Bayer CropScience

Document Title

Summary of the toxicological studies Bixafen + Prothioconazole EC 225 (75 + 150 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013

Document MCP

Section 7: Toxicological studies

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

Date

2015-12-08

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 BIX+PTZ EC 225 specification number 102000013869 version 03.
2) …non-dietary exposure calculations and assessments for operators, workers and bystanders/residents to prothioconazole and its main metabolite prothioconazole-desthio during or after the intended use of the representative formulation PTZ+BIX EC 225.

CP 7.1 Acute toxicity

Bixafen + Prothioconazole EC 225 (75 + 150 g/L) is a fungicide formulation containing the active substances bixafen and prothioconazole at 75 g/L and 150 g/L, respectively.

The acute oral and dermal toxicity studies as well as skin and eye irritation and sensitization studies have been performed in 2007 with batch 2007-002622 of specification 102000013869.

At the time of study conduct the formulation was named
Bixafen & prothioconazole EC 75 + 150

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 can be found in the confidential part of this submission.

Summary of acute toxicity

Type of study	Results	Report, document no.
Acute oral rat LD_{50}	>2000 mg/kg bw	[redacted], M. (2007) CP 7.1.1 Report AT04095 [M-292722-01-1]
Acute dermal rat LD_{50}	>2000 mg/kg bw	[redacted], M. (2007) CP 7.1.2 Report AT04096 [M-292717-01-1]
Acute inhalation rat LC_{50}	May cause respiratory irritation	[redacted], A.; [redacted], F. M. (2015) CP 7.1.3 calculation method [M-532323-01-1]
Acute skin irritation rabbit	Slightly irritating (classification is not triggered)	[redacted], C. (2007) CP 7.1.4 Report AT04080 [M-292508-01-1]
Acute eye irritation rabbit	Irritating	[redacted], C. (2007) CP 7.1.5 Report AT04081 [M-292511-01-1]
Skin sensitisation (Local Lymph Node Assay)	Not sensitizing	[redacted], M. (2007) CP 7.1.1 Report SA 07171 [M-293215-01-1]

Bixafen + Prothioconazole EC 225 (75 + 150 g/L) is of very low toxicity after acute oral and dermal administration.

The formulation was not tested for acute inhalation toxicity. The calculated LC_{50} value does not require a classification for acute inhalation toxicity. The formulation contains a solvent that is classified for STOT SE 3, H335 (May cause respiratory tract irritation). Since its content is above the specified generic concentration limit of 20%, the classification for respiratory tract irritation applies for the formulation BIX + PTZ EC 225 (75 + 150 g/L).

The formulation is slightly irritating to the skin (classification is not triggered) but irritating to the eyes of rabbits. Bixafen + Prothioconazole EC 225 (75+150 g/L) shows no sensitising potential in the Local Lymph Node assay on mice.

These results trigger the following classification/labelling according to Regulation (EC) No 1272/2008 (CLP):

STOT SE cat 3
H 335 (may cause respiratory irritation)
Eye irritation Cat. 2
H319 (causes serious eye irritation)

The applicant, Bayer CropScience, notes that in the past Member States have required for formulations containing prothioconazole at or above 3% a reproductive toxicity labelling as Repro. Cat. 2, H361d (suspected of damaging the unborn child), based on the EFSA proposal to classify prothioconazole as reproductive toxic Repro. Cat. 2 H361d (EFSA Scientific Report (2007)).

In the absence of a harmonised EU classification (ECHA) for prothioconazole, the applicant insists in self-classification of his products. The applicant, Bayer CropScience, is convinced that prothioconazole should not be classified for reproductive toxicity, the arguments for non-classification are provided in a separately submitted position paper ([redacted], M., 2006, M-266455-01-1).

CP 7.1.1 Oral toxicity

Report:	KCP 7.1.1/01 [redacted]; 2007; M-292722-01-1
Title:	Bixafen & prothioconazole EC 75 + 150 - Acute toxicity in the rat after oral administration
Report No.:	AT04095
Document No.:	M-292722-01-1
Guideline(s):	OECD 425 (2006)
Guideline deviation(s):	The test compound is a product known to be stable and homogenous both undiluted and in ready-to-use formulation with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed. This deviation does not limit the assessment of results
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: BIX + PTZ EC 75 + 150 G (bixafen & prothioconazole EC 75 + 150)

Specification no.:	102000013869
Description:	brown liquid
Lot/Batch no:	2007-002622
Content:	bixafen: 77.2 g/L; prothioconazole: 147 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2008-10-04

2. Vehicle: tap water

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu
Age:	approx. 9 – 12 weeks
Weight at dosing:	164 g – 197 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland"
Water:	tap water
Housing:	individually in polycarbonate cages, bedding: low dust wood granulate bedding (Lignocel 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:	16 - 24 h
	after administration:	approx. 2 - 4 h
Group size:	5 females/group	
Post-treatment observation period:	14 days	
Observations:	mortality, clinical signs, body weight, gross necropsy	

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological result*			Occurrence of signs	Time of death	Mortality (%)
2000	1	4	5		20' - 2d	20
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

B. Clinical observations

The following clinical signs were observed: decreased motility, piloerection, temporary creeping gait and temporary tremor.

C. Body weight

There were no toxicologically significant effects on body weight or body weight gain in the surviving animals.

D. Necropsy

In the animal that died during the observation period the following changes were detected: light-coloured, watery change-in-contents of intestine, gas-filled stomach.

The necropsies of the surviving animals performed at the end of the study revealed no particular findings.

III. Conclusion

The test item shows a low toxicity 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],; 2007; M-292717-01-1
Title:	Bixafen & prothioconazole EC 75 + 150 - Acute toxicity in the rat after dermal application
Report No.:	AT04096
Document No.:	M-292717-01-1
Guideline(s):	OECD 402; EEC Directive 67/548, Annex V, Method B.3.; US-EPA OPPTS 870.1200
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: BIX + PTZ EC 75 + 150 G
(bixafen & prothioconazole EC 75 + 150)

Specification no.:	102000013869
Description:	brown liquid
Lot/Batch no:	2007-002622
Content:	bixafen: 77.2 g/L; prothioconazole: 147 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2008-10-04

2. Vehicle: none

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu
Age:	approx. 9 – 13 weeks
Weight at dosing:	males: 234 g – 259 g; females: 207 g – 224 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland"
Water:	tap water
Housing:	individually in polycarbonate cages, bedding: low dust wood granulate bedding (Lignocel 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	2000	30	15.6 - 17.3
females	2000	30	13.8 - 14.9

Application route:	dermal, semi-occlusive dressing
Exposure:	24 hours
Group size:	5 rats/sex/group

Post-treatment observation period:	14 days
Observations:	mortality, clinical signs, skin effects, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality [%]
Male rats						
2000	0	0	5	--	--	0
Females rats						
2000	0	2#	5	3d - 12d	--	0
LD_{50}: >2000 mg/kg bw						

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

\# skin findings only

B. Clinical observations

The following local signs were observed in two females: partial encrustation and partial formation of scale of the test area.

C. Body weight

There were no toxicologically significant effects on body weight or body weight development in males and females.

D. Necropsy

The necropsies performed at the end of the study revealed no particular findings.

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

The formulation Bixafen + Prothioconazole EC 225 (75 + 150 g/L) (Spec. No. 102000013869) was not tested for acute inhalation toxicity.

However, it is possible according to Regulation (EC) 1272/2008 to derive a classification / non-classification by calculating the inhalation LC_{50} value or acute toxicity estimate (ATE_{Mix}) of the formulation based on the concentration and LC_{50} values of its individual ingredients.

The calculation and composition of the formulation are presented in a separate confidential document (M-532323-01-1).

The calculated ATE_{Mix} for BIX + PTZ EC 225 (75 + 150 g/L) (Spec. No. 102000013869) is 23.5 mg/L.

Therefore, the formulation BIX + PTZ EC 225 (75 + 150 g/L) (Spec. No. 102000013869) does not need to be classified for acute inhalation toxicity.

The formulation contains a solvent that is classified for STOT SE 3, H335 (May cause respiratory tract irritation). Since its content is above the specified generic concentration limit of 20%, the classification for respiratory tract irritation applies for the formulation BIX + PTZ EC 225 (75 + 150 g/L) (Spec. No. 102000013869).

Proposed toxicological classification according to Regulation (EC) 1272/2008:
STOT SE cat 3 /H 335 (may cause respiratory irritation)
based on the classification of a certain solvent.

CP 7.1.4 Skin irritation

Report:	KCP 7.1.4/01, [redacted].; 2007; M-292508-01-1
Title:	Bixafen & prothioconazole EC 75 + 150 - Acute skin irritation/corrosion on rabbits
Report No.:	AT04080
Document No.:	M-292508-01-1
Guideline(s):	OECD 404 (2002); EEC Directive 67/548 Annex V - Method B.4. (1967); EPA Health Effects Test Guidelines (OPPTS 870.2500)
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: BIX + PTZ EC 75 + 150 G (bixafen & prothioconazole EC 75 + 150)

Specification no.:	102000013869
Description:	brown liquid
Lot/Batch no:	2007-002622
Content:	bixafen: 77.2 g/L; prothioconazole: 147 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2008-10-04

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	Crl:KBL(NZW)BR

Age:	young adult
Weight at dosing:	2.8 kg - 3.0 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "Ssniff K-Z" 4mm ([redacted], Germany)
Water:	tap water
Housing:	individually in cage units Metall/Noryl by [redacted]

B. Study design and methods

1. Animal assignment and treatment

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

II. Results and discussion

A. Findings

There were no relevant 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	3	3	1	2.3	+	7
	Oedema formation	2	2	1	1.7	--	7
2	Erythema (redness) and eschar formation	1	1	1	1.0	--	7
	Oedema formation	0	0	0	0.0	--	na
3	Erythema (redness) and eschar formation	1	1	1	1.0	--	7
	Oedema formation	0	0	0	0.0	--	na

na = not applicable

Response: -- = negative for mean scores <2.3 Regulation (EC) No 1272/2008 (CLP)
+ = irritant for mean scores ≥2.3 Regulation (EC) No 1272/2008 (CLP)

III. Conclusion

The test item is slightly irritating to the skin of rabbits

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],; 2007; M-292511-01-1
Title:	Bixafen & prothioconazole EC 75 + 150 - Acute eye irritation on rabbits
Report No.:	AT04081
Document No.:	M-292511-01-1
Guideline(s):	OECD 405 (2002); EEC Directive 67/548 Annex V - Method B.5. (1967); EPA Health Effects Test Guidelines (OPPTS 870.2400)
Guideline deviation(s):	none
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: BIX + PTZ EC 75 + 150 G
(bixafen & prothioconazole EC 75 + 150)

Specification no.:	102000013869
Description:	brown liquid
Lot/Batch no:	2007-002622
Content:	bixafen: 77.2 g/L; prothioconazole: 147 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2008-10-04

2. Vehicle: none

3. Test animals

Species:	albino rabbit
Strain:	Crl:KBL(NZW)BR
Age:	young adult
Weight at dosing:	2.6 kg - 3.5 kg
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "Ssniff K-Z" 4mm ([redacted] Germany)
Water:	tap water
Housing:	individually in cage units Metall/Noryl by [redacted]

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.1 mL/animal
Application route:	instillation into the conjunctival sac
Rinsing:	not rinsed for at least 24 hours
Group size:	3 females
Observations:	clinical signs, eye effects, body weight (at beginning of study)

II. Results and discussion

A. Findings

There were no relevant 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	2	2	2	2.0	+	14
	Iritis	1	1	0	0.7	-	3
	Redness conjunctivae	3	3	2	2.7	+	14
	Chemosis conjunctivae	2	1	0	1.0	--	3
2	Corneal opacity	2	2	2	2.0	+	7
	Iritis	1	1	0	0.7	---	3
	Redness conjunctivae	0	0	0	0.0	-	na
	Chemosis conjunctivae	2	2	1	1.7	--	7
3	Corneal opacity	2	2	2	2.0	+	14
	Iritis	1	0	1	0.3	-	2
	Redness conjunctivae	2	2	2	2.0	--	14
	Chemosis conjunctivae	2	1	0	1.0		3

Response for mean scores:	Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema	
-- = negative	<1	<1	<2	<2	Regulation (EC) No. 1272/2008 (CLP)
+ = irritant	≥1 - <3	≥1 - <2	≥2	≥2	Regulation (EC) No. 1272/2008 (CLP)
++ = irreversible effects/ serious damage	≥3	≥1.5			Regulation (EC) No. 1272/2008 (CLP)

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

III. Conclusion

The test item is irritating to the eyes of rabbits with full reversibility within 14 days.

The study result triggers the following classification/labelling:

Regulation (EC) No 1272/2008 (CLP): Cat 2, H319 (causes serious eye irritation)

CP 7.1.6 Skin sensitization

Report:	KCP 7.1.6/01 [redacted]; 2007; M-293215-01-1
Title:	Bixafen + prothioconazole EC 75 + 150 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No.:	SA 07171
Document No.:	M-293215-01-1
Guideline(s):	O.E.C.D. guideline 429 (2002)
Guideline deviation(s):	In the protocol treatment period was defined as Application date in the Study report this period will be reported as Dosing dates.
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: BIX + PTZ EC 75 + 150 G
(bixafen & prothioconazole EC 75 + 150)

Specification no.:	102000013869
Description:	brown liquid
Lot/Batch no:	2007-002622
Content:	bixafen: 77.2 g/L; prothioconazole: 147 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2008-10-04

2. Vehicle: 1% Pluronic Acid in water

3. Test animals

Species:	mouse
Strain:	CBA/J
Age:	at least 8 weeks
Weight at dosing:	18.7 g – 23.2 g
Source:	[redacted], France
Acclimatisation period:	at least 5 days
Diet:	certified rodent pellet diet and irradiated: AO4C 10 (S.A.F.E., [redacted] France)
Water:	tap water
Housing:	individually in suspended, stainless steel, wire mesh cages

B. Study design and methods

1. Animal assignment and treatment

Dose:	0% - 2.5% - 5% - 10%
Application route:	dermal to the dorsal surface of each ear
Application volume:	25 µL/ear
Exposure:	three consecutive days (days 0, 1 and 2)
Group size:	5 females/group
Observations:	mortality, clinical signs, local irritation, body weight (at beginning and termination of study), proliferation index, stimulation index

II. Results and discussion

A. Findings

No mortality and no clinical signs were observed during the study.

No cutaneous reactions were observed at the treated site of treated groups.

No significant body weight changes were observed during the study either in the control or in the treated groups.

Table 7.1.6-1 DPM and Stimulation Index Values

Group	Test Group Name	DPM	Number of lymph nodes	DPM/ node	Stimulation Index Values (SI)*
1	Vehicle control (1% aqueous Pluronic Acid)	3956	10	395.6	
2	bixafen + prothioconazole EC 75 + 150 at 2.5% in 1% aqueous Pluronic Acid	7086	10	708.6	1.8
3	bixafen + prothioconazole EC 75 + 150 at 5% in 1% aqueous Pluronic Acid	6731	10	673.1	1.7
4	bixafen + prothioconazole EC 75 + 150 at 10% in 1% aqueous Pluronic Acid	5257	10	525.7	1.3

DMP = disintegration per minute * SI = DPM of treated group / DPM of control group

Negative lymphoproliferative responses (SI<3) were noted for bixafen + prothioconazole EC 225 (75 + 150 g/L) at all concentrations tested.

There were no confounding effects of irritation or toxicity, so the proliferation values are considered to reflect the sensitization potential of the test substance.

III. Conclusion

The test item is not sensitizing in the Local Lymph Node Assay at all concentrations tested.

The following classification/labelling is triggered:

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

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 'Bixafen + Prothioconazole EC 225' for the use as fungicide in cereals. The formulation contains the active substance prothioconazole (150 g/L). Exposure is estimated using the EFSA guidance on non-dietary risk assessment:

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

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

Following the noting at the Standing Committee meeting in May, the Commission have published a guidance[1] on the implementation of EFSA's non-dietary exposure guidance document which notes that the EFSA guidance will apply to applications submitted from 1 January 2016.

For the approval of active substances under Regulation (EC) No 1107/2009, an acute risk assessment is currently not required.

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

It is known that after foliar spray application of PTZ-containing products diluted PTZ can degrade to prothioconazole-desthio (PTZ-desthio) on plant surfaces, clothing or skin. Accordingly, although PTZ-desthio is not part of the formulation per se non-dietary risk assessments are always performed for PTZ-desthio due to its toxicological properties. No model is available to estimate the conversion of PTZ to PTZ-desthio in a realistic manner. Therefore, risk assessments should always consider measured data whenever such data are available.

Such higher tier data are applied for the estimation of exposure to operators and workers as well as to residents when being exposed via direct drift.

