summary form. From the overview it can be concluded that the study conditions really cover all parameters encountered in Europe for cereal seed sowing:

- areas ranging from 8 ha to 50 ha;
- sowing widths ranging from 3 m up to 6 m;
- mechanical and pneumatic sowing machines.
- loading out of small paper bags or big bags, loading bulked seeds from trailer

The tractors were equipped with a cabin as it is standard practice nowadays. The back window of the tractor was not allways closed during sowing for someof the operators.

Table CP 7.2.1.2-7: Study parameters of replicates

Study	Operator ID	Body weight [kg]	Area treated [ha]	Seed sown [kg]	Seed packaging/Loading procedure	Sowing equipment	No of loading tasks
1	OA	92	49.5	4415	Big bags	6 m pneumatic	5
1	OB	82	14.3	1760	Bulked seed loaded from trailer	3 m mechanical	5
1	OC	130	7.8	1193	25 kg paper bags, 300 kg big bags	3 m pneumatic	12
1	OD	110	16.2	2100	500 kg big bags	3 m mechanical	2
1	OE	97	6.2	1054	50 kg and 70 kg bags	3 m pneumatic	3
1	OF	140	42.8	6200	1000 kg big bags	4 m mechanical	4
1	OG	90	34.0	5700	Bulked seed loaded from trailer	6 m pneumatic	5
1	OH	70	8.5	1210	50 kg bags	3 m mechanical	7
1	OI	93	9.0	1350	50kg bags	3 m pneumatic	4
2	OA	81	6.6	990	Bulked seed loaded from trailer	3 m mechanical	2
2	OB	100	16.9	3290	1000 kg big bags	3 m mechanical	2
2	OC	84	12.5	2300	500 kg big bags	3 m mechanical	5
2	OD	103	12.5	2125	Bulked seed loaded from trailer	3 m mechanical	4
2	OE	92	20.5	2600	600 kg big bags	3 m pneumatic	2

Table CP 7.2.1.2-8: Summary of study parameters

Parameter	Study parameter
Seed sown	Winter barley Winter wheat
Seed treatment	EfA (FS containing 37.5 g/L fluoxostrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole) in an application rate of 200 mL/dt seed to winter barley, 160 mL/dt seed to winter wheat
No. of replicates	14 operators (at 14 locations) combined work cycles (loading and sowing)
Application technique	Sowing with mechanical or pneumatic sowing machines (3 – 6 m working width)
Time	331 to 658 minutes (mean 476 minutes)
Area treated	6.2 to 49.5 ha (mean 18.5 ha)
Sowing rate	89 to 188 kg seed /ha (mean 149 kg seed /ha)
Total a.s. handled	37.5 to 228 g a.s./day (mean 100 g a.s./day)
PPE/clothing	Nitrile gloves: during loading of seeds, during sowing only if necessary (e.g., when handling contaminated surfaces); one layer of clothing

Although detailed exposure data from the studies are not presented in this overview some general observations are summarised nevertheless.

It is remarkable that only 7 replicates (out of 14) had measurable residues of prothioconazole on their outer clothing and only five operators showed measurable residues of prothioconazole on their undergarments.

For prothioconazole-desthio in 5 out of 14 replicates measurable residues were found on the outer clothing but only two operators showed measurable residues on their undergarments.

Only one of the operators had measured residues of both prothioconazole and prothioconazole-desthio concurrently on his undergarments.

Measurable exposure to prothioconazole of the head was determined for 1 replicate. For all other replicates – for prothioconazole as well as for prothioconazole-desthio – the results were "<LOQ".

In each of the studies exposure to prothioconazole and prothioconazole-desthio measured in the hand wash samples was > LOQ for one of the monitored operators

The results of the protective gloves show measurable exposure figures for prothioconazole and prothioconazole desthio only for the second study. For prothioconazole this is due to the lower LOQ. Most of measured values of the second study are smaller or slightly above the LOQ of the first study. The prothioconazole desthio exposure is >LOQ for only one glove sample.

However, one should be aware that residues on protective gloves should be regarded to have an indicative character only, similar to the residues on outer clothing or estimates of potential dermal exposure.

Essential figures for risk assessments should always relate to real actual dermal exposure data whenever they are available.

The potential and actual dermal exposure figures from all studies are listed in Table CP 7.2.1.2-9 for the exposure to prothioconazole and in Table CP 7.2.1.2-10 for the exposure to prothioconazole-desthio. Normalization was performed with regard to the actual bodyweight of the individual operators and the amount of prothioconazole handled per day.

Table CP 7.2.1.2-9: Dermal exposure to prothioconazole (in total mg as well as in mg/kg bw and mg /kg a.s. handled)

Study	Operator ID	Potential dermal exposure			Actual dermal exposure		
		[mg]	[mg/kg bw]	[mg/kg a.s. handled]	[mg]	[mg/kg bw]	[mg/kg a.s. handled]
1	OA	0.475	0.00516	3.146	0.0350	0.000380	0.232
1	OB	0.999	0.01218	18.42	0.0364	0.000444	0.671
1	OC	0.475	0.00365	9.814	0.0350	0.000269	0.723
1	OD	0.473	0.00430	5.363	0.0325	0.000295	0.369
1	OE	0.610	0.00629	10.78	0.0848	0.000874	1.498
1	OF	0.475	0.00339	2.128	0.0350	0.000250	0.157
1	OG	0.777	0.00864	3.415	0.0706	0.000784	0.310
1	OH	0.473	0.00675	8.607	0.0325	0.000464	0.592
1	OI	0.473	0.00508	7.383	0.0325	0.000349	0.508
2	OA	0.240	0.00296	6.396	0.0070	0.000086	0.187
2	OB	0.160	0.00160	1.149	0.0135	0.000135	0.0976
2	OC	0.779	0.00927	9.578	0.0070	0.000083	0.0861
2	OD	1.306	0.01268	16.82	0.0530	0.000514	0.683
2	OE	0.276	0.00300	2.798	0.0355	0.000385	0.359

The results show that potential dermal exposure to prothioconazole and prothioconazole-desthio covers a range of a factor of about 8 (0.160 – 1.306 mg, 0.00160 – 0.0127 mg/kg bw) and 3 (0.072 – 0.170 mg, 0.00052 – 0.00181 mg/kg bw), respectively. Normalized to the amount of a.s. handled potential exposure to prothioconazole and prothioconazole-desthio covers a range of 16 (1.149 – 18.42 mg/kg a.s. handled) and 9 (0.327- 2.995 mg/kg a.s. handled).

For the actual dermal exposure the range of exposure to prothioconazole amounts to a factor of 12 (0.007 – 0.0848 mg, 0.000083 – 0.000874 mg/kg bw). The range of the normalized exposure values covers a range of about 17 (0.0861 – 1.498 mg/kg a.s. handled).

For prothioconazole-desthio this range amounts to a factor of about 7 (0.007 – 0.0509 mg, 0.00007 – 0.000524 mg/kg bw). The range of the normalized exposure values covers a range of about 17 (0.0504 – 0.899 mg/kg a.s. handled).

Table CP 7.2.1.2-10: Dermal exposure to prothioconazole-desthio (in total mg as well as in mg/kg bw)

Study	Operator ID	Potential dermal exposure			Actual dermal exposure		
		[mg]	[mg/kg bw]	[mg/kg a.s. handled]	[mg]	[mg/kg bw]	[mg/kg a.s. handled]
1	OA	0.0730	0.00079	0.483	0.0130	0.000141	0.0861
1	OB	0.148	0.00181	2.735	0.0120	0.000146	0.221
1	OC	0.0730	0.00056	1.508	0.0130	0.000100	0.269
1	OD	0.0720	0.00065	0.817	0.0120	0.000109	0.136
1	OE	0.170	0.00175	2.995	0.0509	0.000524	0.899
1	OF	0.0730	0.00052	0.327	0.0130	0.000093	0.0582
1	OG	0.135	0.00150	0.594	0.0186	0.000206	0.0816
1	OH	0.0720	0.00103	1.311	0.0120	0.000171	0.219
1	OI	0.0720	0.00077	1.125	0.0120	0.000129	0.188
2	OA	0.0870	0.00107	2.321	0.00700	0.000086	0.187
2	OB	0.0870	0.00087	0.627	0.00700	0.000070	0.0504
2	OC	0.121	0.00144	1.484	0.00700	0.000083	0.0861
2	OD	0.140	0.00136	1.803	0.00820	0.000080	0.106
2	OE	0.100	0.00109	1.011	0.00700	0.000076	0.071

The inhalation exposure to prothioconazole and prothioconazole-desthio are presented in Table CP 7.2.1.2-11.

Prothioconazole was found in eight replicates. Residue levels to prothioconazole were in general low. In first study except for one operator residues on all samples were below LOQ or in maximum 3 times the LOQ. Only one operator (OB) had higher residues mainly due to the loading of bulked seeds which resulted in a higher dust emission. In the second study the residue level on the air semplers was in general higher but the absolute figures are still low. Residues of prothioconazole-desthio > LOQ was found on the air samplers of the three operators with the highest residues of prothioconazole.

The higher figures for the replicates with residues <LOQ in study 1 are due to the number of samples (i.e. in study 1 residues on the filter and the filter cassette were measured in two samples separately whereas in study 2 filter and cassette were analyzed as one sample).