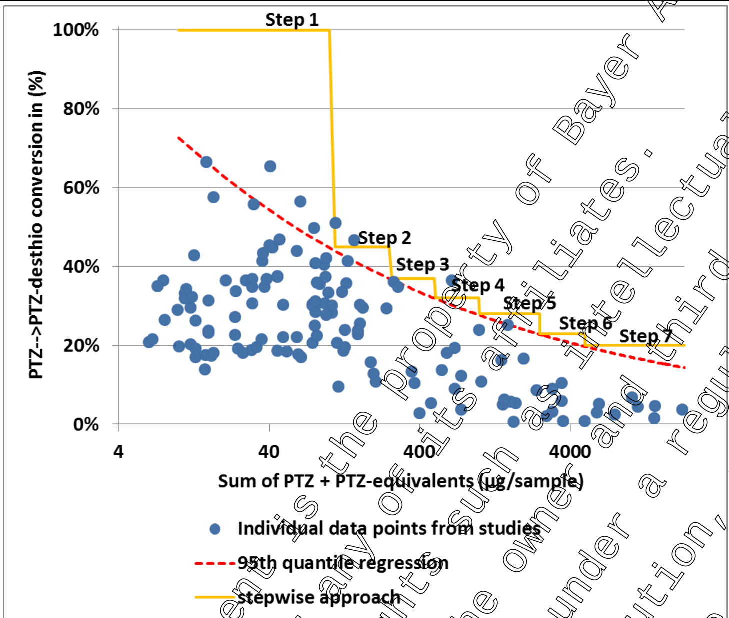
However, it might happen that in certain cases no higher tier data are available, e.g. due to the use on crops which are not covered by any available data. In the following an approach is presented for such cases to estimate the conversion of PTZ to PTZ-desthio based on current experience. This approach considers existing measured conversion rate data from six independent exposure studies (i.e. three operator exposure studies and three studies, in which exposure due to direct drift was determined). In total 144 individual data points are considered for this evaluation. Using the methodology of a non-parametric regression analysis it is demonstrated that the conversion rate is negatively correlated to the initial exposure of PTZ (= amount of PTZ + PTZ-desthio expressed as PTZ equivalents), i.e. high initial exposure levels of PTZ are always associated with low conversion rate to PTZ-desthio and high conversion rates of PTZ to PTZ-desthio were only found at low initial PTZ exposure. This finding has been expressed in a conversion rate equation using quantile regression, a methodology that has already been used to estimate the exposure to operators in the current EFSA guidance[2]. However, for the purpose of risk assessments a more simplified approach, i.e. graded/stepwise approach, is proposed which considers seven exposure levels and corresponding conversion rates. The proposed conversion rates

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

[2] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

refer to the results of a 95th quantile regression analysis which already ensures a highly conservative conversion estimate. Nevertheless, in addition always the upper end values (i.e. the highest values) relevant for the respective step is proposed for the assessment. A visualization of the regression analysis as well as the associated exposure steps of the graded approach are presented in the following Table/Figure:

Table/Figure 7.2-1: Visualization of the regression analysis and the graded PTZ to PTZ-desthio conversion rate approach based on different exposure levels



Conversion rates of PTZ to PTZ-desthio in a graded approach proposed for risk assessment. The dotted line (······) represents the 95th quantile regression computations. The solid line (——) represents the simplified graded approach for risk assessments.

	Exposure to PTZ* (µg/person)	Conversion rate to PTZ-desthio
Step 1	< 100	100%
Step 2	101-250	45%
Step 3	251 – 500	37%
Step 4	501 – 1000	32%
Step 5	1001 – 2500	28%
Step 6	2501 – 5000	23%
Step 7	>5000	20%

* from exposure model calculation

For further information on the methods, the calculations and the data used refer to the following report:

Report:	KCP 7.2/01 [redacted]; 2015; M-537338-01-1
Title:	Development of a non-parametric regression analysis to estimate the conversion rates of prothioconazole (PTZ) to its main metabolite prothioconazole-desthio (PTZ-desthio)
Report No.:	M-537338-01-1
Document No.:	M-537338-01-1
Guideline(s):	not applicable
Guideline deviation(s):	not applicable
GLP/GEP:	**no**

However, in case of the representative formulation 'Bixafen + Prothioconazole EC 225' this conversion rate approach is not needed since appropriate higher tier study data are available.

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)[3] and amounts to **0.01 mg/kg bw/day** including an assessment factor of 100. This AOEL applies wherever women of child-bearing age could be involved.
For the general population a **non-developmental** NOAEL should be selected as the basis for the AOEL; the NOAEL of 2.2 mg/kg bw/day from the PTZ-desthio rat 90-day study is considered appropriate, resulting in an **AOEL** of **0.022 mg/kg bw/day** (especially when considering children, cf. CP 7.2.2).

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

Dermal absorption:
Dermal absorption for **prothioconazole** was evaluated with a formulation that is comparable to the representative formulation using *in vitro* human skin. For further details regarding the formulation comparison please refer to the confidential Document JCP.

As a result of the dermal absorption study the following dermal absorption values are used for the risk assessment based on the critical GAP uses:

- 5% for the concentrate (100 g a.s./L)
- 22% for an intermediate spray concentration (1.25 g a.s./L)
- 35% for a low spray concentration (0.25 g a.s./L)

To obtain also data for **prothioconazole-desthio** the active substance prothioconazole was replaced by prothioconazole-desthio and the lowest spray concentration (0.25 g/L) was investigated.
As a result of the dermal absorption study the following dermal absorption value is used for the risk assessment:

- 14% obtained with a spray concentration of 0.25 g/L

For details see CP 7.3.

CP 7.2.1 Operator exposure

The EFSA guidance on non-dietary risk assessment is used. The critical GAP (cGAP) for operator risk assessment is presented in Table 7.2.1-1.

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

Crop (grouping)	F/ G	Application method	Max. application rate (kg a.s./ha)	Spray volume (L/ha)	Dermal absorption (%)
Rye, Triticale, Spelt, Wheat	F	Field crop sprayer	0.1875	100 – 400	35%
Barley, Oats	F	Field crop sprayer	0.150	100 – 400	35%

F = field; G = greenhouse

[3] 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

The product will be applied with tractor-mounted/-trailed field crop (boom) sprayers. The cGAP in wheat, rye, triticale and spelt results in the highest exposure because the application is conducted with the highest application rate and similar water rates. Exposure due to the use in barley and oats are therefore covered and not presented in this dossier.

Detailed calculations for the cGAP scenario are presented in CP 7.2.1.1.

Summary
A summary of the exposure estimates resulting from the cGAP is presented in the following table. Detailed calculations are presented in CP 7.2.1.1.

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

Substance	PPE	Systemic exposure (mg/kg bw/day)	% of AOEL#
EFSA Model			
Prothioconazole	No PPE 1)	0.0318	**13**
	With PPE 2)	0.0020	**<1**
Measurement of exposure			
Prothioconazole3)	With PPE2)	0.00032	**<1**
Prothioconazole-desthio3)	With PPE2)	0.000084	**<1**
Prothioconazole 4)	With PPE2)	0.00080	**<1**
Prothioconazole-desthio4)	With PPE2)	0.00020	**2**

[1] No PPE: Cotton/polyester working coverall, no gloves
[2] With PPE: Coverall and protective gloves during mixing/loading and application
[3] With PPE: Coverall and protective gloves during mixing/loading and application; parametric estimate of individual systemic exposure
[4] With PPE: Coverall and protective gloves during mixing/loading and application; parametric estimate of normalized exposure data

Assessment
According to the EFSA model systemic exposure of operators to prothioconazole who are wearing no PPE but a working coverall and who work with bare hands is about 13% of the AOEL. Systemic exposure of operators wearing, in addition, protective gloves is <1% of the AOEL of prothioconazole.

The model cannot be used for a realistic estimate of exposure to prothioconazole-desthio. Therefore three compound and crop specific studies are used to assess the concurrent systemic exposure of operators to prothioconazole and prothioconazole-desthio.
The studies were evaluated according to the procedure described in the EFSA guidance and the appropriate percentiles (of the distribution/for the theoretical population) are presented.
Using individual data the parametric estimates (as the higher values) result in systemic exposures of <1% of the AOEL for prothioconazole and <1% of the AOEL for prothioconazole-desthio.
Using normalized data the parametric estimates (as the higher values) result in systemic exposures of <1% of the AOEL for prothioconazole and 2% of the AOEL for prothioconazole-desthio.

Conclusion
Based on these favourable exposure estimates there is no unacceptable risk anticipated for operators with regard to exposure to prothioconazole and prothioconazole-desthio.

CP 7.2.1.1 Estimation of operator exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of operators including the EFSA calculator[4] (version: 20 Mar 2015) .

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

A summary of the input parameters and the exposure output is presented below.

Table 7.2.1.1-1: Summary of operator exposure during application in cereals

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

Substance	prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1875 kg a.s. /ha	Spray dilution = 1.875 g a.s./l	Vapour pressure = low, volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 5	Dermal for in use dilution = 35	Oral = 100	Inhalation = 100	
RVNAS	0.25 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing/loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0504	% of RVNAS	20.18%
	Acute systemic exposure mg/kg bw/day		0.2955	% of RVAAS	
Mixing and Loading		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = No	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0318	% of RVNAS	12.74%
	Acute systemic exposure mg/kg bw/day		0.1586	% of RVAAS	

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

With PPE: Gloves during mixing/loading and application, work wear: arms, body and legs covered

Substance	prothioconazole	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.1875 kg a.s. /ha	Spray dilution = 1.875 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals / Outdoor / Downward spraying / Vehicle-mounted			Buffer = 2-3	Number applications = 2, Application interval = 14 days
Percentage Absoprtion	Dermal for product = 5	Dermal for in use diluation = 35	Oral = 100	Inhalation = 100	
RVNAS	0.25 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0504	% of RVNAS	20.18%
	Acute systemic exposure mg/kg bw/day		0.2955	% of RVAAS	
Mixing and Loading		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application		Gloves = Yes	Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0020	% of RVNAS	0.81%
	Acute systemic exposure mg/kg bw/day		0.0318	% of RVAAS	

CP 7.2.1.2 Measurement of operator exposure

As mentioned before it has been found that prothioconazole in diluted solutions can convert to prothioconazole-desthio (other internal code: SXX 0065) 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 the exposure to prothioconazole as well as to prothioconazole-desthio under real use conditions and thus to get a better basis for a realistic risk assessment.

The first study was already submitted and evaluated for Annex I inclusion of prothioconazole. Since then BCS has conducted two further exposure studies with twelve farmers under real and representative conditions in cereals and canola (one application). These new studies were already provided to CRD and were evaluated under COD 2007/01054.
The studies are also part of the new AOEModel (EFSA Model for operator exposure). However, as the studies were set up as mixer/loader/applicator studies only part of the data are used in the model. In addition, the data in the model are used as prothioconazole-equivalents (sum of exposures to prothioconazole and prothioconazole-desthio) and, hence, do not allow to distinguish between exposure to prothioconazole and prothioconazole-desthio.

Therefore, it is reasonable to make use of the compound and crop specific study data as higher tier for the assessment of exposure to prothioconazole and prothioconazole-desthio.

For Annex I renewal of prothioconazole all studies are referenced again and are evaluated according to the new EFSA guidance.

Report:	KCP 7.2.1.2/01 [redacted],; 2002; M-040604-01-1
Title:	Determination of exposure to JAU 6476 and JAU 6476-desthio (SXX 0665) during mixing/loading and application of JAU 6476 in cereals
Report No.:	MR-036/02
Document No.:	M-040604-01-1
Guideline(s):	not specified
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.
A total of eight applications at three different spray timings involving three different male operators were monitored. The operators were employees of Bayer AG (now: Bayer CropScience) and were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during the actual season (May/June 2000) on a field belonging to an agricultural test site of Bayer AG (now: Bayer CropScience) in Monheim (Germany). With each application about 20 ha were treated using spray equipment that was appropriate and representative (tractor drawn/mounted ground boom sprayer). During the first two spray timings equipment for larger field sizes was used (28 m boom, 2500 L water tank volume) whereas during the third spray timing an equipment for smaller field sizes was chosen (15 m boom, 800 L water tank volume). The tractors used were all equipped with a cabin.

Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal body exposure when wearing only one layer of clothing.
Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during mixing/loading whereas during application gloves had only been worn if the operator had to handle contaminated surfaces, e.g. correcting a machine malfunction.

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 personal powered air pump.

Field recovery samples to assess the stability of prothioconazole and prothioconazole-desthio were performed on all sampling media exposed appropriately on each spraying occasion.

The spraying lasted between 2.5 h and 3.5 h. On completion of the spraying the cap and the gloves were sampled and also a hand wash was performed. The operators continued to wear the other dosimeter clothes for some further hours to give a total of about 7 h (one exception: ca. 5.2 h) to provide some

information on the proportion of conversion of prothioconazole to prothioconazole-desthio during the time of almost a full work day.

Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results < LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ.

Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio.

The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in Table 7.2.1.2-1 and Table 7.2.1.2-2. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.

On eight samples of the outer clothing measurable amounts of prothioconazole were found; in four of these samples and in one additional sample also prothioconazole-desthio could be quantified (out of a total of 32 samples). The percentage of conversion with respect to total "prothioconazole-equivalents" was found to be very variable, ranging from 3% to nearly 50%.
Also on gloves and in some of the hand wash solutions prothioconazole and prothioconazole-desthio were found. The corresponding percentages of prothioconazole-desthio to total “prothioconazole equivalents” cover the range from 1% to 60%.

With regard to inhalation exposure only prothioconazole was found and only in two filters. For both samples the amount of prothioconazole was at the level of LOQ (0.1 µg/sample).

Spray tank samples which were also analyzed showed that prothioconazole-desthio amounted from 0.1% up to about maximum 1% of total "prothioconazole-equivalents", with a mean of 0.22%.

Table CP 7.2.1.2-1: Exposure to prothioconazole

Operator ID	Prothioconazole [mg/person/day]			Prothioconazole [mg/kg bw]			Prothioconazole [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A1	1.99	0.0450*	0.0042*	0.0209	0.000474	0.000044	0.502	0.0114	0.00105
B1	5.09	0.0450*	0.0048	0.0636	0.000563	0.000059	1.262	0.0112	0.00118
C1	3.71	0.0450*	0.0042*	0.0516	0.000625	0.000058	0.922	0.0112	0.00103
B2	1.79	0.0450*	0.0048	0.0223	0.000563	0.000059	0.443	0.0112	0.00118
C2	14.81	0.0499	0.0042*	0.206	0.000693	0.000058	3.676	0.0124	0.00103
A3	11.26	0.0450*	0.0021*	0.119	0.000474	0.000022	2.773	0.0111	0.00051
C3	21.61	0.0483	0.0021*	0.270	0.000604	0.000026	5.322	0.0119	0.00051
B3	14.05	0.0450*	0.0021*	0.195	0.000625	0.000029	3.459	0.0111	0.00051

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 7.2.1.2-2: Exposure to prothioconazole-desthio

Operator ID	Prothioconazole-desthio [mg/person/day]			Prothioconazole-desthio [mg/kg bw]			Prothioconazole-desthio [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A1	0.101	0.0150*	0.0042*	0.00106	0.000158	0.000044	0.0255	0.00379	0.00105
B1	0.089	0.0150*	0.0042*	0.00111	0.000188	0.000052	0.0221	0.00372	0.00103
C1	0.084	0.0150*	0.0042*	0.00117	0.000208	0.000058	0.0208	0.00372	0.00103
B2	0.139	0.0150*	0.0042*	0.00174	0.000188	0.000052	0.0345	0.00372	0.00103
C2	0.255	0.0150*	0.0042*	0.00354	0.000208	0.000058	0.0633	0.00372	0.00103
A3	0.542	0.0150*	0.0021*	0.00571	0.000158	0.000022	0.1335	0.00370	0.00051
C3	0.819	0.0150*	0.0021*	0.0102	0.000188	0.000026	0.2017	0.00370	0.00051
B3	0.684	0.0202	0.0021*	0.00950	0.000281	0.000029	0.1685	0.00498	0.00051

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

III Conclusion

A final conclusion of all study results is given under "overall summary and conclusions".

Report: KCP 7.2.1.2/02 [redacted].; 2015; M-285798-02-1
Title: Determination of exposure during mixing/loading and application of Proline in cereals
Report No.: MR-156/05
Document No.: M-285798-02-1
Guideline(s): not specified
Guideline deviation(s): not specified
GLP/GEP: yes

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.

A total of five applications involving five different male operators were monitored. The operators were independent farmers and were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during May to June 2005 on fields in the surroundings of [redacted] (Germany). The areas treated ranged from 19 ha to 67 ha. Each of the operators performed a day's work according to his average usual working practice. Three operators used equipment for smaller field sizes (15 m boom, 1000 L water tank volume) whereas in two cases equipment for larger sizes was used (18/30 m boom, 3000/4000 L water tank volume). The tractors used were all equipped with a cabin. However, depending on the weather and the equipment some operators left the back and/or front window open as well as the roof opening. Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal exposure when wearing only one layer of clothing.

The operators were not forced to wear a cap if this was not in accordance to their normal working clothes and behavior. One operator made use of this option.

Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during mixing/loading whereas during application gloves were only worn in case the operator had to handle contaminated surfaces, e.g. un-/folding the boom manually or correcting a machine malfunction like blocked or lost nozzles.

If operators took off their outer clothes during a break they received Kleenguard suits to be worn above the inner dosimeters. Afterwards, the Kleenguard suits were sampled as a whole.

One incident occurred during a mixing/loading cycle of one operator: as he was not accustomed yet to a new water supply system the tank ran over and he got splashes of spray liquid on his clothes. He received a second set of clothing but all data are included in his overall exposure evaluation.

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 personal powered air pump.

Field recoveries were set up at two sites. All sampling media were used and exposed appropriately.

The monitoring lasted between 5 h and 8 h, corresponding to a normal full work day. On completion of the last spraying all dosimeters were sampled and also a hand wash was performed.

Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results <LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ.

Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio.

The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in Table 7.2.1.2-3 and Table 7.2.1.2-4. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.

Table CP 7.2.1.2-3: Exposure to prothioconazole

Operator ID	Prothioconazole [mg/person/day]			Prothioconazole [mg/kg bw]			Prothioconazole [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A	11.32	0.1705	0.00327	0.151	0.00227	0.000044	0.809	0.0122	0.00023
B	3.90	0.0625	0.00104*	0.0390	0.000625	0.000010	0.974	0.0156	0.00026
C	9.07	0.0900*	0.00268*	0.107	0.00106	0.000031	1.296	0.0129	0.00038
D	1.30	0.0500*	0.00104*	0.0153	0.000588	0.000012	0.0992	0.00382	0.00008
E	1.72	0.0475*	0.00104*	0.0215	0.000594	0.000013	0.325	0.00896	0.00020

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 [mg/person/day]			Prothioconazole-desthio [mg/kg bw]			Prothioconazole-desthio [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A	1.239	0.1372	0.00104*	0.0165	0.00183	0.000014	0.0885	0.00980	0.00007
B	0.438	0.0203	0.00104*	0.00438	0.000203	0.000010	0.1096	0.00508	0.00026
C	0.746	0.0300*	0.00268*	0.00878	0.000353	0.000031	0.1066	0.00429	0.00038
D	0.231	0.0170*	0.00104*	0.00272	0.000200	0.000012	0.0176	0.00130	0.00008
E	0.138	0.0160*	0.00104*	0.00173	0.000200	0.000013	0.0260	0.00302	0.00020

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

On 12 samples of the outer clothing measurable amounts of prothioconazole were found; in eight of these samples and in one additional sample also prothioconazole-desthio could be quantified (out of a total of 24 samples). The percentage of conversion with respect to total "prothioconazole-equivalents" was found to be very variable, ranging from 5% to 56%. Also on gloves and in some of the hand wash solutions prothioconazole and prothioconazole-desthio were found. The corresponding percentages of prothioconazole-desthio to total “prothioconazole equivalents” cover the range from 3% to 60%.
With regard to inhalation exposure only prothioconazole was found and only in two filters (of one operator). For both samples the amount of prothioconazole was at the level of LOQ.

III Conclusion

A final conclusion of all spray application results are given under "overall summary and conclusions".

Report:	KCP 7.2.1.2/03[redacted],;[redacted]; 2007; M-286545-01-1
Title:	Determination of exposure during mixing/loading and application of prothioconazole in cereals and canola
Report No.:	MR-244/07
Document No.:	M-286545-01-1
Guideline(s):	not specified
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.
A total of seven applications involving seven different male operators were monitored. The operators were independent farmers or employees of a farm cooperative. They were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during May to June 2006 on fields in the surroundings of [redacted] (Germany). The areas treated ranged from 23 ha to 180 ha. Each of the operators performed a day's work or at least 5 hours according to his average usual working practice. Three operators used equipment for smaller field sizes (15/21 m boom, 840 - 1500 L water tank volume) whereas in four cases equipment for larger sizes was used (24/36 m boom, 2600/4000 L water tank volume). The tractors used were all equipped with a cabin. However, depending on the weather and the equipment some operators left the back and/or front window open as well as the roof opening.

Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal exposure when wearing only one layer of clothing.
The operators were not forced to wear a cap if this was not in accordance to their normal working clothes and behavior. Four operators made use of this option.

Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during mixing loading whereas during application gloves were only worn in case the operator had to handle contaminated surfaces, e.g. un-/folding the boom manually or correcting a machine malfunction like blocked or lost nozzles.
If operators took off their outer clothes during a break they received Kleenguard suits to be worn above the inner dosimeters. Afterwards, the Kleenguard suits were sampled as a whole.

In addition to the usual spraying also the following occurrences were monitored: one operator had some blocked nozzles and brushed them off several times; another operator replaced the outer spray nozzles by blind nozzles in order to avoid spraying of the adjacent field.

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 personal powered air pump.

Field recoveries were set up at one site. All sampling media were used and exposed appropriately.

The whole monitoring lasted between 5 h and 9 h. On completion of the last spraying all dosimeters were sampled and also a hand wash was performed.

Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results <LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ.

Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio.

The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in Table 7.2.1.2-5 and Table 7.2.1.2-6. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.

Table CP 7.2.1.2-5: Exposure to prothioconazole

Operator ID	Prothioconazole [mg/person/day]			Prothioconazole [mg/kg bw]			Prothioconazole [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A	3.58	0.0683	0.00208*	0.0436	0.000833	0.000025	0.777	0.0148	0.00045
B	8.13	0.0550*	0.00572	0.0739	0.000500	0.000052	0.636	0.00430	0.00045
C	7.90	0.0593	0.00208*	0.0669	0.000503	0.000018	0.252	0.00190	0.00007
D	0.668	0.0450*	0.00208*	0.00795	0.000536	0.000025	0.0557	0.00375	0.00017
E	3.88	0.0497	0.00353	0.0408	0.000523	0.000037	0.692	0.00888	0.00063
F	6.28	0.0475*	0.00312	0.0675	0.000511	0.000034	0.884	0.00669	0.00044
H	6.74	0.0560	0.00208*	0.0561	0.000467	0.000017	0.449	0.00373	0.00014

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 7.2.1.2-6: Exposure to prothioconazole-desthio

Operator ID	Prothioconazole-desthio [mg/person/day]			Prothioconazole-desthio [mg/kg bw]			Prothioconazole-desthio [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A	0.607	0.0160*	0.00208*	0.00704	0.000195	0.000025	0.132	0.00348	0.00045
B	0.272	0.0274	0.00208*	0.00248	0.000249	0.000019	0.0213	0.00214	0.00016
C	0.654	0.0390	0.00208*	0.00554	0.000331	0.000018	0.0209	0.00125	0.00007
D	0.141	0.0150*	0.00208*	0.00168	0.000179	0.000025	0.0118	0.00125	0.00017
E	0.701	0.0227	0.00208*	0.00738	0.000239	0.000022	0.125	0.00405	0.00037
F	0.399	0.0160*	0.00208*	0.00429	0.000172	0.000022	0.0562	0.00225	0.00029
H	0.303	0.0185	0.00208*	0.00252	0.000154	0.000017	0.0202	0.00123	0.00014

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

On 18 samples of the outer clothing measurable amounts of prothioconazole were found and in 17 samples also prothioconazole-desthio could be quantified (out of a total of 28 samples). The percentage of conversion with respect to total "prothioconazole-equivalents" was found to be very variable, ranging from 2% to 77%. In three samples of the undergarments prothioconazole was found and in four samples prothioconazole-desthio. The corresponding percentage of conversion was in the range of 5% to 52%.
Also on gloves and in some of the hand wash solutions prothioconazole and prothioconazole-desthio were found. The corresponding percentages of prothioconazole-desthio to total “prothioconazole equivalents” cover the range from 2% to 72%.

With regard to inhalation exposure only prothioconazole was found and only in three filters. The amount of prothioconazole was at the level of LOQ up to four times the LOQ.

III Conclusion

A final conclusion of <u>all</u> spray application results are given under “overall summary and conclusions”.

Overall summary and conclusions

All studies were designed as mixer/loader/applicator-studies as this type of study reflects best the real work situation of farmers in Europe when performing ground boom spraying. In total, twenty replicates – performed by fifteen operators – were monitored.
The first study – conducted in 2000 – had to be performed under confined conditions as the active substance was still under development. Therefore, the area treated was restricted to 20 ha, nevertheless different types of application equipment were used. Three Bayer employees were involved as operators.
The second study was conducted in 2005. As prothioconazole had received national approval at that time the study was conducted with five professional farmers in their fields.
In the third study seven professional farmers represented the operators spraying prothioconazole containing products in their fields.

In Tables 7.2.1.2-7 and 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 with regard to downward directed boom spraying:

- areas ranging from 19 ha to 80 ha, one replicate even at 180 ha;
- boom widths ranging from 15 m (to be unfolded/folded manually and automatically) up to 36 m with a self-propelled sprayer;
- spray tank volumes ranging from 800 L up to 4000 L.

The tractors were equipped with a cabin as it is standard practice nowadays.

Table CP 7.2.1.2-7: Study parameters of replicates

Study	Operator ID	Area treated [ha]	Equipment	No. of tasks load // appl.
01	A1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	B1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	C1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	B2	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	C2	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	A3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
01	C3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
01	B3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
02	A	67	Tractor-drawn boom 30 m, 4000 L spray tank	4 // 4
02	B	19	Tractor-mounted boom 15 m (manual folding), 1000 L tank	4 // 4
02	C	33	Tractor-mounted boom 15 m, 1100 L spray tank	7 // 6
02	D	49	Tractor-drawn boom 18 m, 3000 L spray tank	3 // 3
02	E	25	Tractor-mounted boom 15 m, 1000 L spray tank	6 // 6
03	A	23	Tractor-mounted boom 15 m (manual folding), 840 L tank	9 // 9
03	B	64	Self-propelled 24 m boom, 4000 L spray tank	4 // 4
03	C	180	Self-propelled 36 m boom, 4000 L spray tank	14 // 14
03	D	60	Self-propelled 24 m boom, 2600 L spray tank	6 // 6
03	E	30	Tractor-mounted boom 15 m (manual folding), 1000 L tank	6 // 6
03	F	35	Tractor-mounted boom 21 m, 1500 L spray tank	8 // 8
03	H	80	Tractor-drawn boom 24 m, 4000 L spray tank	4 // 4

Table CP 7.2.1.2-8: Summary of study parameters

Parameter	Study parameter
Formulation	250 g/L prothioconazole (Proline EC)/ 160 g/L prothioconazole (Input EC)
Crop	Cereals/canola (1 application)
No. of replicates	15 operators/20 replicates (at 13 locations) combined work cycles (mix/load/application)
Application technique	Downward directed boom sprayer: Tractor (closed cabin) + boom (15 – 36 m boom)
Time	1.9 – 8.7 h (mean: 5 h, all data) 4.8 – 8.7 h (mean: 6.7 h with reports MR-156/05 and MR-244/07)
Area treated	19 – 180 ha/day (mean: 41 ha, all data; 55 ha with reports MR-156/05 and MR-244/07)
Application rate	175 g (canola) – 200 g prothioconazole/ha
Water volume	150 to 300 L/ha
Total a.s. handled	4 to 31.3 kg a.s./day
In-use concentration	0.8 to 1.5 g a.s./L

PPE/clothing	Nitrile gloves: during mixing/loading, during application 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 though 17 replicates (out of 20) had measurable residues of prothioconazole on their outer clothing only three operators showed measurable residues of prothioconazole on their undergarments.
For prothioconazole-desthio in 15 out of 20 replicates measurable residues were found on the outer clothing but only three 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.

Exposure of the head was determined for 15 replicates (out of 20). In all cases – for prothioconazole as well as for prothioconazole-desthio – the results were "<LOQ".
Hence, it is acceptable that these results can also be extrapolated to the other five replicates to calculate a hypothetical head exposure.

The results of the protective gloves show higher exposure figures for the first study as compared to the second and the third. The reason for this is mainly due to the fact that most of the farmers in study 02 and study 03 (who had the possibility) rinsed the gloves under water before taking them off. This is in accordance with good occupational hygiene practice and therefore, any farmer who was going to behave like this was let to proceed as he was used to.

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 as well as the inhalation results from all studies are listed in Table 7.2.1.2-9 for the exposure to prothioconazole and in Table 7.2.1.2-10 for the exposure to prothioconazole-desthio. Normalization was performed with regard to the actual bodyweight of the individual operators as well as to kg active substance handled.

Table CP 7.2.1.2-9: Exposure to prothioconazole

Operator ID	Prothioconazole [mg/person/day]			Prothioconazole [mg/kg bw]			Prothioconazole [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A1	1.99	0.0450*	0.00416*	0.0209	0.000474	0.000044	0.502	0.0114	0.00105
B1	5.09	0.0450*	0.00476	0.0636	0.000563	0.000059	1.262	0.0112	0.00118
C1	3.71	0.0450*	0.00416*	0.0516	0.000625	0.000058	0.922	0.0112	0.00103
B2	1.79	0.0450*	0.00476	0.0223	0.000563	0.000059	0.443	0.0112	0.00118
C2	14.81	0.0499	0.00416*	0.206	0.000693	0.000058	3.676	0.0124	0.00103
A3	11.26	0.0450*	0.00208*	0.119	0.000474	0.000022	2.773	0.0111	0.00051
C3	21.61	0.0483	0.00208*	0.270	0.000604	0.000026	5.322	0.0119	0.00051
B3	14.05	0.0450*	0.00208*	0.195	0.000625	0.000029	3.459	0.0111	0.00051
A	11.32	0.1705	0.00327	0.151	0.00227	0.000044	0.809	0.0122	0.00023
B	3.90	0.0625	0.00104*	0.0390	0.000625	0.000010	0.974	0.0156	0.00026
C	9.07	0.0900*	0.00265*	0.107	0.00106	0.000031	1.296	0.0129	0.00038
D	1.30	0.0500*	0.00104*	0.0153	0.000588	0.000012	0.0992	0.00382	0.00008
E	1.72	0.0475*	0.00104*	0.0215	0.000594	0.000013	0.325	0.00896	0.00020
A	3.58	0.0683	0.00208*	0.0436	0.000833	0.0000253	0.377	0.0148	0.00045
B	8.13	0.0550*	0.00572	0.0739	0.000500	0.000052	0.636	0.00430	0.00045
C	7.90	0.0593	0.00208*	0.0669	0.000503	0.000018	0.252	0.00190	0.00007
D	0.668	0.0450*	0.00208*	0.00795	0.000536	0.000025	0.0557	0.00375	0.00017
E	3.88	0.0497	0.00353	0.0408	0.000523	0.000037	0.692	0.00888	0.00063
F	6.28	0.0475*	0.00312	0.0675	0.000511	0.000034	0.884	0.00669	0.00044
H	6.74	0.0560	0.00208*	0.0561	0.000467	0.000017	0.449	0.00373	0.00014

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

The results show that potential dermal exposure to prothioconazole covers a range of about 33 (0.668 – 21.61 mg, 0.00795 – 0.270 mg/kg bw) up to 90 (0.0557 – 5.322 mg/kg a.s.) while for prothioconazole-desthio the range amounts to about 15 (0.0840 – 1.239 mg, 0.00106 – 0.0165 mg/kg bw and 0.0118 – 0.202).

For actual dermal exposure the range of exposure to prothioconazole amounts to a factor of 4 up to 8 depending on the normalization (0.0450 – 0.171 mg, 0.000467 – 0.00227 mg/kg bw, 0.00190 – 0.0156 mg/kg a.s.).

For prothioconazole-desthio the range amounts to a factor of about 8 to 12 (0.0150 – 0.137 mg, 0.000154 – 0.00183 mg/kg bw, 0.00123 – 0.00980 mg/kg a.s.).