Table CP 7.2.1.2-11: Inhalation exposure to prothioconazole and to prothioconazole-desthio (in total mg as well as in mg/kg bw)

Study	Operator ID	Prothioconazole Inhalation exposure [µg]	[µg/kg bw]	[µg/kg a.s. handled]	Prothioconazole-desthio Inhalation exposure [µg]	[µg/kg bw]	[µg/kg a.s. handled]
1	OA	1.040	0.0113	6.887	1.040	0.0113	6.887
1	OB	30.63	0.3735	565.1	5.702	0.0695	105.2
1	OC	3.353	0.0258	69.28	1.040	0.0080	21.49
1	OD	1.040	0.0095	11.80	1.040	0.0095	11.80
1	OE	2.589	0.0267	45.73	1.040	0.0107	18.37
1	OF	1.759	0.0126	7.879	1.040	0.0074	4.659
1	OG	3.635	0.0404	15.97	1.040	0.0116	4.569
1	OH	1.040	0.0149	18.94	1.040	0.0149	18.94
1	OI	1.040	0.0112	16.25	1.040	0.0112	16.25
2	OA	0.520	0.0064	13.87	0.520	0.0064	13.87
2	OB	6.560	0.0656	47.27	1.670	0.0167	12.03
2	OC	5.940	0.0707	73.04	0.520	0.0062	6.394
2	OD	13.65	0.1325	175.9	2.500	0.0243	32.21
2	OE	5.830	0.0634	59.01	0.520	0.0057	5.263

Assessment of operator exposure

A risk assessment is presented in the following for the active substances prothioconazole and its conversion product prothioconazole-desthio when applying 'Prothioconazole FS 100'. Calculations are performed for operators during seed treatment and seed sowing using the experimentally determined specific exposures.

Calculation of operator exposure during cereal seed treatment

For the calculation of the operator exposure during cereal seed treatment data of the study conducted with EfA FS 76.25 are used. This database covers a wide range of technical equipment, technical standards and working conditions and includes a large number of replicates.

EfA FS 76.25 contains 37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole and is applied in an application rate 120 to 200 mL/100 kg seed corresponding to 3 to 5 g prothioconazole/100 kg seed. A two to three times higher application rate is foreseen for the active substance prothioconazole during the treatment of cereal seeds with 'Prothioconazole FS 100'. To evaluate the operator exposure to prothioconazole and prothioconazole-desthio the measured exposure values of each single operator will be corrected with the factor 3.

The following assumptions are made:

Operator body weight:	individual body weight of the operators
Dermal absorption:	
Prothioconazole	25%
Prothioconazole-desthio	6%
Inhalation absorption	100% for prothioconazole and prothioconazole-desthio

The calculation of the systemic exposure is performed according to the following equation:

$$\textbf{Systemic exposure [mg/kg bw/day]} = \frac{\textbf{((ADE x DA) + PIE) x CF}}{\textbf{BW}}$$

ADE = Actual dermal exposure [µg/day]

PIE = Potential inhalation exposure [µg/day]

DA = Dermal absorption [%]

BW = individual body weight of the respective operator

CF = Correction factor (3 for prothioconazole and prothioconazole-desthio)

The results of the evaluation and the comparison of the observed operator exposure [mg/kg bw/day] to the AOELs are summarized in the following table:

Table CP 7.2.1.2-12: Operator exposure to prothioconazole during seed treatment and comparison of the observed operator exposure to the AOEL (actual exposure, with PPE)

Operator ID	Body weight [kg]	Actual dermal exposure [µg/day]	Potential inhalation exposure [µg/day]	Systemic exposure [mg/kg bw/day]	% of AOEL [0.25 mg/kg bw/day]
OA	85	38.98	2.986	0.00045	0.2
OB	100	39.32	5.841	0.00047	0.2
OC	65	84.66	7.996	0.00135	0.5
OD	85	116.0	1.040	0.00106	0.4
OE	100	35.00	4.700	0.00040	0.2
OF	65	53.31	1.591	0.00069	0.3
OG	82	35.00	4.786	0.00050	0.2
OH	83	72.01	3.472	0.00078	0.3
OI	82	50.51	2.988	0.00057	0.2
OK	83	123.2	4.144	0.00126	0.5
OL	85	32.50	1.958	0.00036	0.1
OM	70	32.50	1.616	0.00042	0.2
ON	85	35.67	2.748	0.00041	0.2
OO	70	36.79	3.404	0.00054	0.2
OP	80	81.93	1.040	0.00081	0.3
OR	90	37.57	1.040	0.00035	0.1
OS	80	49.36	1.040	0.00050	0.2
OT	90	61.70	1.040	0.00055	0.2
O8A	65	69.62	1.040	0.00085	0.3
O8B	90	35.00	1.040	0.00033	0.1
O8C	65	46.22	1.040	0.00058	0.2
O8D	90	100.0	1.040	0.00087	0.3
O8E	75	46.15	1.040	0.00050	0.2
O8F	75	51.63	1.040	0.00056	0.2
O8G	80	42.90	2.784	0.00051	0.2
O8H	80	32.50	4.190	0.00046	0.2
O8I	68	40.70	2.188	0.00055	0.2
O8K	88	37.50	3.958	0.00045	0.2
O8L	65	37.50	1.689	0.00051	0.2
O8M	68	39.25	1.040	0.00048	0.2
O8N	88	35.00	1.040	0.00033	0.1

Summary statistic

Statistic	With PPE	
	mg/kg bw/d	% of AOEL
Empirical 75th percentile	0.00063	0.3
Empirical 95th percentile	0.00116	0.5
Maximum	0.00135	0.5
Parametric 75th percentile	**0.000714**	**0.3**
Log normal?	no	

Table CP 7.2.1.2-13: Operator exposure to prothioconazole-desthio during seed treatment and comparison of the observed operator exposure to the AOEL (actual exposure, with PPE)

Operator ID	Body weight [kg]	Actual dermal exposure [µg/day]	Potential inhalation exposure [µg/day]	Systemic exposure [mg/kg bw/day]	% of AOEL [0.01 mg/kg bw/day]
OA	85	16.43	1.040	0.000071	0.7
OB	100	13.18	1.040	0.000055	0.5
OC	65	21.72	1.040	0.000108	1.1
OD	85	31.71	1.040	0.000104	1.0
OE	100	12.75	1.040	0.000054	0.5
OF	65	27.95	1.040	0.000125	1.3
OG	82	10.00	1.040	0.000060	0.6
OH	83	10.00	1.040	0.000059	0.6
OI	82	10.00	1.040	0.000060	0.6
OK	83	12.54	1.040	0.000065	0.6
OL	85	10.02	1.040	0.000058	0.6
OM	70	9.00	1.040	0.000068	0.7
ON	85	10.10	1.040	0.000058	0.6
OO	70	9.00	1.040	0.000068	0.7
OP	80	14.01	1.040	0.000071	0.7
OR	90	10.60	1.040	0.000056	0.6
OS	80	11.00	1.040	0.000064	0.6
OT	90	10.86	1.040	0.000056	0.6
O8A	65	11.00	1.040	0.000078	0.8
O8B	90	10.00	1.040	0.000055	0.5
O8C	65	11.44	1.040	0.000080	0.8
O8D	90	17.24	1.040	0.000069	0.7
O8E	75	11.25	1.040	0.000069	0.7
O8F	75	11.68	1.040	0.000070	0.7
O8G	80	12.38	1.040	0.000067	0.7
O8H	80	12.73	1.040	0.000068	0.7
O8I	68	15.79	1.040	0.000088	0.9
O8K	88	14.00	1.040	0.000064	0.6
O8L	65	11.00	1.040	0.000078	0.8
O8M	68	13.27	1.040	0.000081	0.8
O8N	88	10.00	1.040	0.000056	0.6

Summary statistic

Statistic	With PPE	
	mg/kg bw/d	% of AOEL
Empirical 75th percentile	0.00007	0.7
Empirical 95th percentile	0.00011	1.1
Maximum	0.00013	1.3
Parametric 75th percentile	**0.00008**	**0.8**
Log normal?	no	

Calculation of operator exposure during sowing of treated cereal seeds

Systemic operator exposure to prothioconazole and prothioconazole desthio is calculated based on the study results in two alternative ways.

A) Calculation of the systemic exposure for each operator with the not normalised study results and individual body weights of the operators.
B) Calculation of the systemic exposure based on normalised dermal and inhalation exposure values (mg/kg a.s. handled) considering a default sowing rate and area sown as well as a standard body weight.

For the estimation of the systemic exposure of operators to prothioconazole and prothioconazole-desthio the actual dermal exposure figures are used.

A) Estimate based on not normalised study results

EfA FS 76.25 contains 37.5 g/L fluoxastrobin, 25 g/L prothioconazole, 10 g/L triazoxide, and 3.75 g/L tebuconazole and is applied in an application rate 120 to 200 mL/100 kg seed corresponding to 3 to 5 g prothioconazole/100 kg seed. A two to three times higher application rate is foreseen for the active substance prothioconazole during the treatment of cereal seeds with 'Prothioconazole FS 100'. To evaluate the operator exposure to prothioconazole and prothioconazole-desthio the measured exposure values of each single operator will be corrected with the factor 3.