Table CP 7.2.1.2-10: Exposure to prothioconazole-desthio

Operator ID	Prothioconazole-desthio [mg/person/day]			Prothioconazole-desthio [mg/kg bw]			Prothioconazole-desthio [mg/kg a.s. handled]		
	PDE	ADE	IE	PDE	ADE	IE	PDE	ADE	IE
A1	0.101	0.0150*	0.00416*	0.00106	0.000158	0.000044	0.0255	0.00379	0.00105
B1	0.089	0.0150*	0.00416*	0.00111	0.000188	0.000052	0.0221	0.00372	0.00103
C1	0.084	0.0150*	0.00416*	0.00117	0.000208	0.000058	0.0208	0.00372	0.00103
B2	0.139	0.0150*	0.00416*	0.00174	0.000188	0.000052	0.0345	0.00372	0.00103
C2	0.255	0.0150*	0.00416*	0.00354	0.000208	0.000058	0.0633	0.00372	0.00103
A3	0.542	0.0150*	0.00208*	0.00571	0.000158	0.000022	0.1335	0.00370	0.00051
C3	0.819	0.0150*	0.00208*	0.0102	0.000188	0.000026	0.2017	0.00370	0.00051
B3	0.684	0.0202	0.00208*	0.00950	0.000281	0.000029	0.1685	0.00498	0.00051
A	1.239	0.1372	0.00104*	0.0165	0.00183	0.000014	0.0885	0.00980	0.00007
B	0.438	0.0203	0.00104*	0.00438	0.000203	0.000010	0.1096	0.00508	0.00026
C	0.746	0.0300*	0.00268*	0.00878	0.000353	0.000031	0.1066	0.00429	0.00038
D	0.231	0.0170*	0.00104*	0.00272	0.000200	0.000012	0.0176	0.00130	0.00008
E	0.138	0.0160*	0.00104*	0.00173	0.000200	0.000013	0.0260	0.00302	0.00020
A	0.607	0.0160*	0.00208*	0.00704	0.000195	0.000025	0.132	0.00348	0.00045
B	0.272	0.0274	0.00208*	0.00248	0.000249	0.000019	0.0213	0.00214	0.00016
C	0.654	0.0390	0.00208*	0.00554	0.000331	0.000018	0.0209	0.00125	0.00007
D	0.141	0.0150*	0.00208*	0.00168	0.000179	0.000025	0.0118	0.00125	0.00017
E	0.701	0.0227	0.00208*	0.00738	0.000239	0.000022	0.125	0.00405	0.00037
F	0.399	0.0160*	0.00208*	0.00429	0.000172	0.000022	0.0562	0.00225	0.00029
H	0.303	0.0185	0.00208*	0.00252	0.000154	0.000017	0.0202	0.00123	0.00014

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

With regard to <u>inhalation</u> it is remarkable that only prothioconazole was found and also only in a few replicates. The absolute residues of prothioconazole determined on the sampling devices were very low and did not exceed a level of four times the LOQ (0.1 µg/sample).
Prothioconazole-desthio was not found in any sample.
The higher figures for the first five replicates in study 01 are due to the number of sampling devices used (i.e. exchange of device per each task and work cycle as opposed to one device only for mixing/loading and another for application in studies 02 and 03 and for the last three replicates in study 01).

With regard to the formation of prothioconazole-desthio all these data are in good agreement with the hypothesis based on observations that the formation of prothioconazole-desthio on surfaces is related to the process of drying, the concentration of prothioconazole in a solution, and the nature of the surface on which prothioconazole impinges and dries.
It is also very important to put the **percentage of conversion into perspective with** regard to the **absolute amounts** that were found.

The remarkable fact is that a low exposure to prothioconazole does not necessarily lead to a high conversion to prothioconazole-desthio, but it is obvious that the **highest percentage of conversion always occurs where very low absolute amounts of prothioconazole and prothioconazole-desthio are found.**

Estimation of systemic operator exposure

In the following systemic exposure of operators to prothioconazole and prothioconazole-desthio is estimated using the data of the field studies. The algorithms applied are according to the new EFSA guidance.

Basically the estimation can follow two different approaches:

a) Systemic exposure is calculated for each operator individually using his individual exposure data and body weight and from this data set the relevant percentiles are derived;
b) Relevant percentiles are derived from the normalized exposure data for actual dermal and inhalation exposure (in mg/kg a.s.). Systemic exposure is calculated by applying the dermal absorption value to the relevant dermal exposure figure and adding inhalation exposure. For the parameters 'application rate', 'treated area' and 'body weight' standard default values are used.

With regard to dermal exposure only actual dermal exposure data are used as this reflects the real conditions while potential dermal exposure corresponds to an operator wearing nothing (= naked).

A) Estimation according to individual data

The following assumptions are made:

Operator body weight:	individual body weight of the operators
Dermal absorption:	
Prothioconazole	35%
Prothioconazole-desthio	14%
Inhalation absorption:	
Prothioconazole	100%
Prothioconazole-desthio	100%

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

Systemic exposure [mg/kg bw/day] = (ADE x DA) + IE

ADE = Actual dermal exposure [mg/kg body weight]
IE = Inhalation exposure [mg/kg body weight]
DA = Dermal absorption [%]

Table CP 7.2.1.2-11: Exposure to prothioconazole [mg/kg bw/day]

Operator ID	Prothioconazole [mg/kg bw]	Systemic exposure to prothioconazole [mg/kg bw]

	ADE	IE	actual*	% of AOEL
A1	0.000474	0.000044	0.00021	0.08
B1	0.000563	0.000059	0.00026	0.10
C1	0.000625	0.000058	0.00028	0.11
B2	0.000563	0.000059	0.00026	0.10
C2	0.000693	0.000058	0.00030	0.12
A3	0.000474	0.000022	0.00019	0.08
C3	0.000604	0.000026	0.00024	0.09
B3	0.000625	0.000029	0.00025	0.10
A	0.00227	0.000044	0.00084	0.34
B	0.000625	0.000010	0.00023	0.09
C	0.00106	0.000031	0.00040	0.16
D	0.000588	0.000012	0.00022	0.09
E	0.000594	0.000013	0.00022	0.09
A	0.000833	0.000025	0.00032	0.13
B	0.000500	0.000052	0.00023	0.09
C	0.000503	0.000018	0.00019	0.08
D	0.000536	0.000025	0.00021	0.08
E	0.000523	0.000037	0.00022	0.09
F	0.000511	0.000034	0.00021	0.08
H	0.000467	0.000017	0.00018	0.07

ADE = actual dermal exposure, IE = inhalation exposure
*actual systemic exposure corresponds to an operator wearing work clothing, gloves during mixing/loading and when handling contaminated surfaces

Statistical summary

Statistical parameter	Systemic exposure to prothioconazole Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.00026	0.10
Empirical 95th percentile	0.00042	0.17
Maximum	0.00084	0.34
Parametric 75th percentile	**0.00032**	**0.13**
Log normality	No	

Table CP 7.2.1.2-12: Exposure to prothioconazole-desthio [mg/kg bw/day]

Operator ID	Prothioconazole-desthio [mg/kg bw]		Systemic exposure to prothioconazole-desthio [mg/kg bw]	
	ADE	IE	actual*	% of AOEL
A1	0.000158	0.000044	0.000066	0.66
B1	0.000188	0.000052	0.000078	0.78
C1	0.000208	0.000058	0.000087	0.87
B2	0.000188	0.000052	0.000078	0.78
C2	0.000208	0.000058	0.000087	0.87
A3	0.000158	0.000022	0.000044	0.44
C3	0.000188	0.000026	0.000052	0.52
B3	0.000281	0.000029	0.000068	0.68
A	0.00183	0.000014	0.000270	2.70
B	0.000203	0.000010	0.000039	0.39
C	0.000353	0.000051	0.000081	0.81
D	0.000200	0.000012	0.000040	0.40
E	0.000200	0.000013	0.000041	0.41
A	0.000195	0.000025	0.000053	0.53
B	0.000249	0.000019	0.000054	0.54
C	0.000331	0.000018	0.000064	0.64
D	0.000179	0.000025	0.000050	0.50
E	0.000239	0.000022	0.000055	0.55
F	0.000172	0.000022	0.000046	0.46
H	0.000154	0.000017	0.000039	0.39

ADE = actual dermal exposure, IE = inhalation exposure
*actual systemic exposure corresponds to an operator wearing work clothing, gloves during mixing/loading and when handling contaminated surfaces

Statistical summary

Statistical parameter	Systemic exposure to prothioconazole-desthio Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.000078	0.78
Empirical 95th percentile	0.000096	0.96
Maximum	0.000270	2.70
Parametric 75th percentile	**0.000084**	**0.84**
Log normality	No	

B) Estimation according to normalised data

The following assumptions are made:

Crop:		Cereals
Work rate:		50 ha/day
Application rate:		0.1875 kg a.s./ha
Operator body weight:		60 kg
Dermal absorption:		
	Prothioconazole	35%
	Prothioconazole-desthio	14%
Inhalation absorption:		
	Prothioconazole	100%
	Prothioconazole-desthio	100%

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

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

ADE = Relevant percentile of actual dermal exposure [mg/kg a.s. handled]

IE = Relevant percentile of inhalation exposure [mg/kg a.s. handled]

DA = Dermal absorption [%]

BW = Standard body weight [kg]

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

Table CP 7.2.1.2-13: Exposure to prothioconazole [mg/kg a.s.] and prothioconazole-desthio [mg/kg a.s.]

Operator ID	Prothioconazole [mg/kg a.s. handled]		Prothioconazole-desthio [mg/kg a.s. handled	
	ADE	IE	ADE	IE
A1	0.0114	0.00105	0.00379	0.00105
B1	0.0112	0.00118	0.00372	0.00103
C1	0.0112	0.00103	0.00372	0.00103
B2	0.0112	0.00118	0.00372	0.00103
C2	0.0124	0.00103	0.00372	0.00103
A3	0.0111	0.00051	0.00370	0.00051
C3	0.0119	0.00051	0.00370	0.00051
B3	0.0111	0.00051	0.00498	0.00051
A	0.0122	0.00023	0.00980	0.00007
B	0.0156	0.00026	0.00508	0.00026
C	0.0129	0.00038	0.00429	0.00038
D	0.00382	0.00008	0.00130	0.00008
E	0.00896	0.00020	0.00302	0.00020
A	0.0148	0.00045	0.00348	0.00045
B	0.00430	0.00045	0.00214	0.00016
C	0.00190	0.00007	0.00125	0.00007
D	0.00375	0.00017	0.00125	0.00017
E	0.00885	0.00063	0.00405	0.00037
F	0.00669	0.00044	0.00225	0.00029
H	0.00373	0.00014	0.00125	0.00014
Statistical parameter	actual dermal mg/kg a.s.	inhalation mg/kg a.s.	actual dermal mg/kg a.s.	inhalation mg/kg a.s.
Empirical 75th percentile	0.0120	0.00073	0.00385	0.00064
Empirical 95th percentile	0.0149	0.00118	0.00531	0.00103
Maximum	0.0156	0.00118	0.00980	0.00105
Parametric 75th percentile	0.0125	0.00072	0.00451	0.00063
Log normality	No	Yes	No	Yes

ADE = actual dermal exposure, IE = inhalation exposure

The resulting statistical summary is shown below:

Statistical summary

Statistical parameter	Systemic exposure to **prothioconazole** Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.00077	0.31
Empirical 95th percentile	0.00100	0.40
Maximum	0.00104	0.42
Parametric 75th percentile	**0.00080**	**0.32**

Statistical parameter	Systemic exposure to **prothioconazole-desthio** Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.00018	1.8
Empirical 95th percentile	0.00028	2.8
Maximum	0.00038	3.8
Parametric 75th percentile	**0.00020**	**2.0**

CP 7.2.2 Bystander and resident exposure

Table CP 7.2.2-1 summarises the critical GAP for the representative formulation PTZ+BIX EC 225 (150+75 g/L) relevant for residential exposure to prothioconazole (PTZ) and its main metabolite prothioconazole-desthio (PTZ-desthio).

Table CP 7.2.2-1 – Application parameters for PTZ+BIX EC 225

F/G/I	Application technique	Crop	Maximum application rate		water volume
			L product/ha	kg PTZ/ha	L/ha
F	Tractor mounted ground boom spraying	Cereals	1.25	0.1875	100-400

F = Field use, G = Greenhouse use, I = Indoor use

Table CP 7.2.2-2 provides an overview of models and studies used to estimate residential exposure to PTZ and PTZ-desthio. PTZ-desthio is not part of the formulation *per se*, but it is known that PTZ can degrade to PTZ-desthio on plant surfaces, clothing or skin during the drying process after foliar spray application of PTZ containing products. Concerning non-dietary exposure risk assessments it has to be noted that for the time being no model is available to estimate the conversion of PTZ to PTZ-desthio and hence the corresponding exposure to PTZ-desthio. Therefore, wherever possible risk assessments should consider measured data.

For the representative formulation PTZ+BIX EC 225 two crop specific drift exposure studies in cereals with PTZ containing products have been conducted and are used to assess residential exposure to PTZ and PTZ-desthio due to direct drift. However, for the prospective Post-AIR process of PTZ containing products chapter CP 7.2 introduces a non-parametric regression analysis to estimate conservatively the conversion of PTZ to PTZ-desthio in cases where a direct dermal exposure to the product or its dilution has to be estimated and no measured values are available. For the purpose of risk assessments a more simplified, i.e. graded stepwise approach is proposed which considers seven exposure levels and corresponding conversion rates.

Table CP 7.2.2-2 – Overview of models and studies used for the resident exposure assessment.

Routes of exposure	PTZ Tier 1	PTZ Tier 2	PTZ-desthio
Spray drift	EFSA* (75^{th} + Mean)	Measurement of exposure (75^{th} + Mean)	Measurement of exposure (75^{th} + Mean)
Vapour	EFSA*	EFSA*	EFSA
Surface deposits	EFSA* (75^{th} + Mean)	EFSA* (75^{th} + Mean)	EFSA* (75^{th} + Mean), only one application considered due to rapid dissipation
Entry into treated crops	EFSA* (75^{th} + Mean)	EFSA* (75^{th} + Mean)	EFSA* (75^{th} + Mean), DFR value from study.

* EFSA = in accordance with the *EFSA guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products.(2014)*[5]

Consideration on the AOEL of PTZ and PTZ-desthio relevant for resident exposure

Residential exposure estimates has to be calculated for two population subgroups: Adults and children at the age of four. For PTZ-desthio the currently used AOEL of 0.01 mg/kg is based on the NOAEL of 1 mg/kg bw/day for rudimentary 14th ribs derived from the PTZ-desthio supplementary rat developmental toxicity study. This is considered appropriate for women of childbearing age but not for the general population. For the general population a non-developmental NOAEL should be selected as the basis for the AOEL; the NOAEL of 2.2 mg/kg bw/day from the PTZ-desthio rat 90-day study is considered appropriate. Thus the following AOELs are used to assess residential exposure:

PTZ: 0.25 mg/kg bw/day for the whole population

PTZ-desthio: 0.01 mg/kg bw/day for women of childbearing age (i.e. the residential adult as the worst case)

0.022 mg/kg bw/day for the general population (i.e. the residential child as the worst case))

For more details please refer to Appendix 1 of the Document MCA: Section 5.

Resident exposure to spray drift, vapour, surface deposits and entry into treated crops is assessed separately using the 75th percentile estimates. In addition the means of the exposure routes are summed up.

The results of the exposure calculations are summarised in Tables CP 7.2.2-3 to CP 7.2.2-5

[5] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Table CP 7.2.2-3 – Predicted systemic exposure to <u>PTZ</u> as a proportion of the AOEL (Tier 1)

Tier 1, PTZ		Adult[1]			Child[1]		
Routes of exposure	**Analyte**	**75th centile (mg/kg bw/day)**	**in % of AOEL[#]**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL[#]**	**Mean (mg/kg bw/day)**
Spray drift (acc. to EFSA)	PTZ	0.00265*	1.1%	0.00124*	0.01120*	4.5%	0.00612*
Vapour (acc. to EFSA)	PTZ	0.00023	0.1%	0.00023	0.00107	0.4%	0.00107
Surface deposits (acc. to EFSA)	PTZ	0.00077**	0.3%	0.00056**	0.00191**	0.8%	0.00141**
Entry into treated crops (acc. to EFSA)	PTZ	0.01061**	4.2%	0.00846**	0.01909**	7.6%	0.01522**
	PTZ	**Sum of all pathways: in % of AOEL[#]:**		0.01049 4.2%	**Sum of all pathways: in % of AOEL[#]:**		0.02382 9.5%

[1]Considered bodyweight: adult = 60 kg, child = 10 kg
[#] AOEL of PTZ: 0.25 mg/kg bw/day
* Dermal absorption used: 22% from the intermediate dose
** Dermal absorption used: 35% from the low dose

Table CP 7.2.2-4 – Predicted systemic exposure to <u>PTZ</u> as a proportion of the AOEL (Tier 2)

Tier 2, PTZ, refinement		Adult[1]			Child[1]		
Routes of exposure	**Analyte**	**75th centile (mg/kg bw/day)**	**in % of AOEL[#]**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL[#]**	**Mean (mg/kg bw/day)**
Spray drift (measurement of exposure)	PTZ	**0.00041***	**0.2%**	**0.00024***	**0.00105***	**0.4%**	**0.00071***
Vapour (acc. to EFSA)	PTZ	0.00023	0.1%	0.00023	0.00107	0.4%	0.00107
Surface deposits (acc. to EFSA)	PTZ	0.00077**	0.3%	0.00056**	0.00191**	0.8%	0.00141**
Entry into treated crops (acc. to EFSA)	PTZ	0.01061**	4.2%	0.00846**	0.01909**	7.6%	0.01522**
	PTZ	**Sum of all pathways: in % of AOEL[#]:**		**0.00949 3.8%**	**Sum of all pathways: in % of AOEL[#]:**		**0.01841 7.4%**

[1]Considered bodyweight: adult = 60 kg, child = 10 kg
[#] AOEL of PTZ: 0.25 mg/kg bw/day
* Dermal absorption used: 22% from the intermediate dose
** Dermal absorption used: 35% from the low dose
Values in **bold** differ from tier 1

Table CP 7.2.2-5 – Predicted systemic exposure to PTZ-desthio as a proportion of the AOEL

PTZ-desthio		Adult[1]			Child[1]		
Routes of exposure	**Analyte**	**75th centile (mg/kg bw/day)**	**in % of AOEL#**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL#**	**Mean (mg/kg bw/day)**
Spray drift (measurement of exposure)	PTZ-desthio	0.00011*	1.1%	0.00007*	0.00025*	1.1%	0.00018
Vapour (acc. to EFSA)	PTZ-desthio	0.00023	2.3%	0.00023	0.00107	4.9%	0.00107
Surface deposits (acc. to EFSA, 1 appl.)	PTZ-desthio	0.00016*	1.6%	0.00012*	0.00049*	2.2%	0.00035
Entry into treated crops (acc. to EFSA, with DFR study)	PTZ-desthio	0.00048*	4.8%	0.00038*	0.00086*	3.9%	0.00068
	PTZ-desthio	**Sum of all pathways: in % of AOEL#:**		0.0008 8.0%	**Sum of all pathways: in % of AOEL#:**		0.00228 10.4%

[1]Considered bodyweight: adult = 60 kg, child = 10 kg
[#] AOEL of PTZ-desthio: Adult (women of childbearing age): 0.01 mg/kg bw/day
Child: 0.022 mg/kg bw/day

***** Dermal absorption used: 14%

Assessment

Resident/bystander exposure to PTZ and PTZ-desthio is estimated to be well below the respective AOEL.

Based on these exposure estimates there is no unacceptable risk anticipated for residents/bystanders with regard to exposure to prothioconazole and prothioconazole-desthio.

CP 7.2.2.1 Estimation of bystander and resident exposure

Four pathways of residential exposure have to be considered according to the new EFSA guidance[6]:

- spray drift
- vapour
- surface deposits
- entry into treated crops

Consideration on residential exposure due to spray drift

Exposure to PTZ is calculated according to EFSA (Tier 1) and using study results (Tier 2). A dermal absorption value of 22% is used for the exposure calculations. This value derived from the intermediate dose tested in an *in vitro* study and covers the highest in use concentration being the worst case for spray drift exposure. For more details please refer to chapter CP 7.3.

[6] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

As indicated exposure to PTZ-desthio is assessed considering measured data. A dermal absorption value of 14% is used for the exposure calculations.

Consideration on residential exposure due to vapour

Exposure to PTZ and PTZ-desthio are calculated according to EFSA. A worst case conversion of 100% from PTZ to PTZ-desthio is assumed.

Consideration on residential exposure due to surface deposits

Exposure to PTZ is calculated according to EFSA. A dermal absorption value of 35% is used for the exposure calculations. This is the highest dermal absorption value found in the above mentioned study. For more details please refer to chapter CP 7.3.

Exposure to PTZ-desthio is calculated according to EFSA but considering only one instead of two applications due to the rapid dissipation of residues found in the conducted DFR study (chapter CP 7.3.2.3). A conversion from PTZ to PTZ-desthio of 100% is assumed for the exposure to surface deposits. Taking into account the different molar weights of PTZ (344.3 g/mol) and PTZ-desthio (312.2 g/mol) the maximum application rates in mg a.s./cm² are continuously corrected by the molar ratio (i.e. 1.103).

Consideration on residential exposure due to entry into treated crops

Exposure to PTZ is calculated according to EFSA. A maximum dermal absorption value of 35% is used for the exposure calculations.

Exposure to PTZ-desthio is calculated according to EFSA, but using measured DFR values instead of defaults. For more details on the DFR value please refer to chapter CP 7.3.2.3. A dermal absorption value of 14% is used for the exposure calculations.

Spray drift

The exposure of residents via *direct spray drift* is calculated using the following equation:

$$SER_{spray} = (MSC \times DE \times DA \times LCF + MSC \times IE \times IA)/BW$$

SER_{spray}	= Systemic exposure of residents from spray drift (mg/kg bw/day)	
MSC	= Maximum Spray Concentration	1.875 mg PTZ/ml (0.1875 kg PTZ/100 L water)
DE	= Dermal Exposure (ml/person)	75th centile, EFSA default: Adult: 0.47 ml/adult Child: 0.33 ml/child Mean: Adult: 0.22 ml/adult Child: 0.18 ml/child
IE	= Inhalation exposure (ml/person)	75th centile, EFSA default: Adult: 0.00010 ml/adult Child: 0.00022 ml/child Mean: Adult: 0.00009 ml/adult Child: 0.00017 ml/child
DA	= Dermal absorption (%)	PTZ: 22%
IA	= Inhalation absorption (%)	PTZ: 100%
LCF	= Adjustment for light clothing	82%
BW	= Body weight (kg)	Adult: 60 kg Child: 10 kg

Detailed exposure calculations:

PTZ exposure from spray drift, 75th centile calculations:

SER_{spray}, Adult:
= (1.875 mg/ml x 0.47 ml/adult x 22% x 82% + 1.875 mg/ml x 0.00010 ml/adult x 100%) /60 kg
= 0.00265 mg/kg bw/day

SER_{spray}, Child:
= (1.875 mg/ml x 0.33 ml/adult x 22% x 82% + 1.875 mg/ml x 0.00022 ml/adult x 100%) /10 kg
= 0.01120 mg/kg bw/day

PTZ exposure from spray drift, Mean calculations:

SER_{spray}, Adult:
= (1.875 mg/ml x 0.22 ml/adult x 22% x 82% + 1.875 mg/ml x 0.00009 ml/adult x 100%) /60 kg
= 0.00124 mg/kg bw/day

SER_{spray}, Child:
= (1.875 mg/ml x 0.18 ml/adult x 22% x 82% + 1.875 mg/ml x 0.00017 ml/adult x 100%) /10 kg
= 0.00612 mg/kg bw/day

PTZ-desthio exposure from spray drift:

See chapter *CP 7.2.2.2: Measurement of bystander and resident exposure.*

Vapour

The exposure of residents via *vapour* is calculated using the following equation:

SER_{vapour} = (VC x IR x IA)

$SER_{svapour}$	= Systemic exposure of residents from vapour (mg/kg bw/day)	
VC	= Vapour concentration (mg/m³)	PTZ: 0.001 mg/m³ PTZ-desthio: 0.001 mg/m³ (assuming 100% conversion of PTZ to PTZ-desthio)
IR	= Inhalation rate (m³/kg/day)	75th centile + Mean Adult: 0.23 m³/kg/day Child: 1.07 m³/kg/day
IA	= Inhalation absorption (%)	PTZ: 100% PTZ-desthio: 100%

Detailed exposure calculations:

PTZ exposure from vapour, 75th centile + Mean calculations:

SER_{vapour}, Adult:
= 0.001 mg/m³ x 0.23 m³/kg/day x 100%
= 0.00023 mg/kg bw/day

SER_{vapour}, Child:
= 0.001 mg/m³ x 1.07 m³/kg/day x 100%
= 0.00107 mg/kg bw/day

PTZ-desthio exposure from vapour, 75th centile + Mean calculations:

SER_{vapour}, Adult:
= 0.001 mg/m³ x 0.23 m³/kg/day x 100%
= 0.00023 mg/kg bw/day

SER_{vapour}, Child:
= 0.001 mg/m³ x 1.07 m³/kg/day x 100%
= 0.00107 mg/kg bw/day

Surface deposits

Exposure from surface deposits may occur *via* the dermal route only (adult) or *via* the dermal and oral route combined (child).

Dermal exposure

Dermal exposure from *surface deposits* is based on the following equation:

$$SER_{surface\_d} = (AR \times MAF \times D \times TTR \times TC \times H \times DA)/BW$$

$SER_{surface\_d}$	= Systemic exposure of residents from surface deposits via the dermal route (mg/kg bw/day)	
AR	= Application rate (mg/cm²)	PTZ: **0.001875 mg PTZ/cm²** PTZ-desthio: **0.0017 mg PTZ-desthio/cm²** (No higher tier data are available. Accordingly 100% conversion is assumed as tier one, corrected for molar ratio (1.103))
MAF	= Multiple Application Factor	PTZ: **1.724** (for two applications, considering a default DT50 of 30 days and an interval of 14 days) PTZ-desthio: **1** (Results of the DFR study confirm rapid dissipation and no accumulation was observed. For details please refer to CP 7.2.3.2)
D	= Drift (%)	75th centile: **5.6%** Mean: **4.1%**
TTR	= Turf Transferable Residues (%)	**5%**
TC	= Transfer coefficient (cm²/h)	Adult: **7300 cm²/h** Child: **2600 cm²/h**
H	= Exposure duration (hours)	**2 hours**
DA	= Dermal absorption (%)	PTZ: **35%** PTZ-desthio: **14%**
BW	= Body weight (kg)	Adult: **60 kg** Child: **10 kg**

Detailed exposure calculations:

PTZ,dermal exposure from surface deposits, 75th centile

$SER_{surface\_d}$, Adult:
= (0.001875 mg/cm² x 1.724 x 5.6% x 5% x 7300 cm²/hour x 2 hours x 35%)/60 kg
= 0.00077 mg/kg bw/day

$SER_{surface\_d}$, Child:
= (0.001875 mg/cm² x 1.724 x 5.6% x 5% x 2600 cm²/hour x 2 hours x 35%)/10 kg
= 0.00165 mg/kg bw/day

PTZ,dermal exposure from surface deposits, Mean

$SER_{surface\_d}$, Adult:
= (0.001875 mg/cm² x 1.724 x 4.1% x 5% x 7300 cm²/hour x 2 hours x 35%)/60 kg
= 0.00056 mg/kg bw/day

$SER_{surface\_d}$, Child:
= (0.001875 mg/cm² x 1.724 x 4.1% x 5% x 2600 cm²/hour x 2 hours x 35%)/10 kg
= 0.00121 mg/kg bw/day

PTZ-desthio,dermal exposure from surface deposits, 75th centile

$SER_{surface\_d}$, Adult:
= (0.0017 mg/cm² x 1 x 5.6% x 5% x 7300 cm²/hour x 2 hours x 14%)/60 kg
= 0.00016 mg/kg bw/day

$SER_{surface\_d}$, Child:
= (0.0017 mg/cm² x 1 x 5.6% x 5% x 2600 cm²/hour x 2 hours x 14%)/10 kg
= 0.00035 mg/kg bw/day

PTZ-desthio,dermal exposure from surface deposits, Mean

$SER_{surface\_d}$, Adult:
= (0.0017 mg/cm² x 1 x 4.1% x 5% x 7300 cm²/hour x 2 hours x 14%)/60 kg
= 0.00012 mg/kg bw/day

$SER_{surface\_d}$, Child:
= (0.0017 mg/cm² x 1 x 4.1% x 5% x 2600 cm²/hour x 2 hours x 14%)/10 kg
= 0.00025 mg/kg bw/day

Children's hand to mouth transfer

Children's hand to mouth transfer is calculated using the following equation:

$$SER_{surface\_HTM} = (AR \times MAF \times D \times TTR \times SE \times SA \times Freq \times H \times OA)/BW$$

SER$_{surface_HTM}$	= Systemic oral exposure via the hand to mouth route (mg/kg bw/day)	
AR	= Application rate (mg/cm²)	PTZ: **0.001875 mg PTZ/cm²** PTZ-desthio: **0.0017 mg PTZ-desthio/cm²** (No higher tier data are available. Accordingly 100% conversion is assumed as tier one, corrected for molar ratio (1.103))
MAF	= Multiple Application Factor	PTZ: **1.724** (for two applications, considering a default DT50 of 30 days and an interval of 14 days) PTZ-desthio: **1** (Results of the DFR study confirm rapid disspation and no accumulation was observed. For details please refer to CP 7.2.3.2)
D	= Drift (%)	75th centile: **5.6%** Mean: **4.1%**
TTR	= Turf Transferable Residues (%)	**5%**
SE	= Saliva extraction factor (%)	**50%**
SA	= Surface area of hands (cm²)	**20 cm²**
Freq	= Frequency of hand to mouth	**9.5 events/hour**
H	= Exposure duration (hours)	**2 hours**
OA	= Oral absorption (%)	PTZ: **100%** PTZ-desthio: **100%**
BW	= Body weight (kg)	Child: **10 kg**

Detailed exposure calculations:

PTZ,oral exposure from hand to mouth transfer, 75th centile

SER$_{surface_HTM}$, Child:
= (0.001875 mg/cm² x 1.724 x 5.6% x 5% x 50% x 20cm² x 9.5 events/hour x 2 hours x 100%)/10 kg
= 0.00017 mg/kg bw/day

PTZ,oral exposure from hand to mouth transfer, Mean

SER$_{surface_HTM}$, Child:
= (0.001875 mg/cm² x 1.724 x 4.1% x 5% x 50% x 20cm² x 9.5 events/hour x 2 hours x 100%)/10 kg
= 0.00013 mg/kg bw/day

PTZ-desthio, oral exposure from hand to mouth transfer, 75th centile

SER$_{surface_HTM}$, Child:
= (0.0017 mg/cm² x 1 x 5.6% x 5% x 50% x 20cm² x 9.5 events/hour x 2 hours x 100%)/10 kg
= 0.00009 mg/kg bw/day

PTZ-desthio, oral exposure from hand to mouth transfer, Mean

$SER_{surface\ HTM}$, Child:
= (0.0017 mg/cm² x 1 x 4.1% x 5% x 50% x 20cm² x 9.5 events/hour x 2 hours x 100%)/10 kg
= 0.00007 mg/kg bw/day

Children's object to mouth transfer

Children's object to mouth transfer is calculated using the following equation:

$$SER_{surface\_OTM} = (AR \times MAF \times D \times DRP \times IgR \times OA)/BW$$

$SER_{surface\_OTM}$	= Systemic oral exposure via the object to mouth route (mg/kg bw/day)	
AR	= Application rate (mg/cm²)	PTZ: **0.001875 mg PTZ/cm²** PTZ-desthio: **0.0017 mg PTZ-desthio/cm²** (No higher tier data are available. Accordingly 100% conversion is assumed as tier one, corrected for molar ratio (1.103))
MAF	= Multiple Application Factor	PTZ: **1.724** (for two applications, considering a default DT50 of 30 days and an interval of 14 days) PTZ-desthio: **1** (Results of the DFR study confirm rapid disspation and no accumulation was observed. For details please refer to CP 7.2.3.2)
D	= Drift (%)	75th centile: **5.6%** Mean: **4.1%**
DPR	Dislodgeable Residue Percentage (%)	**20%**
IgR	Ingestion rate for mouthing (cm² of grass/day)	**25 cm²** of grass/day
OA	= Oral absorption (%)	PTZ: **100%** PTZ-desthio: **100%**
BW	= Body weight (kg)	Child: **10 kg**

Detailed exposure calculations:

PTZ, oral exposure from object to mouth transfer, 75th centile

$SER_{surface\_OTM}$, Child:
= (0.001875 mg/cm² x 1.724 x 5.6% x 20% x 25 cm²/day x 100%)/10 kg
= 0.00009 mg/kg bw/day

PTZ, oral exposure from object to mouth transfer, Mean

$SER_{surface\_OTM}$, Child:
= (0.001875 mg/cm² x 1.724 x 4.1% x 20% x 25 cm²/day x 100%)/10 kg
= 0.00007 mg/kg bw/day

PTZ-desthio, oral exposure from object to mouth transfer, 75th centile

$SER_{surface\_OTM}$, Child:
= (0.0017 mg/cm² x 1 x 5.6% x 20% x 25 cm²/day x 100%)/10 kg
= 0.00005 mg/kg bw/day

PTZ-desthio, oral exposure from object to mouth transfer, Mean

$SER_{surface\_OTM}$, Child:
= (0.0017 mg/cm² x 1 x 4.1% x 20% x 25 cm²/day x 100%)/10 kg
= 0.00003 mg/kg bw/day

Overall exposure to surface deposits

PTZ
Adult: $SER_{surface\_d}$
75th centile: **= 0.00077 mg/kg bw/day**
Mean: **= 0.00056 mg/kg bw/day**

Child: $SER_{surface\_d}$ + $SER_{surface\_HTM}$ + $SER_{surface\_OTM}$
75th centile: = (0.00165 + 0.00017 + 0.00009) mg/kg bw/day
= 0.00191 mg/kg bw/day

Mean: = (0.00121 + 0.00013 + 0.00007) mg/kg bw/day
= 0.00141 mg/kg bw/day

PTZ-desthio
Adult: $SER_{surface\_d}$
75th centile: **= 0.00016 mg/kg bw/day**
Mean: **= 0.00012 mg/kg bw/day**

Child: $SER_{surface\_d}$ + $SER_{surface\_HTM}$ + $SER_{surface\_OTM}$
75th centile: = (0.00035 + 0.00009 + 0.00005) mg/kg bw/day
= 0.00049 mg/kg bw/day

Mean: = (0.00025 + 0.00007 + 0.00003) mg/kg bw/day
= 0.00035 mg/kg bw/day

Entry into treated crops

The exposure to residents from *entry into treated crops* is calculated using the following equation:

SER_{entry}= (AR x DFR x MAF x TC x H x DA)/(BW x 1000)