The following assumptions are made:

Operator body weight: individual body weight of the operators
Dermal absorption:
Prothioconazole 25%
Prothioconazole-desthio 6%
Inhalation absorption 100% for prothioconazole and prothioconazole-desthio

The calculation of the systemic exposure is performed according to the following equation:

$$\textbf{Systemic exposure [mg/kg bw/day]} = \frac{((ADE \times DA) + PIE) \times CF}{BW}$$

ADE = Actual dermal exposure [µg/day]
PIE = Potential inhalation exposure [µg/day]
DA = Dermal absorption [%]
BW = individual body weight of the respective operator
CF = Correction factor (3 for prothioconazole and prothioconazole-desthio)

Table CP 7.2.1.2-14: Calculation of systemic operator exposure to prothioconazole using a representative operator exposure study conducted during loading and

sowing (not normalized study results, actual exposure, with PPE)

Study/ Operator	Body weight [kg]	Actual dermal exposure [µg/day]	Potential inhalation exposure [µg/day]	Systemic exposure [mg/kg bw/day]	% of AOEL [0.25 mg/kg bw/day]
1/OA	92	35.00	1.040	0.000319	0.13
1/OB	82	36.40	30.63	0.001454	0.58
1/OC	130	35.00	3.353	0.000279	0.11
1/OD	110	32.50	1.040	0.000250	0.10
1/OE	97	84.80	2.589	0.000736	0.29
1/OF	140	35.00	1.759	0.000225	0.09
1/OG	90	70.60	3.635	0.000710	0.28
1/OH	70	32.50	1.040	0.000393	0.16
1/OI	93	32.50	1.040	0.000296	0.12
2/OA	81	7.00	0.520	0.000084	0.03
2/OB	100	13.50	6.560	0.000298	0.12
2/OC	84	7.00	5.940	0.000275	0.11
2/OD	103	53.00	13.65	0.000783	0.31
2/OE	92	35.50	5.830	0.000480	0.19

Summary statistic

Statistic	With PPE	
	mg/kg bw/d	% of AOEL
Empirical 75th percentile	**0.000652**	**0.3**
Empirical 95th percentile	0.00102	0.4
Maximum	0.00145	0.6
Parametric 75th percentile	0.000620	0.2
Log normal?	yes	

Table CP 7.2.1.2-15: Calculation of systemic operator exposure to prothioconazole-desthio using a representative operator exposure study conducted during loading and

sowing (not normalized study results, actual exposure, with PPE)

Study/ Operator	Body weight [kg]	Actual dermal exposure [µg/day]	Potential inhalation exposure [µg/day]	Systemic exposure [mg/kg bw/day]	% of AOEL [0.01 mg/kg bw/day]
1/OA	92	13.00	1.040	0.000059	0.6
1/OB	82	12.00	5.702	0.000235	2.3
1/OC	130	13.00	1.040	0.000042	0.4
1/OD	110	12.00	1.040	0.000048	0.5
1/OE	97	50.90	1.040	0.000127	1.3
1/OF	140	13.00	1.040	0.000039	0.4
1/OG	90	18.60	1.040	0.000072	0.7
1/OH	70	12.00	1.040	0.000073	0.8
1/OI	93	12.00	1.040	0.000057	0.6
2/OA	81	7.00	0.520	0.000035	0.3
2/OB	100	7.00	1.670	0.000063	0.6
2/OC	84	7.00	0.520	0.000034	0.3
2/OD	103	8.20	2.500	0.000087	0.9
2/OE	92	7.00	0.520	0.000031	0.3

Summary statistic

Statistic	With PPE	
	mg/kg bw/d	% of AOEL
Empirical 75th percentile	0.000075	0.75
Empirical 95th percentile	0.000165	1.65
Maximum	0.000235	2.35
Parametric 75th percentile	**0.000090**	**0.9**
Log normal?	yes	

B) Estimate based on normalised study results

The following assumptions are made:

Crop:	Cereals
Drilling rate:	180 kg/ha
Work rate:	15 ha/day
Application rate:	10 g a.s./100 kg seed
Amount of a.s. handled:	270 g a.s./day
Operator body weight:	60 kg
Dermal absorption:	
Prothioconazole	25%
Prothioconazole-desthio	6%
Inhalation absorption	100% for prothioconazole and prothioconazole-desthio

The calculation of the systemic exposure is performed according to the following equation:

$$\textbf{Systemic exposure [mg/kg bw/day]} = \frac{\textbf{((ADE x DA) + PIE) x AH}}{\textbf{BW}}$$

ADE = Actual dermal exposure [mg/kg a.s. handled]

PIE = Potential inhalation exposure [mg/kg a.s.handled]

DA = Dermal absorption [%]

BW = standard body weight [kg]

AH = Amount of a.s. handled [kg]

Table CP 7.2.1.2-16a: Operator exposure to prothioconazole during loading and sowing (normalized study results, actual exposure, with PPE)

	Study ID	ADE [mg/kg a.s.]	IE [µg/kg a.s.]
1	OA	0.232	6.89
1	OB	0.671	565.10
1	OC	0.723	69.28
1	OD	0.369	11.80
1	OE	1.498	45.73
1	OF	0.157	7.879
1	OG	0.310	15.97
1	OH	0.592	18.94
1	OI	0.508	16.25
2	OA	0.187	13.87
2	OB	0.0976	17.27
2	OC	0.0861	73.04
2	OD	0.683	175.90
2	OE	0.359	59.01
Minimum		0.0861	6.89
Maximum		1.498	565.10
75th percentile		0.651	66.71
95th percentile		0.994	312.1
75th parametric estimate		0.623	83.43
Log normal		yes	yes

ADE = actual dermal exposure, IE = inhalation exposure

Table CP 7.2.1.2-16b: Calculation of systemic operator exposure to prothioconazole using a representative operator exposure study conducted during loading and sowing (normalized study results, actual exposure, with PPE)

	Actual dermal exposure [mg/kg a.s. handled]	**Potential inhalation exposure** [mg/kg a.s. handled]	**Systemic exposure** [mg/kg bw/day]	**% of AOEL** [0.25 mg/kg bw/day]
Empirical 75th percentile	0.651	0.0667	0.00103	0.4
Empirical 95th percentile	0.994	0.312	0.00252	1.0
Maximum	1.498	0.565	0.00423	1.7
Parametric 75th percentile	**0.623**	**0.0834**	**0.00108**	**0.4**

Table CP 7.2.1.2-17a: Operator exposure to prothioconazole-desthio during loading and sowing (normalized study results, actual exposure, with PPE)

Study	Operator ID	ADE [mg/kg a.s.]	IE [µg/kg a.s.]
1	OA	0.0861	6.89
1	OB	0.221	105.20
1	OC	0.269	21.49
1	OD	0.136	11.80
1	OE	0.899	18.37
1	OF	0.0582	4.659
1	OG	0.0816	4.569
1	OH	0.219	18.94
1	OI	0.188	16.25
2	OA	0.187	13.87
2	OB	0.0504	12.03
2	OC	0.0861	6.39
2	OD	0.106	32.21
2	OE	0.071	5.26
Minimum		0.0504	4.57
Maximum		0.899	105.20
75th percentile		0.211	18.80
95th percentile		0.489	57.76
75th parametric estimate		0.242	24.20
Log-normal		yes	yes

ADE = actual dermal exposure, IE = inhalation exposure

Table CP 7.2.1.2-17b: Calculation of systemic operator exposure to prothioconazole-desthio using a representative operator exposure study conducted during loading and sowing (normalized study results, actual exposure, with PPE)

	Actual dermal exposure [mg/kg a.s. handled]	**Potential inhalation exposure** [mg/kg a.s. handled]	**Systemic exposure** [mg/kg bw/day]	**% of AOEL** [0.01 mg/kg bw/day]
Empirical 75th percentile	0.211	0.0188	0.000142	1.4
Empirical 95th percentile	0.489	0.0578	0.000392	3.9
Maximum	0.899	0.105	0.000715	7.2
Parametric 75th percentile	**0.242**	**0.0242**	**0.000174**	**1.7**

Summary

For a reasonable conservative assessment the 75th percentile is used for the estimates of exposure to prothioconazole and prothioconazole-dethio. The selection rule proposed in the EFSA Guidance considers the higher value of the empirical and the parametric percentile as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen.

Table CP 7.2.1.2-18: Summary of the experimental determined operator exposure during seed treatment and loading/sowing (actual exposure, with PPE)

	Substance	PPE	Total systemic exposure (mg/kg bw/day)	% of AOEL#
Seed Treatment	Prothioconazole	With PPE1)	0.00071	**0.3**
	Prothioconazole-desthio	With PPE1)	0.00008	**0.8**
Loading /sowing (not normalized study results)	Prothioconazole	With PPE2)	0.00065	**0.3**
	Prothioconazole-desthio	With PPE2)	0.00009	**0.9**
Loading /sowing (normalized study results)	Prothioconazole	With PPE2)	0.00108	**0.4**
	Prothioconazole-desthio	With PPE2)	0.00017	**1.7**

1) Standard protective garment; protective gloves are worn during calibration, mixing and loading, cleaning.
2) Standard protective garment; protective gloves are worn when direct contact to treated seeds is given.

Based on these results there is no unacceptable risk anticipated for operators during seed treatment and when loading and sowing treated seeds. According to good agricultural practice the use of adequate work clothing (e.g. trousers and a long sleeved shirt as well as sturdy footwear) is considered. Protective gloves should always be worn when handling the product and when getting into contact with treated seeds or contaminated surfaces.