SER_{entry}	= Systemic dermal exposure due to entry into treated crops (mg/kg bw/day)	
AR	= Application Rate (kg a.s./ha)	**0.1875 kg PTZ/ha**
DFR	= Dislodgeable Foliar Residues (µg a.s./cm²/kg a.s./ha)	PTZ: **3 µg PTZ/cm²/kg PTZ/ha**. PTZ-desthio: **0.58 µg PTZ-desthio/cm²/kg PTZ/ha** (from DFR study, for more details please refer to chapter CP 7.2.3.2)
MAF	= Multiple Application Factor	PTZ: **1.724** (for two applications considering a default DT50 of 30 days and an interval of 14 days) PTZ-desthio: **1** (Results from DFR study already consider two applications)
TC	= Transfer coefficient (cm²/h)	Adult: 75th centile: **7500 cm²/h** Mean: **5980 cm²/h** Child: A factor of **0.3** to the adult TC
H	= Exposure duration (hours)	**0.25 hours**
DA	= Dermal Absorption (%)	PTZ: **35%** PTZ-desthio: **14%**
BW	= Body weight (kg)	Adult: **60 kg** Child: **10 kg**

Detailed exposure calculations:

PTZ, dermal exposure from entry into treated crops, 75th centile

SER_{entry}, Adult:
=(0.1875 kg/ha x 3 µg/cm²/kg/ha x 1.724 x 7500 cm²/hour x 0.25 hours x 35%) /(60 kg x1000)
= 0.01061 mg/kg bw/day

SER_{entry}, Child:
=(0.1875 kg/ha x 3 µg/cm²/kg/ha x 1.724 x 7500 cm²/hour x 0.3 x 0.25 hours x 35%) /(10 kg x1000)
= 0.01909 mg/kg bw/day

PTZ, dermal exposure from entry into treated crops, Mean

SER_{entry}, Adult:
=(0.1875 kg/ha x 3 µg/cm²/kg/ha x 1.724 x 5980 cm²/hour x 0.25 hours x 35%) /(60 kg x1000)
= 0.00846 mg/kg bw/day

SER_{entry}, Child:
=(0.1875 kg/ha x 3 µg/cm²/kg/ha x 1.724 x 5980 cm²/hour x 0.3 x 0.25 hours x 35%) /(10 kg x1000)
= 0.01522 mg/kg bw/day

PTZ-desthio, dermal exposure from entry into treated crops, 75th centile

SER_{entry}, Adult:
=(0.1875 kg/ha x 0.58 µg/cm²/kg/ha x 1 x 7500 cm²/hour x 0.25 hours x 14%) /(60 kg x1000)
= 0.00048 mg/kg bw/day

SER_{entry}, Child:
=(0.1875 kg/ha x 0.58 µg/cm²/kg/ha x 1 x 7500 cm²/hour x 0.3 x 0.25 hours x 14%) /(10 kg x1000)
= 0.00086 mg/kg bw/day

PTZ-desthio, dermal exposure from entry into treated crops, Mean

SER_{entry}, Adult:
=(0.1875 kg/ha x 0.58 µg/cm²/kg/ha x 1 x 5980 cm²/hour x 0.25 hours x 14%) /(60 kg x1000)
= 0.00038 mg/kg bw/day

SER_{entry}, Child:
=(0.1875 kg/ha x 0.58 µg/cm²/kg/ha x 1 x 5980 cm²/hour x 0.3 x 0.25 hours x 14%) /(10 kg x1000)
= 0.00068 mg/kg bw/day

CP 7.2.2.2 Measurement of bystander and resident exposure

Two independent direct drift datasets with prothioconazole containing products were generated in two field studies in cereals using tractor mounted sprayers equipped with regular flat fan nozzles.
In both studies dermal exposure of bystanders (represented by display dummies or mannequins) at various distances downwind from the sprayed area has been determined. Both studies were conducted under GLP by Bayer CropScience in Germany. Both studies where designed to cover use parameters in terms of wind speed (which is considered to be the main parameter impacting on spray drift), which are relevant for ground boom spray applications in the field i.e. according to good agricultural practice wind speed should not exceed 5 m/s. Nevertheless, with respect to real practice the predominant number of applications is in general conducted at maximum wind speeds of about 2.5 m/s to ensure proper distribution and subsequent efficacy of the product. Due to higher drift associated with higher wind speeds the distribution of the spray onto the crop is then less homogenous. In addition it has been found during the second study that with higher wind speeds wind conditions are less stable which further contributes to less homogenous distribution.

The application dose rate was either 200 g PTZ/ha (PTZ + SPX EC 460 study) or 187.5 g PTZ/ha (BIX + PTZ EC 225 study), respectively. In both studies the minimum water rate of 100 L/ha was applied.

A summary of both studies is provided below.

Report:	KCP 7.2.2.2/01 [redacted]; [redacted]; 2015; M-510333-01-1
Title:	Exposure of bystanders / residents to spiroxamine and prothioconazole from spray applications with Input in cereals using standard spray nozzles
Report No.:	MR-14/075
Document No.:	M-510333-01-1
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 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

I. Material and methods

This report summarises the results of field testing conducted in Germany to determine the dermal and inhalation exposure of bystanders/residents via direct spray drift to prothioconazole (PTZ), its main metabolite prothioconazole-desthio (PTZ-desthio) and spiroxamine (SPX) at various distances downwind from the sprayed area while applying PTZ + SPX EC 460 in winter wheat. PTZ + SPX EC 460 is formulated as an emulsifiable concentrate comprising the two active ingredients SPX (300 g/L) and PTZ (160 g/L). The spray application was performed with a commercial field crop boom sprayer with 28 m boom width. PTZ + SPX EC 460 was applied with the label specific rate of 1.25 L/ha (nominal 375 g a.s./ha SPX and 200 g/L PTZ) using standard spray nozzles (TeeJet XR 110-03). Water from local sources was used to make up the spray mixture. A water volume of 100 L/ha was applied.

Spray application with PTZ + SPX EC 460 was performed in homogeneous winter wheat (BBCH 55, height 60 cm) grown on commercial agricultural land around Bayer CropScience AG's headquarter in D-40789 Monheim, Alfred-Nobel-Str. 50, Germany. The most appropriate headland was selected based on the prevailing wind direction to obtain a track as near as possible to 90° to the prevailing wind direction, representing worst case conditions to persons in the vicinity affected by drift. The site allowed to position replicates of mannequins at 2 m, 5 m and 8 m distances downwind in order to monitor a range of potential distances where bystanders or residents may be exposed during application.
A total of eighteen mannequins representing nine adult and nine child bystanders/residents were monitored. The dermal exposure was determined with whole-body dosimeters (WBD). Each mannequin wore dosimeters consisting of a short-sleeved T-shirt and shorts above long underwear (long johns and shirt) and a ski mask covering the head. The long sleeves of the shirts also cover the hands of the mannequins. Thus, an additional hand dosimeter was therefore not included. This clothing scheme allowed the determination of potential dermal exposure representing a person with virtually no clothing as well as actual dermal exposure representing a lightly dressed person wearing only little clothing. Inhalation exposure was determined by the use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter, located in the virtual breathing zone of the adult and child dummy.

On completion of the spray swath, the spray droplets were allowed to settle for approximately 30 min before study personnel removed the dosimeters from the mannequins, sealed the samples in labelled polyethylene bottles and transferred them to the test facility for storage in freezers until analysis. At the beginning of the day, study personnel fortified sets of unexposed samples of WBD sections and air sampling tubes with known quantities of PTZ, its main metabolite PTZ-desthio and SPX. Dosimeter samples were exposed to ambient conditions at a location near, but isolated from, the test plot. At the end of the work day, these field control samples were collected and handled as described above. All samples were stored at approx. – 20° C prior to extraction and analysis.

Residues of PTZ, PTZ-desthio and SPX were extracted from samples using LC/MS/MS detection system.

The Limit of Quantification (LOQ) for residues of PTZ, PTZ desthio and SPX were 1 µg per dermal sample and 0.1 µg per IOM filter.

Potential dermal exposure was calculated as the sum of the residues detected on the short sleeved T-shirt and shorts, the underwear (long sleeved T-shirt and long underwear trousers) and the ski mask. Actual dermal exposure was calculated as the sum of the residues detected on the underwear (long sleeved T-shirt and long underwear trousers) and the ski mask.

II. Findings

The mean wind speed was 2.3 m/s. The average wind direction deviation from the worst case 90° angle was 9.9°. The temperature and the humidity were in average 30.7°C and 46.4%, respectively.

Field recoveries which were set up during the study showed that the residues were stable.

The residues of prothioconazole and prothioconazole-desthio on air samples were found to be below the LOQ (0.1 µg/sample) for all the mannequins and therefore not presented here.

Rates of actual dermal exposure to prothioconazole and prothioconazole-desthio at the most relevant distance of 2 m are presented in Table CP 7.2.2-1 together with findings from the second spray drift study. Actual dermal exposure values measured at 5 m and 8 m distance, which are mostly significantly lower than at 2 m distance, are not presented here, but can be found in the study report.

Report:	KCP 7.2.2.2/02[redacted],;[redacted]; 2015; M-536654-02-1
Title:	Amendment no.1 to final report of study ID: P-666-15-1700 - Dermal exposure of bystanders / residents to prothioconazole and its main metabolite prothioconazole-desthio from tractor mounted/trailed boom sprayers with Aviator XPRO EC 225 in cereals
Report No.:	P666151700
Document No.:	M-536654-02-1
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 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Guideline deviation(s):	not applicable
GLP/GEP:	**yes**

I. Material and methods

This report summarises the results of field testing conducted in Germany to determine the dermal exposure of bystanders/residents via direct spray drift to prothioconazole (PTZ) and its main metabolite prothioconazole-desthio (PTZ-desthio) at various distances downwind from the sprayed area while applying BIX + PTZ EC 225 in winter wheat. BIX + PTZ EC 225 is formulated as an emulsifiable concentrate comprising the two active ingredients PTZ (150 g/L) and bixafen (75 g/L). The spray application was performed with a commercial field crop boom sprayer with 18 m boom width. BIX + PTZ EC 225 was applied with the label specific rate of 1.25 L/ha (nominal 187.5 g/ha prothioconazole) using standard spray nozzles (TeeJet XR 110-03). Water from local sources was used to make up the spray mixture. A water volume of 100 L/ha was applied.

Spray application with BIX + PTZ EC 225 was performed in homogeneous winter wheat (BBCH 56, height 60 cm) grown on commercial agricultural land around Bayer CropScience AG's headquarter in D-40789 Monheim, Alfred-Nobel-Str. 50, Germany. The most appropriate headland was selected based on the prevailing wind direction to obtain a track as near as possible to 90° to the prevailing wind direction, representing worst case conditions to persons in the vicinity affected by drift. The site allowed to position replicates of mannequins at 2 m and 5 m distances downwind in order to monitor a range of potential distances where bystanders or residents may be exposed during application.
A total of twenty mannequins representing ten adult and ten child bystanders/residents were monitored. The dermal exposure was determined with whole-body dosimeters (WBD). Each mannequin wore dosimeters consisting of a short-sleeved T-shirt and shorts above long underwear (long johns and shirt) and a ski mask covering the head. The long sleeves of the shirts also cover the hands of the mannequins. Thus, an additional hand dosimeter was therefore not included. This clothing scheme allowed the determination of potential dermal exposure representing a person with virtually no clothing as well as actual dermal exposure representing a lightly dressed person wearing only little clothing. No Inhalation exposure was determined, since the results of the first study revealed that residues of PTZ and PTZ-desthio on the inhalation sampling devices were always below the limit of quantification.

On completion of the spray swath, the spray droplets were allowed to settle for approximately 30 min before study personnel removed the dosimeters from the mannequins, sealed the samples in labelled polyethylene bottles and transferred them to the test facility for storage in freezers until analysis. At the beginning of the day, study personnel fortified sets of unexposed samples of WBD sections with known quantities of prothioconazole and prothioconazole-desthio. Dosimeter samples were exposed to ambient conditions at a location near, but isolated from, the test plot. At the end of the work day, these field control samples were collected and handled as described above. All samples were stored at approx. –20° C prior to extraction and analysis.

Residues of PTZ and PTZ-desthio were extracted from samples using LC/MS/MS detection system.

The Limit of Quantification (LOQ) for residues of PTZ and PTZ desthio were 6 µg per dermal sample.

Potential dermal exposure was calculated as the sum of the residues detected on the short sleeved T-shirt and shorts, the underwear (long sleeved T-shirt and long underwear trousers) and the ski mask. Actual dermal exposure was calculated as the sum of the residues detected on the underwear (long sleeved T-shirt and long underwear trousers) and the ski mask.

II. Findings

The mean wind speed was 3.8 m/s. The average wind direction deviation from the worst case 90° angle was 28°. The temperature and the humidity were in average 15.1°C and 47.7%, respectively.

Field recoveries which were set up during the study showed that the residues were stable

Rates of actual dermal exposure to PTZ and PTZ-desthio at the most relevant distance of 2 m are presented in Table CP 7.2.2-1 together with findings from the first spray drift study. Actual dermal exposure values measured at 5 m distance, which are in most cases significantly lower than at 2 m distance, are not presented here, but can be found in the study report.

Actual dermal exposure

Exposure to PTZ and PTZ-desthio are presented in µg a.s./person.
Values below the LOQ were considered and presented as ½ of the respective LOQ

Table CP 7.2.2-1: Compiled actual dermal exposure data from both bystander studies I) PTZ + SPX EC 460, II) BIX + PTZ EC 225)

Dist-ance	Study	Adult Sample ID	Residues (µg/person)		Child Sample ID	Residues (µg/person)	
			PTZ	PTZ-desthio		PTZ	PTZ-desthio
2 m	PTZ + SPX EC 460	A1	47.8	30.0	a1	24.3	11.8
		A2	65.7	29.9	a2	24.1	12.8
		A3	78.2	62.1	a3	28.3	15.3
2 m	BIX + PTZ EC 225	A1	3*	3*	a1	3*	3*
		A2	26.1	17.2	a2	9.27	3*
		A3	66.4	26.7	a3	23.0	7.20
		A4	112	44.1	a4	62.9	16.8
		A5	120	31.6	a5	67.6	13.6
Mean			***64.9***	***30.6***		***30.3***	***10.4***
a) 75th centile			86.7	34.7		37.0	14.0
b) 75th parametric estimate			***111.3***	***47.8***		***40.0***	***14.9***

* ½ LOQ

The high variability of the exposure values within the second spray drift study (with BIX+PTZ EC 225) can be explained by the unstable wind conditions during the swaths. The measured mean wind speed during the entire spray duration was at 3.8 m/s. However, when the tractor was passing the first dummy pair (adult A1 and child a1) the wind speed was with 2 m/s - 2.5 m/s at the lower range of observed wind speeds. When passing the last dummies (adult A5 and child a5) 30 seconds later, the wind speed was, however, in a range of around 5 m/s - 6 m/s, and thus significantly higher than at the beginning of the study start. For details please refer to the study report.

Spray drift calculations

Consideration on dermal exposure

According to the new EFSA guidance (2014)[7] for risk assessments in relation to longer term exposure, exposures should, as a default, be derived as the higher of: (a) the 75th percentile of the distribution of measurements in the sample or (b) a statistical estimate of the 75th for the theoretical population of measurements from which the sample was derived (parametric estimate). Values used for the calculation of bystander exposure to the representative spray formulation BIX+PTZ EC 225 are highlighted in ***bold-italic*** in Table CP 7.2.2-1.

Consideration on inhalation exposure

Inhalation exposure results from the bystander study conducted with PTZ + SPX EC 460 have shown that the residues of PTZ and PTZ-desthio on the inhalation sampling devices were in all cases below the Limit of Quantification (0.05 µg/sample). However, since the pumps used in the study to mimic the breathing rate were running at 2 L/min the exposure values have to be corrected according to the breathing rates given in the EFSA guidance (i.e. 32 L/min for the child and 40 L/min for the adult).

[7] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Since this correction would then lead to artificially high inhalation exposure values, inhalation exposures are here simply calculated using default inhalation exposure values taken from the EFSA guidance.