CP 7.2.2 Bystander and resident exposure

A bystander is a person

• who is located within or directly adjacent to the area where pesticide application or treatment is in process or has been made

• whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of exposure

A resident is considered to be a person who lives in the vicinity of the application. Exposure of residents might be expected where drift of residues and subsequent deposition in areas adjacent to the application area can be assumed (e.g. spray applications in the field). In certain cases vapour drift could be another source for resident exposure.

In this context it has to be taken into account that with the intended use of 'Prothioconazole FS 100' treatment of the seeds is performed in professional seed treatment plants where no person is around whose presence is quite incidental and unrelated to the work. Furthermore, no other (uninvolved) persons are allowed to enter the plant. Concerning sowing of the seed again it has to be taken into account that the seeds are placed directly into the ground and immediately afterwards the seeds are covered with soil.

Hence, with normal use conditions there is no exposure scenario expected that could involve the bystander or resident.

Accordingly, concerning the intended use of 'Prothioconazole FS 100' bystander- and resident exposure is considered to be not relevant.

CP 7.2.2.1 Estimation of bystander and resident exposure

Considered to be not applicable with the intended use of 'Prothioconazole FS 100'.

For details please refer to CP 7.2.2.

CP 7.2.2.2 Measurement of bystander and resident exposure

Considered to be not applicable with the intended use of 'Prothioconazole FS 100'.

For details please refer to CP 7.2.2.

CP 7.2.3 Worker exposure

The only intended use of 'Prothioconazole FS 100' is dressing seeds prior to sowing. During sowing the seeds are immediately covered by soil. Consequently no re-entry scenario is given that could result in worker exposure.

Therefore, worker exposure to 'Prothioconazole FS 100' is considered to be not applicable.

CP 7.2.3.1 Estimation of worker exposure

Considered to be not applicable with the intended use of 'Prothioconazole FS 100'.

For details please refer to CP 7.2.3.

CP 7.2.3.2 Measurement of worker exposure

Considered to be not applicable with the intended use of 'Prothioconazole FS 100'.

For details please refer to CP 7.2.3.

CP 7.3 Dermal adsorption

The extent of dermal absorption of PTZ-desthio (prothioconazole-desthio) formulated as a dilution of the 'Prothioconazole FS 100' (PTZ FS 100) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following section along with the mean values based on the study results and following application of the new EFSA[2] guidance rules. The study summary and conclusion and recommendation regarding the dermal absorption of PTZ-desthio formulated as a dilution of the FS 100 formulation is given below.

Report:	KCP 7.3/01 [redacted], 2015, M-540994-01-1
Title:	The in vitro percutaneous absorption of radiolabelled JAU 6476-desthio in a 5 g/L dilution of the prothioconazole FS 100 formulation through human skin
Report No.:	796869
Document No.:	M-540994-01-1
Guideline(s):	OECD Guideline for Testing of Chemicals, Guideline 428: Skin Absorption: In Vitro Method (2004). OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 28. Guidance Document for the Conduct of Skin Absorption Studies (2004). European Commission Guidance Document on Dermal Absorption Sanco/222/2000/Rev. 7 (19 March 2004) Scientific Opinion on Dermal Absorption (EFSA Journal, 2012, 10(4): 2665).
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods

Human skin: Source: [redacted], UK.

Number and sex: 4 donors, 1 male and 3 female.

Anatomical region: 3 Abdomen and breast.

Thickness: 370 to 400 µm.

Test Material:

Non-radiolabelled: Batch: AE 1194888-PU-01.

Purity = 99.5% w/w.

Radiolabelled: [triazole-UL-^{14}C]-PTZ-desthio.

[2] 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.

Batch: KML 9567.

Specific activity: 2.45 MBq/mg.

Radiopurity of the formulation: 98.5%.

Formulation: The formulation used in this experiment was a 5 g/L dilution of the PTZ FS 100 formulation (specification number 102000030977) containing PTZ-desthio (5 g/L).

Test system: A static diffusion cell system (PermeGear Inc) was used. The static diffusion cells were placed in a manifold on a magnetic stirrer plate heated *via* a circulating water bath to maintain the skin surface temperature at 32°C ± 1°C.

The surface area of exposed skin within the cells was 0.64 cm^2. The receptor chamber volume was nominally 5 mL, with each receptor chamber individually marked with the actual volume by the manufacturer.

The receptor fluid was PBS containing PEG (*ca* 6%, w/v), streptomycin (0.1 mg/mL), penicillin G (100 units/mL) and sodium azide (0.01%, w/v). The pH was adjusted to 7.4, and the receptor fluid was degassed by sonication for 10 min after being made before being stored in a refrigerator set to maintain a temperature of 4°C prior to use on the study

Skin integrity: Skin samples were allowed to equilibrate at 32°C ± 1°C for *ca* 30 min. Phosphate buffered saline (1 mL) was then added to the donor chamber and the skin samples were allowed to equilibrate for a further *ca* 30 min. The electrical resistance was then measured using a Tinsley Databridge (Model 6401) set at low voltage alternating current, 1000 Hz with a maximum voltage of 300 mV root-mean-squared (rms) in the parallel equivalent circuit mode. Any skin sample exhibiting a resistance less than 10.9 kΩ was excluded from subsequent absorption measurements. A cross reference of skin cell number, donor number and electrical resistance (kΩ) is presented in Appendix 7. The phosphate buffered saline was removed from the skin surface, the skin was rinsed with water (2-3 mL) and dried with tissue paper.