The exposure of residents to PTZ and PTZ-desthio from *spray drift using measured values* is calculated as follows:

SER_{spray}= (ADE x DA + MSC x IE x IA)/BW

SER_{spray}	= Systemic exposure of residents from spray drift (mg/kg bw/day)	
ADE	= Actual dermal exposure (mg/person)	*Actual dermal exposure, 75th centile, <u>PTZ</u>:* Adult: 111.3 µg/adult = 0.1113 mg/adult Child: 46.0 µg/child = 0.046 mg/child *Actual dermal exposure, Mean, <u>PTZ</u>:* Adult: 64.9 µg/adult = 0.0649 mg/adult Child: 30.6 µg/child = 0.0306 mg/child *Actual dermal exposure, 75th centile, <u>PTZ-desthio</u>:* Adult: 47.8 µg/adult = 0.0478 mg/adult Child: 14.9 µg/child = 0.0149 mg/child *Actual dermal exposure, Mean, <u>PTZ-desthio</u>:* Adult: 30.3 µg/adult = 0.0303 mg/adult Child: 10.4 µg/child = 0.0104 µg/child
MSC	= Maximum Spray Concentration	1.875 mg PTZ/ml (0.1875 kg PTZ/100 L water)
IE	= Inhalation exposure (ml/person)	75th centile, EFSA default: Adult: 0.00010 ml/adult Child: 0.00022 ml/child Mean, EFSA default: Adult: 0.00009 ml/adult Child: 0.00017 ml/child
DA	= Dermal absorption (%)	<u>PTZ</u>: 22% <u>PTZ-desthio</u>: 14%
IA	= Inhalation absorption (%)	<u>PTZ</u>: 100% <u>PTZ-desthio</u>: 100%
BW	= Body weight (kg)	Adult: 60kg Child: 10 kg

Detailed exposure calculations:

<u>PTZ</u> exposure from spray drift, 75th centile calculations:

<u>*SER_{spray}, Adult:*</u>
= (0.1113 mg/adult x 22% + 1.875 mg/ml x 0.00010 ml/adult x 100%) /60 kg
= 0.00041 mg/kg bw/day

<u>*SER_{spray}, Child:*</u>
= (0.0460 mg/child x 22% + 1.875 mg/ml x 0.00022 ml/adult x 100%) /10 kg
= 0.00105 mg/kg bw/day

<u>PTZ</u> exposure from spray drift, Mean calculations:

SER_{spray}, Adult:
= (0.0649 mg/adult x 22% + 1.875 mg/ml x 0.00009 ml/adult x 100%) /60 kg
= 0.00024 mg/kg bw/day

SER_{spray}, Child:
= (0.0306 mg/child x 22% + 1.875 mg/ml x 0.00017 ml/adult x 100%) /10 kg
= 0.00071 mg/kg bw/day

PTZ-desthio exposure from spray drift, 75th centile calculations:

SER_{spray}, Adult:
= (0.0478 mg/adult x 14% + 1.875 mg/ml x 0.00010 ml/adult x 100%) /60 kg
= 0.00011 mg/kg bw/day

SER_{spray}, Child:
= (0.0149 mg/child x 14% + 1.875 mg/ml x 0.00022 ml/adult x 100%) /10 kg
= 0.00025 mg/kg bw/day

PTZ-desthio exposure from spray drift, Mean calculations:

SER_{spray}, Adult:
= (0.0303 mg/adult x 14% + 1.875 mg/ml x 0.00009 ml/adult x 100%) /60 kg
= 0.00007 mg/kg bw/day

SER_{spray}, Child:
= (0.0104 mg/child x 14% + 1.875 mg/ml x 0.00017 ml/adult x 100%) /10 kg
= 0.00018 mg/kg bw/day

CP 7.2.3 Worker exposure

Table CP 7.2.2-1 summarises the critical GAP for the representative formulation PTZ+BIX EC 225 (150 + 75 g/L) relevant for worker exposure to prothioconazole (PTZ) and its main metabolite prothioconazole-desthio (PTZ-desthio).

Table CP 7.2.3-1 – Application parameters for PTZ+BIX EC 225

Application technique	Crop	Task	Maximum application rate (kg PTZ/ha)	Max no of application	Interval (days)
Tractor mounted ground boom spraying	Cereals	Inspection	0.1875	2	14

Worker exposure is calculated according to the new EFSA guidance[8] with the relevant exposure scenario *inspection in cereals*. The results of the exposure calculations are summarised in Table CP 7.2.3-2. Details on the calculations are presented in chapter CP 7.2.3.1 and CP 7.2.3.2.

[8] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Table CP 7.2.3-2 Predicted systemic worker exposure to PTZ and PTZ-desthio as a proportion of the AOEL

Routes of exposure	Scenario	Analyte	Systemic Exposure (mg/kg bw/day)[1]	in % of AOEL [#]
Entry into treated crops	Inspection in cereals	PTZ	0.01584	6.3%
		PTZ-desthio	0.00071	7.1%

[1]Considers a dermal absorption of 35% for PTZ and 14% for PTZ-desthio, for PTZ a default DFR is used (3 µg PTZ/cm²/kg PTZ/ha), for PTZ-desthio a DFR of 0.58 µg PTZ-desthio/cm²/kg PTZ/ha from a foliar residue study is used
[#] AOEL of PTZ: 0.25 mg/kg bw/day, PTZ-desthio: 0.01 mg/kg bw/day

Assessment

Worker exposure to PTZ and PTZ-desthio is estimated to be well below the respective AOEL.

Based on these exposure estimates there is no unacceptable risk anticipated for workers with regard to exposure to prothioconazole and prothioconazole-desthio.

CP 7.2.3.1 Estimation of worker exposure

Worker exposure is calculated according to the new EFSA guidance[9] with the relevant exposure *inspection in cereals* using the following equation:

SDE_W= (DFR x AR x (MAF) x TC x WH x DA) / BW

	Product	BIX+PTZ EC 225
SDE_W	= Systemic Dermal Exposure of Workers (mg/kg bw/day)	
	Crop type	Cereals
	Worker's task	Inspection
AR	= Application Rate of active substance (kg a.s./ha)	0.1875 kg a.s./ha
MAF	= Multiple Application Factor	PTZ: 1.724 (for two applications, considering a default DT50 of 30 days and an interval of 14 days) PTZ-desthio: 1 (Results of the DER study directly consider two applications with a minimum interval of 14 days)
DA	= Dermal Absorption of the in-use dilution (%)	PTZ: 35 % PTZ-desthio: 14%
DFR	= Dislodgeable Foliar Residue ($\mu g/cm^2$ of foliage/kg a.s. applied/ha)	PTZ: 3 µg PTZ/cm²/kg PTZ/ha. PTZ-desthio: 0.58 µg PTZ-desthio/cm²/kg PTZ/ha (from DFR study, for more details please refer to chapter 7.2.3.1)
WH	= Working hours (hrs)	2 hrs
TC	= Dermal Transfer Coefficient - arms, body and legs covered (cm^2/hr)	1400cm²/hr
BW	= Bodyweight (kg)	60 kg

Detailed exposure calculations:

PTZ, worker exposure from entry into treated crops

SDE_W:
=(3 µg/cm²/kg/ha x 0.1875 kg/ha x 1.724 x 1400 cm²/hr x 2 hrs x 35%) /(60 kg x1000)
= 0.01584 mg/kg bw/day

PTZ-desthio, worker exposure from entry into treated crops

SDE_W:
=(0.58 µg/cm²/kg/ha x 0.1875 kg/ha x 1 x 1400 cm²/hr x 2 hrs x 14%) /(60 kg x1000)
= 0.00071 mg/kg bw/day

For more details on the DFR value for PTZ-desthio (0.58 µg/cm²/kg/ha) please refer to the following chapter CP 7.2.3.2.

[9] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

CP 7.2.3.2 Measurement of worker exposure

Following foliar spray treatment the dislodgeable foliar residues of prothioconazole (PTZ) and its main metabolite prothioconazole-desthio (PTZ-desthio) were determined on wheat. Two studies including three supervised residue trials has been conducted: One in Southern Europe (Portugal) and two in Northern Europe (Germany, Northern France). Summaries of both studies and results are presented below.

1) DFR study on wheat, conducted in Germany with an application rate of 200 g PTZ/ha

Report:	KCP 7.2.3.2/01 [redacted]; 2013; M-455270-01-1
Title:	Determination of the dislodgeable foliar residues (DFR) of prothioconazole in/on wheat after spray application of JAU 6476 & KWG 4168 EC 460 in the field in Germany
Report No.:	12-2901
Document No.:	M-455270-01-1
Guideline(s):	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a))
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and methods

In the study 12-2901 the magnitude of the dislodgeable foliar residues of PTZ and PTZ-desthio in washings of leaves after two spray applications with PTZ+SPX EC 460 was determined.
The study included one supervised residue trial conducted in Northern Europe (Germany) during the 2012 season.
The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 7.2.3.2-1: Application summary

Trial no. Country	Formulation	Application							
		Appl. mode	No. of appl.	Interval (days)	Growth stage (BBCH code)	Test item rate (L/ha)	Water rate (L/ha)	Active substance	Appl. rate (kg a.s./ha)
12-2901-01 Germany	PTZ+SPX EC 460	SPI	2	14	47 - 61	1.25	150	PTZ	0.2

Appl.: Application
SPI: Spraying

The analyses were conducted according to the following analytical method(s):

Table 7.2.3.2-2: Summary of analytical method criteria relevant to this study

Active substance	Analytes	Method number	Limit of quantitation [µg/L]	Limit of quantitation [µg/cm²]	Sample material	Measurement principle
PTZ	PTZ	01354/M001	5	0.005	leaf washings	HPLC-MS/MS
	PTZ-desthio					

The average laboratory recoveries for PTZ were within the acceptable range of 94% – 99%.

The average field spike recoveries for PTZ as sum of PTZ and PTZ-desthio (expressed as PTZ) ranged between 29% and 87%.

The average laboratory recoveries for PTZ-desthio were within the acceptable range of 90% – 98%.

The average field spike recoveries for PTZ-desthio ranged between 81% and 97%.

No residues above the LOQ were found in the control samples.

The levels of residues of PTZ and PTZ-desthio are summarised in the table XXX together with the findings from the second field study conducted in France and Portugal.

2) DFR study on wheat, conducted in Northern France and Portugal with an application rate of 188 g PTZ/ha

Report:	KCP 7.2.3.2/02[redacted], 2015; M-507834-01-1
Title:	Determination of the dislodgeable foliar residues (DFR) of prothioconazole and BYF 00587 in/on wheat after spraying of Bixafen & Prothioconazole EC 225 in the field in France (North) and Portugal
Report No.:	14-2907
Document No.:	M-507834-01-1
Guideline(s):	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and methods

In the study 14-2907 the magnitude of the dislodgeable foliar residues of PTZ and PTZ-desthio in washings of leaves after two spray applications with BIX+PTZ EC 225 was determined.
The study included two supervised residue trial conducted in Southern Europe (Portugal) and Northern Europe (France) during the 2014 season.
The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 7.2.3.2-3 Application summary

Trial no. Country	Formulation	Application							
		Appl. mode	No. of appl.	Interval (days)	Growth stage (BBCH code)	Test item rate (L/ha)	Water rate (L/ha)	Active substance	Appl. rate (kg a.s./ha)
14-2907-01 France	Bixafen & Prothioconazole EC 225	SPI	1	-	47	1.25	200	PTZ	0.188
			2	14	65				
14-2907-02 Portugal	Bixafen & Prothioconazole EC 225	SPI	1	-	47	1.25	200	PTZ	0.188
			2	14	65				

Appl.: Application
SPI: Spraying

The leaf samples were taken randomised from the three topmost leaf level.

The analyses were conducted according to the following analytical method(s):

Table 7.2.3.2-4: Summary of analytical method criteria relevant to this study

Active substance	Analytes	Method number	Limit of quantitation [µg/L]	Limit of quantitation [µg/cm²]	Sample material	Measurement principle
PTZ	PTZ	01354/M001	10	0.01	leaf washings	HPLC-MS/MS
	PTZ-desthio					

The average laboratory recoveries for PTZ were within the acceptable range of 92% – 103% with an overall average of 96%.

The overall average field spike recoveries for PTZ as sum of PTZ and PTZ-desthio (expressed as PTZ) in trial 14-2907-02 (Portugal) and in trial 14-2907-01 (France) were 50% and 57%, respectively.

The average laboratory recoveries for PTZ-desthio were within the acceptable range of 86% – 103% with an overall average of 92%.

The overall average field spike recoveries for PTZ-desthio in trial 14-2907-01 (Portugal) and in trial 14-2907-01 (France) were 81% and 83%, respectively.

No residues above the LOQ were found in the control samples.

The levels of residues of PTZ and PTZ-desthio are summarised in the following Table 7.2.3.2-5 together with the findings from the field trial conducted in Germany.

Results and Discussion

In both studies average field spike recoveries for PTZ were very low and not within an acceptable range. Consequently no residue values for PTZ from both studies were taken into account for the exposure calculations of workers to BIX+PTZ EC 225 and are thus not presented in Table 7.2.3.2-5, but can be found in the study reports. Instead, default for 1 values according to EFSA (3 µg/cm²/kg a.s. applied/ha) are used to assess worker exposure in chapter CP 7.2.3.1.

The results from both studies for PTZ-desthio are summarised in the following Table 7.2.3.2-5.

Table 7.2.3.2-5: Residue summary of both DFR studies on wheat.

Trial No. / Country	DALT	Residues [µg/cm²] Average values of sub-plots T1, T2 and T3		
		Germany (0.200 kg a.s./ha)	Portugal (0.1875 kg a.s./ha)	France (0.1875 kg a.s./ha)
		PTZ-desthio	PTZ-desthio	PTZ-desthio
12-2901 Germany 14-2907-01 France 14-2907-02 Portugal	-0	< 0.005	< 0.010	< 0.010
	0	0.096	0.090	0.057
	1	0.083	0.012	0.039
	2	0.012 (d3)	< 0.010	0.012
	7	< 0.005	< 0.010	< 0.010
	14/-0	< 0.005	< 0.010 (d13/-1)	< 0.010
	0	***0.116***	0.100	0.064
	1	0.067	0.046	< 0.010
	3	0.008	0.024	< 0.010
	7	< 0.005 (d8)	< 0.010 (d6)	< 0.010
	14	< 0.005	< 0.010 (d15)	< 0.010

DALT = Days after last treatment; a.s. = active substance; "-0": before the last application

After each treatment in all trials dislodgeable foliar residues of PTZ-desthio declined rapidly leading to residue values below the LOQ within 7 days after application.

Conclusion

The results show that there is a rapid dissipation for PTZ-desthio. No increase or accumulation of residues on the leave surface was observed with the second application. The maximum measured residues in all three trials were found directly after the application in Germany and amounted to ***0.116 µg/cm²*** for PTZ-desthio. Taking into account an application rate of 0.200 kg PTZ/ha the normalised DFR value leads to **0.58 µg PTZ-desthio/cm²/kg a.s./ha.**

Exposure calculations

For worker re-entry exposure calculations considering a DFR value of 0.58 µg PTZ-desthio/cm²/kg PTZ/ha after the intended use of the representative formulation BIX+PTZ EC 225 please refer to chapter *CP 7.2.3.1: Estimation of worker exposure*.

DFR study results are additionally used to estimate residential exposure to PTZ-desthio due to entry into treated crops. For details please refer to chapter *CP 7.2.2.1: Estimation of bystander and resident exposure*.

CP 7.3 Dermal adsorption

Prothioconazole (PTZ)

For the representative formulation BIX+PTZ EC 225 a dermal absorption of 5% for the neat formulation, 22% for the intermediate dose and 35% for the low dose is used for PTZ. These values derived from a human *in vitro* dermal absorption study conducted with the formulation BIX+PTZ+TBZ EC 275. According to the EFSA guidance on dermal absorption[10] both formulations are closely related and thus dermal absorption data from BIX+PTZ+TBZ EC 275 can also be used for the representative formulation BIX+PTZ EC 225. A detailed bridging statement including a comparison of the ingredients of both formulations is provided in the confidential Document JCP. A summary and a conclusion of the study conducted with BIX+PTZ+TBZ EC 275 is provided below:

Report:	KCP 7.3/01 [redacted]; 2014; M-482967-01-1
Title:	The in vitro percutaneous absorption of radiolabelled prothioconazole in the concentrate bixafen+prothioconazole+tebuconazole EC 275 formulation and two in-use spray dilutions through human skin
Report No.:	34840
Document No.:	M-482967-01-1
Guideline(s):	OECD 428 (April 2008)
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods

Human skin: Source: [redacted] Glasgow.
Number and sex: 5 donors, male and female.
Anatomical region: 4 Abdomen and 1 back.
Thickness: 370 to 400 µm.

Test Material:

Non-radiolabelled: Batch: AE 1344248 00 1B99 0002.
Purity: 99.8% w/w.

Radiolabelled: [triazole-UL-^{14}C]-prothioconazole.
Batch: KML 9657.
Specific activity: 2.28 MBq/mg.
Radiopurity of the formulation: 97.5%.

Formulation: The formulation used in this experiment was the BIX+PTZ+TZB EC 275 formulation (specification number 102000014326 containing prothioconazole (100 g/L), bixafen (75 g/L) and tebuconazole (100 g/L). It was used at three nominal concentrations of PTZ: neat; 500 g/L, 1.25 g/L and 0.25 g/L.

Test system: An automated flow-through diffusion cell apparatus ([redacted] UK) was used. The flow-through diffusion cells were placed in a manifold heated *via* a circulating water bath set to maintain the skin surface temperature at 32°C ± 1°C. The cells were connected to multi-channel peristaltic pumps from their afferent ports with the receptor fluid effluent dropping *via* fine bore tubing into scintillation vials on a fraction collector. The surface area of exposed skin within the cells was

[10] 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.