Treatment: The neat formulation was applied over the surface of the stratum corneum of nine samples of skin (3.14 cm^2) using a positive displacement pipette set to deliver 31.4 µL (10 µL/cm^2). The spray dilutions were applied over the surface of the stratum corneum (0.64 cm^2) using a positive displacement pipette set to deliver 6.4 µL (10 µL/cm^2). To accurately quantify the concentration of test preparations applied to the skin samples, representative aliquots of the test preparations were taken at the time of dosing. These samples were mixed with methanol:scintillation fluid (1:5, v/v; 12 mL) and analysed by liquid scintillation counting.

Sampling: Receptor fluid aliquots were collected at 1, 2, 4, 8 and 12 h post dose as described in Section 6.11. All receptor fluid samples were mixed with

methanol:scintillation fluid (1:5 v/v; 12 mL) and analysed by liquid scintillation counting.

At 8 h post dose, the both static and dynamic cells were washed by applying commercial hand wash soap (50 µL) to each skin sample and gently rubbing into the skin surface using a tissue swab. The skin was then washed with 10 aliquots (0.5 mL per aliquot) of an aqueous commercial soap solution (2%, v/v).

At 24 hours the stratum corneum was removed with 20 successive tape strips. The skin sample was rotated 90° after each tape strip unless any epidermis was removed. If epidermis was removed, rotation was stopped and details of epidermis removal documented. Each tape strip was placed into an individual vial containing methanol:scintillation fluid (1:5, v/v; 12 mL) and then analysed by liquid scintillation counting. The skin under the cell flange (unexposed skin) was cut away from the exposed skin. The exposed and unexposed skin samples were placed into separate vials containing Solvable® (2 mL). The skin samples were placed into a waterbath set to 60°C to aid solubilisation. When fully dissolved, stannous chloride solution (0.2 g/mL in ethanol; 150 µL) and scintillation fluid (10 mL) was added to the skin samples and analysed by liquid scintillation counting.

Radioassay: All samples were counted together with representative blanks using a liquid scintillation analyser (Packard 2100-TR) with automatic quench correction by external standards. Representative blank sample values were subtracted from sample count rates to give net d.p.m. per sample. Prior to analysis, samples were allowed to stabilise with regard to light and temperature.

Findings:

The PTZ-desthio was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

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

The study results are presented in Table CP 7.3-1.

Table CP 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-PTZ-desthio in an FS 100 formulation at the rate of 5 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)	
Dose Levels	5 g/L	
Species	Human (n=8)	
	Mean	SD
SURFACE COMPARTMENT		
Skin swabs (total)[a]	93.70	3.04
Surface Dose (1st two tape-strips)	0.44	0.46
Donor chamber	0.66	0.64
Total % non-absorbed	94.80	2.34
SKIN COMPARTMENT		
Skin[b]	0.77	0.40
Stratum corneum[c]	0.61	0.42
Total % at dose site	***1.38***	***0.66***
RECEPTOR COMPARTMENT		
Total % directly absorbed[d]	***2.74***	***1.28***
STUDY: Total % Potentially Absorbable[e]	4.12	1.69
TOTAL % RECOVERY	98.92	1.52
Evaluation according to EFSA Guidance		
absorption >75% within half of study duration	No (71%)	
standard deviation >25%	Yes	
recovery <95%	No	
Adjusted Total % Potentially Absorbable[f]	**6**	

[a]: sum of radioactivity found in swabs at 8h and 24h.
[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
[f]: values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***

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 extent of dermal absorption of PTZ-desthio (prothioconazole-desthio) formulated as a dilution of the 'Prothioconazole FS 100' (PTZ FS 100) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following section along with the mean values based on the study results and following application of the new EFSA guidance rules. A conclusion and recommendation regarding the dermal absorption of PTZ-desthio formulated as a dilution of the FS 100 formulation is given below.

The mean percentage of PTZ-desthio in the FS 100 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the 5 g/L dilution was 4.1% for the human skin. Applying the new EFSA guidance this value adjusts to 6%.

According to the new EFSA guidance[3] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that 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. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-PTZ-desthio in a 5 g/L dilution of the PTZ FS 100 formulation:

- 6% for the neat formulation (5 g/L)

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

[3] 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.