0.64 cm^2. The receptor chamber volume was 0.25 mL. The peristaltic pumps were adjusted to maintain a flow-rate of 1.5 mL/h ± 0.15 mL/h.

The receptor fluid was tissue culture medium containing PEG (*ca* 6%, w/v), glucose (*ca* 1%, w/v), streptomycin (0.1 mg/mL), penicillin G (100 units/mL) and sodium azide (0.01%, w/v). The receptor fluid was degassed by sonication for *ca* 10 min after being made and was stored in a refrigerator set to maintain a temperature of 4°C prior to use on the study.

Skin integrity: Sections of split-thickness skin membrane, *ca* 1.5 x 1.5 cm, were cut and positioned on the receptor chamber of the diffusion cell, which contained a magnetic stirrer bar. The donor chamber was tightened into place with screws and the prepared cells were then placed in the heated manifold and connected to the peristaltic pump. A magnetic stirrer was switched on to mix the contents of the receptor chamber. An equilibration period of *ca* 15 min was allowed while receptor fluid was pumped through the receptor chambers at 1.5 mL/h ± 0.15 mL/h. The effluent was then collected for *ca* 30 min and retained as blank samples for use in the tritiated water barrier integrity assessment.

Tritiated water (250 µL, *ca* 100,000 disintegrations per minute [d.p.m.]) was applied to the surface of each skin sample and the donor chamber occluded. Penetration of tritiated water was assessed by collecting receptor fluid for 1 h and analysing the sample by liquid scintillation counting. The mean d.p.m. applied for the tritiated water was calculated from the mock tritiated water samples taken at the time of dosing. The percentage absorption was then calculated for each skin sample from the 1 h receptor fluid sample collected. Any human skin sample exhibiting absorption greater than 0.6% of the applied dose was excluded from subsequent absorption measurements. At the end of the 1 h period, residual tritiated water was removed from the skin surface. The skin surface was then rinsed with water and dried with tissue paper. An equilibration period of *ca* 2.25 h was allowed prior to collection of the pre-dose sample which was collected for *ca* 0.5 h.

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

Sampling: The absorption of the radiolabelled test item was assessed by collection of receptor fluid in hourly fractions from 0 to 8 h post dose and then 2 hourly fractions from 8 to 24 h post dose. All receptor fluid samples were mixed with scintillation fluid (10 mL) and analysed by liquid scintillation counting. At 8 h post dose, the 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 h post dose, each diffusion cell was disconnected from the receptor fluid pump lines. The underside of the skin was rinsed (receptor rinse) with receptor fluid (*ca* 1.5 mL)

The stratum corneum was removed with 20 successive tape strips (3M Scotch™ Magic Tape) and individually placed into 20 mL scintillant vials containing methanol:scintillation fluid (1:5, v/v; 12 mL).

Radioassay: All samples, except for tritiated water samples, were counted for 5 min together with representative blanks using a liquid scintillation analyser (Packard 2100-TR) with automatic quench correction by external standard. 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. The tritiated water samples were treated as above, except that they were subject to liquid scintillation counting for 1 min only.

Findings
Prothioconazole 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 the following Table.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- prothioconazole in an EC 275 formulation at the rates of 100 g/L, 1.25 g/L and 0.25 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)					
Dose Levels	Neat formulation: High dose (100 g/L)		Dilution: Intermediate dose (1.25 g/L)		Dilution: Low dose (0.25 g/L)	
Species	Human (n=8)		Human (n=9)		Human (n=10)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Dislodgeable dose (24h)[a]	93.34	7.91	74.87	6.18	59.46	9.61
Donor chamber	1.93	0.81	2.86	1.31	4.11	1.46
Surface Dose (1st two tape-strips)	1.21	0.55	3.67	1.42	5.89	3.37
Total % non-absorbed	**96.50**	**6.72**	**81.40**	**5.49**	**69.46**	**7.69**
SKIN COMPARTMENT						
Skin [b]	***1.75***	***2.10***	7.35	3.39	10.58	5.23
Stratum corneum [c]	2.16	0.97	8.62	2.89	14.67	6.25
Total % at dose site	***3.91***	***2.89***	***15.97***	***4.59***	***25.25***	***7.37***
RECEPTOR COMPARTMENT						
Total % directly absorbed [d]	***0.76***	***1.50***	***0.77***	***0.63***	***2.01***	***1.43***
STUDY: Total % Potentially Absorbable [e]	4.67	4.25	16.74	5.03	27.26	7.96
TOTAL % RECOVERY	**101.2**	**4.19**	**98.14**	**2.25**	**96.72**	**2.03**
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	Yes		No		No	
standard deviation >25%	Yes		Yes		Yes	
recovery <95%	No		No		No	
adjusted: Total % Potentially Absorbable [f]	**5**		**22**		**35**	

[a]: sum of radioactivity found in swabs at 8 h and 24h and on the pipette tip.
[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 dermal penetration through human dermatomed skin of [14C]-prothioconazole in the bixafen + prothioconazole + tebuconazole EC 275 formulation was investigated at three concentrations corresponding to the neat product (100 g /L) and to two representative dilutions (1.25 and 0.25 g/L), respectively.

The mean percentage of prothioconazole in the EC 275 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 4.7% for human skin. Applying the new EFSA guidance this value adjusts to 5%.

The mean percentage of prothioconazole in the EC 275 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 16.7% for human skin. Applying the new EFSA guidance this value adjusts to 22%.

The mean percentage of prothioconazole in the EC 275 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 27.3% for human skin. Applying the new EFSA guidance this value adjusts to 35%.

According to the new EFSA guidance[11] 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 met in the high dose group of 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 [14C]-prothioconazole in the BIX+PTZ+TBZ EC 275 formulation:

- **5% for the neat formulation (100 g/L)**
- **22% for the intermediate dose (1.25 g/L)**
- **35% for the low dose (0.25 g/L).**

As already mentioned above according to the EFSA guidance on dermal absorption[12] the formulation tested and the representative formulation are closely related and thus dermal absorption data from BIX+PTZ+TBZ EC 275 can also be used for the representative formulation BIX+PTZ EC 225. A detailed bridging statement including a comparison of the ingredients of both formulations is provided in the confidential Document JCP.

Prothioconazole-desthio (PTZ-desthio)

For Annex I BCS has submitted *in vivo* dermal absorption data from the rhesus monkey, where PTZ was replaced by PTZ-desthio in an SC 480 formulation (BCS document No: M-083510-01-1). A value of 20% dermal absorption was deemed as being appropriate for the use in non-dietary exposure calculations and is quoted in the EFSA scientific report list of endpoints[13]. For Annex I renewal four

[11] 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.

[12] 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.

[13] EFSA Scientific Report (2007) 106, 1-98, Conclusion on the peer review of prothioconazole.

further *in vitro* studies with human skin have been conducted to strengthen the EU wide accepted value of 20%. These *in vitro* studies were performed independently by Bayer CropScience and by Syngenta with different formulations but following the same study design and using the same Contract Research Organisation ([redacted], UK). The findings from these four studies were subsequently summarised in a position paper to provide a proposal for a default dermal absorption value for PTZ-desthio in spray dilutions for use in non-dietary risk assessments. Evaluations are based on the latest EFSA guidance for dermal absorption[14] with the use of a "Many to One" or "Category"[15] approach. The default value should then be taken in a tier 1 approach in the absence of product specific dermal absorption values.

A summary of the position paper is given below.

Report:	KCP 7.3/02[redacted]; 2015; M-537337-01-1
Title:	A proposal for a default dermal absorption value for prothioconazole-desthio based upon a "Many to One" approach
Report No.:	M-537337-01-1
Document No.:	M-537337-01-1
Guideline(s):	not applicable
Guideline deviation(s):	not applicable
GLP/GEP:	**no**

I. Material and methods

The four human skin *in vitro* studies have all been performed in the same contract research laboratory ([redacted], UK) according to the same study plans.

The general study design used in these studies was to use radiolabelled PTZ-desthio at concentrations representing the highest anticipated spray dilution for the formulation being tested expecting this to exhibit the highest potential dermal absorption. Three studies used EC formulations and one study used an SC formulation.

Each test used 10 replicates from at least 4 different skin donors. The absorption of the radiolabelled test item was assessed by collection of receptor fluid in hourly fractions from 0 to 8 h post dose and then 2 hourly fractions from 8 to 24 h post dose.

II. Findings

The potentially absorbable dermal absorption values calculated according to the latest EFSA guidance for the newly available *in vitro* studies using human skin are presented in Table 7.3-2.

[14] 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.

[15] OECD Health and Safety Publications Series on Testing and Assessment N° 156, Guidance Notes on Dermal Absorption, ENV/JM/MONO(2011)36.

Table 7.3-2: Potentially Absorbable fraction of [^{14}C]-PTZ-desthio after *in vitro* application to human skin in 4 different formulation spray dilutions

Study	[^{14}C]-PTZ-desthio concentration (g/L)	Formulation type	Potentially Absorbable	Composition Source
BCS 1	0.25	EC	**14%**	BCS document No M-296559-03-2
BCS 2	0.25	EC	**20%**	BCS document No M-387587-03-2
SYN 1	0.375	EC	**14%**	Evaluated by CRD under COP 2015/00658
SYN 2	0.375	SC	**11%**	Evaluated by CRD under COP 2014/02183

The dermal absorption values measured for 2 formulation types ranged from 11% to 20%.

These data corroborate the currently used results obtained from the *in vivo* rhesus monkey studies and indicate that the EU wide accepted value of 20% is both appropriate and sufficiently conservative to be used as a default value in non-dietary risk assessments when no product specific dermal absorption values are available and the in-use dilution is not significantly lower than 0.25 g/L.

However, for the representative formulation BIX + PTZ EC 225 a dermal absorption of 14% is used for PTZ-desthio. This value derived from a human *in vitro* dermal absorption study conducted with the formulation BIX+PTZ+TBZ EC 275. According to the EFSA guidance on dermal absorption[16] both formulations are closely related and thus dermal absorption data from BIX+PTZ+TBZ EC 275 can also be used for the representative formulation BIX+PTZ EC 225. A detailed comparison of the ingredients of both formulations is included in the confidential Document JCP. A summary and a conclusion of the study conducted with BIX+PTZ+TBZ EC 275 is provided below:

Report:	KCP 7.3/03 [redacted]; 2014; M-480824-01-1
Title:	The in vitro percutaneous absorption of radiolabelled JAU6476-desthio in the bixafen+prothioconazole+tebuconazole EC 275 formulation lowest concentration in-use spray dilution through human skin
Report No.:	34839
Document No.:	M-480824-01-1
Guideline(s):	OECD Guideline for the testing of Chemicals. Skin Absorption In Vitro Method Guideline 428: (April 2004). OECD Environmental Health and Safety Publication Series on Testing and Assessment No 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004). EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption, EFSA Journal 2012: 10(4): 2665.
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

[16] 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.

Material and methods

Human skin: Source: [redacted] Glasgow.
Number and sex: 5 donors, female.
Anatomical region: Abdomen.
Thickness: 320 to 400 µm.

Test Material:

Non-radiolabelled: Batch: AE 1194888.
Purity = 99.5% w/w.

Radiolabelled: [triazole-UL-^{14}C]-prothioconazole-desthio.
Batch: KML 9567.
Specific activity: 2.45 MBq/mg.
Radiopurity of the formulation: >98%.

Formulation: The formulation used in this experiment was the BIX+PTZ+TZB EC 275 formulation (specification number 102000014326 containing prothioconazole (100 g/L), bixafen (100 g/L) and tebuconazole (100 g/L). It was used at a nominal concentration of PTZ-desthio of 0.25 g/L.

Test system: An automated flow-through diffusion cell apparatus ([redacted], UK) was used. The flow-through diffusion cells were placed in a manifold heated *via* a circulating water bath set to maintain the skin surface temperature at 32°C ± 1°C. The cells were connected to multi-channel peristaltic pumps from their afferent ports with the receptor fluid effluent dropping *via* fine bore tubing into scintillation vials on a fraction collector. The surface area of exposed skin within the cells was 0.64 cm^2. The receptor chamber volume was 0.25 mL. The peristaltic pumps were adjusted to maintain a flow-rate of 1.5 mL/h ± 0.15 mL/h.
The receptor fluid was tissue culture medium containing PEG (*ca* 6%, w/v), glucose (*ca* 1%, w/v), streptomycin (0.1 mg/mL), penicillin G (100 units/mL) and sodium azide (0.01%, w/v). The receptor fluid was degassed by sonication for *ca* 10 min after being made and was stored in a refrigerator set to maintain a temperature of 4°C prior to use on the study.

Skin integrity: Sections of split-thickness skin membrane, *ca* 1.5 x 1.5 cm, were cut and positioned on the receptor chamber of the diffusion cell, which contained a magnetic stirrer bar. The donor chamber was tightened into place with screws and the prepared cells were then placed in the heated manifold and connected to the peristaltic pump. A magnetic stirrer was switched on to mix the contents of the receptor chamber. An equilibration period of *ca* 15 min was allowed while receptor fluid was pumped through the receptor chambers at 1.5 mL/h ± 0.15 mL/h. The effluent was then collected for *ca* 30 min and retained as blank samples for use in the tritiated water barrier integrity assessment.
Tritiated water (250 µL, *ca* 100,000 disintegrations per minute [d.p.m.]) was applied to the surface of each skin sample and the donor chamber occluded. Penetration of tritiated water was assessed by collecting receptor fluid for 1 h and analysing the sample by liquid scintillation counting. The mean d.p.m. applied for the tritiated water was calculated from the mock tritiated water samples taken at the time of dosing. The percentage absorption was then calculated for each skin sample from the 1 h receptor

fluid sample collected. Any human skin sample exhibiting absorption greater than 0.6% of the applied dose was excluded from subsequent absorption measurements. At the end of the 1 h period, residual tritiated water was removed from the skin surface. The skin surface was then rinsed with water and dried with tissue paper. An equilibration period of *ca* 2.25 h was allowed prior to collection of the pre-dose sample which was collected for *ca* 0.5 h.

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

Sampling: The absorption of the radiolabelled test item was assessed by collection of receptor fluid in hourly fractions from 0 to 8 h post dose and then 2 hourly fractions from 8 to 24 h post dose. All receptor fluid samples were mixed with scintillation fluid (10 mL) and analysed by liquid scintillation counting.
At 8 h post dose, the 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 h post dose, each diffusion cell was disconnected from the receptor fluid pump lines. The underside of the skin was rinsed (receptor rinse) with receptor fluid (*ca* 1.5 mL).
The stratum corneum was removed with 20 successive tape strips (3M Scotch™ Magic Tape) and individually placed into 20 mL scintillant vials containing methanol:scintillation fluid (1:5, v/v; 12 mL).

Radioassay: All samples, except for tritiated water samples, were counted for 5 min together with representative blanks using a liquid scintillation analyser (Packard 2100-TR) with automatic quench correction by external standard. 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. The tritiated water samples were treated as above, except that they were subject to liquid scintillation counting for 1 min only.

Findings:
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 the following Table:

Table 7.3-3: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- PTZ-desthio in an EC 275 formulation at the rate 0.25 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)	
Dose Levels	Dilution: Low dose (0.25 g/L)	
Species	Human (n=10)	
	Mean	SD
SURFACE COMPARTMENT		
Skin Excess (24h)[a]	78.80	3.66
Donor chamber	1.75	0.83
Surface Dose (1st two tape-strips)	2.54	1.10
Total % non-absorbed	83.10	3.49
SKIN COMPARTMENT		
Skin [b]	4.14	1.78
Stratum corneum [c]	5.31	1.80
Total % at dose site	***9.44***	2.90
RECEPTOR COMPARTMENT		
Total % directly absorbed [d]	***5.03***	0.98
STUDY: Total % Potentially Absorbable [e]	14.47	3.30
TOTAL % RECOVERY	97.57	2.71
Evaluation according to EFSA Guidance		
absorption >75% within half of study duration	No	
standard deviation >25%	No	
recovery <95%	No	
adjusted: Total % Potentially Absorbable [f]	**14**	

[a]: sum of radioactivity found in swabs at termination and in surrounding swabs.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
[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 dermal penetration through human dermatomed skin of [^{14}C]-PTZ-desthio in the EC 275 formulation was investigated at the lowest spray dilution concentration of 0.25 g/L.

The mean percentage of PTZ-desthio in the EC 275 formulation spray dilution that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours was 14.04% for human skin. Applying the new EFSA guidance this value adjusts to 14%.

According to the new EFSA guidance[17] 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

[17] 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.

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. Neither of these criteria was met and therefore the application of the guidance results in the following values for [^{14}C]-PTZ-desthio in the BIX+PTZ+TBZ EC 275 formulation:

14% for the low dose (0.25 g/L).

As already mentioned above according to the EFSA guidance on dermal absorption[18] the formulation tested and the representative formulation are closely related and thus dermal absorption data from BIX+PTZ+TBZ EC 275 can also be used for the representative formulation BIX+PTZ EC 225. A detailed comparison of the ingredients of both formulations is included in the confidential Document JCP.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

[18] EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption.