Bayer CropScience

Document Title

Summary of the toxicological studies
Bixafen + Fluoxastrobin + Prothioconazole EC 190 (40+50+100 g/L)

Data Requirements

EU Regulation 1107/2009 & EU Regulation 284/2013
Document MCP
Section 7: Toxicological studies

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

Date

2015-12-18

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

CP 7.1 Acute toxicity

BIX+FXA+PTZ EC 190 (40+50+100 g/L) is a fungicide formulation containing 40 g/L of bixafen, 50 g/L fluoxastrobin and 100 g/L prothioconazole.

The acute toxicity of BIX+FXA+PTZ EC 190 has been fully assessed by CRD when the product was first approved under COP2010/01354.

The following acute tests were performed:

LD_{50} oral (rat), LD_{50} dermal (rat), skin irritation (rabbit), eye irritation (rabbit) and skin sensitization (LLNA). Results of all studies are summarized in the following table:

Table 7-1: Summary of acute toxicity studies

Type of study	Results	References
Acute oral rat, female	$LD_{50\ cut\ off}$ > 5000 mg/kg bw	CP 7.1.1/01, M-388101-01-1 [1]
Acute dermal rat, male and female	LD_{50} > 2000 mg/kg bw	CP 7.1.2/01 M-388099-01-1 [2]
Acute inhalation rat (calculation method)	ATE_{mix}: LC_{50} 4.2 mg/L	CP 7.1.3/01
Skin irritation rabbit, female	Not irritant	CP 7.1.4/01 M-388107-01-1 [3]
Eye irritation rabbit, female	Slightly irritant	CP 7.1.5/01 M-388106-01-1 [4]
Skin sensitization test, LLNA in mice, female	Sensitising	CP 7.1.6/01 M-368814-01-1 [5]

Therefore, in accordance with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, the formulation BIX+FXA+PTZ EC 190 is classified and should be labelled as follows:

Skin sensitisation: Category 1
H317 May cause an allergic skin reaction.

Eye irritation: Category 2
H319 Causes serious eye irritation

Acute Toxicity Category 4
H332 Harmful if inhaled

STOT-SE Category 3
H335 May cause respiratory irritation

[1] This study was already submitted in the UK for COP 2010/01354 under Report.No. AT05947.
[2] This study was already submitted in the UK for COP 2010/01354 under Report.No. AT05946.
[3] This study was already submitted in the UK for COP 2010/01354 under Report.No. AT05952.
[4] This study was already submitted in the UK for COP 2010/01354 under Report.No. AT05951.
[5] This study was already submitted in the UK for COP 2010/01354 under Report.No. SA 10126.

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

CP 7.1.1 Oral toxicity

Report:	KCP 7.1.1/01 [redacted]; 2010; M-388101-01-1
Title:	Bixafen+fluoxastrobin+prothioconazole EC 40+50+100 g/L - Acute toxicity in the rat after oral administration
Report No.:	AT05947
Document No.:	M-388101-01-1
Guideline(s):	Regulation (EC) No 1907/2006 (Reach); EEC Directive 440/2008 Part B - Method B.1. tris; OECD 423 (2001); EPA Health Effects Test Guidelines (OPPTS 870.1100); EPA 712-C-98-190 (1998)
Guideline deviation(s):	The test item is a product known to be stable and homogenous in both undiluted and in ready-to-use formulation with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed. The deviation does not limit the assessment of results
GLP/GEP:	**yes**

Material and Methods

The formulation BIX+FXA+PTZ EC 190, a yellow turbid liquid (batch number: 2010-000848) contained the active ingredients bixafen (BYF 00587) at the nominal concentration of 40 g/L (41.50 g/L certified by analysis), fluoxastrobin (HEC 5725 E-ISO) at the nominal concentration of 50 g/L (51.71 g/L certified by analysis) and prothioconazole (JAU 6476) at the nominal concentration of 100 g/L (102.0 g/L certified by analysis).

The test compound was formulated in tap water; the administration volume was 10 mL/kg bw. The test material was administered *per os* first at a single dose (2000 mg/kg) by gavage to 3 fasted female Wistar rats. As no compound mortality occurred three additional animals were treated with the same dose.

Table 7.1.1-1: Acute oral toxicity in female rats

Dose (mg/kg bw)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} cut-off (mg/kg bw)
(1st) 2000	0/3/3	45' - 6h	--	≥ 5000
(2nd) 2000	0/3/3	4h - 6h	--	

*number of dead animals/number of animals with clinical signs/number of animals tested.

Findings

- Mortality: no death occurred.
- Clinical signs: only decreased motility was observed.
- Body weights: there were no toxicological effects on body weights or body weight gain.
- Necropsy: no particular findings.

Conclusion

The acute oral $LD_{50\text{-cut off}}$ of BIX+FXA+PTZ EC 190 formulation in rats was greater or equal to 5000 mg/kg bw.

According to the Regulation (EC) No 1272/2008, the formulation is labeled as follows:
None

CP 7.1.2 Dermal toxicity

Report:	KCP 7.1.2/01 [redacted]; 2010; M-388099-01-1
Title:	Bixafen+fluoxastrobin+prothioconazole EC 40+50+100 g/L - Acute toxicity in the rat after dermal application
Report No.:	AT05946
Document No.:	M-388099-01-1
Guideline(s):	Regulation (EC) No 1907/2006 (REACH); EEC Directive 440/2008 Part B - Method B.3.; OECD 402 (1987); EPA Health Effects Test Guidelines (OPPTS 870.1200); EPA 712-C-98-192, August 1998
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and Methods

The formulation BIX+FXA+PTZ EC 190, a yellow turbid liquid (batch number: 2010-000848) contained the active ingredients bixafen (BYF 00587) at the nominal concentration of 40 g/L (41.50 g/L certified by analysis), fluoxastrobin (REC 6725 E-ISO) at the nominal concentration of 50 g/L (51.71 g/L certified by analysis) and prothioconazole (JAU 6476) at the nominal concentration of 100 g/L (102.0 g/L certified by analysis).

One day before the start of the treatment the back and flanks of 5 male and 5 female Wistar rats were shorn. They received a single dermal dose of 2000 mg/kg bw of the pure liquid test compound applied semi-occlusively. After an exposure time of 24 hours, the fixing bandage and the gauze strip were removed and the treated area was rinsed with tepid water using soap and gently patting the area dry.

Table 7.1.2-1: Acute dermal toxicity in rats

	Dose (mg/kg bw)	Toxicological findings*	Duration of signs	Onset of death after (days)	LD_{50} (mg/kg bw)
Male	2000	0/0/5	--	--	> 2000
Female	2000	0/0/5	--	--	> 2000

* number of dead animals/number of animals with clinical signs/number of animals in the group

Findings

- Mortality: no death occured.
- Clinical signs: no clinical signs were observed.
- Body weights: there were no toxicological effects on body weights or body weight gain related to the test compound.
- Necropsy: no particular findings at the end of the study.

Conclusion

The dermal LD_{50} of the BIX+FXA+PTZ EC 190 formulation was greater than 2000 mg/kg bw for rats.

According to the Regulation (EC) No 1272/2008, the formulation is labeled as follows:
None

CP 7.1.3 Inhalation toxicity

Acute inhalation testing with BIX+FXA+PTZ EC 190 has not been performed. Inhalation toxicity testing with BIX+FXA+PTZ EC 190 is not triggered according to Regulation (EC) No 1107/2009, as well as COMMISSION REGULATION (EU) No 284/2013 because the neat product

- is not a gas or liquefied gas,
- is not a smoke generating plant protection product or fumigant,
- is not to be used with fogging/misting equipment,
- is not a vapour releasing plant protection product,
- is not supplied in an aerosol dispenser,
- is not in a form of a powder or granules containing a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis),
- is not to be applied from aircraft in cases where inhalation exposure is relevant,
- does not contain active substances with a vapour pressure > 1×10^{-2} Pa and is to be used in enclosed spaces such as warehouses or glasshouses.

Furthermore, according to COMMISSION REGULATION (EU) No 284/2013 an inhalation toxicity study only has to be conducted if >1% of the preparation (i.e., the commercial formulation) is inhalable (i.e., particle or droplet size < 50 µm) during application.

- The product BIX+FXA+PTZ EC 190 is not applied as an undiluted product to the fields. Therefore, no particles of respirable size of the neat product can be formed during application.
- BIX+FXA+PTZ EC 190 is applied as a highly diluted spray solution. Due to the intended application rates and dilutions the concentration of BIX+FXA+PTZ EC 190 in the spray droplets in general amount to <1% (corresponding to <0.5% of the active ingredients in the spray droplets).
- Applying the logic of the requirement of COMMISSION REGULATION (EU) No 284/2013 for inhalation toxicity testing to the practical use of BIX+FXA+PTZ EC 190, the inhalability of BIX+FXA+PTZ EC 190 amounts to <1% only due to the dilution of the product in the spray solution. This is below the trigger value for the conduct of an inhalation toxicity study for classification purposes. Furthermore, since it is unrealistic to assume that 100% of the spray droplets are inhalable (requiring solely droplets <50 µm; a value far below 10% can be expected based on measurements of droplet size distribution for standard nozzles), an additional safety factor is given.

Based on the consideration above on particle/droplet size distribution and the low inhalation toxicity of the active ingredients bixafen (LC50 >5.3 mg/L), fluoxastrobin (LC50 >5 mg/L) and prothioconazole (LC50 >4.9 mg/L maximum technically attainable concentration) the product BIX+FXA+PTZ EC 190 has not to be classified and labelled with regard to inhalation toxicity.

Testing of the neat product of the similar formulation FXA+PTZ EC 200 showed moderate toxicity after acute inhalation (M-533854-01-1). The toxicity is most likely caused by a co-formulant contained in both products (FXA+PTZ EC 200 at ca. 45%, BIX+FXA+PTZ EC 190 at ca. 24%). As acute inhalation toxicity data for the co-formulant itself are not available, for BIX+FXA+PTZ EC 190 the ATEmix of 4.2 mg/L has been calculated using the formula for mixtures containing more than 10% of ingredients with unknown acute toxicity. The ATEmix of 4.2 mg/L would require a classification in Acute Toxicity Category 4 according to Regulation (EC) 1272/2008, although the inhalability of BIX+FXA+PTZ EC 190 is considered to be below the threshold for inhalation toxicity testing due to the dilution in the spray solution.

According to the Regulation (EC) 1272/2008, the test article should be labelled as follows:

Acute Toxicity Category 4 H332 (harmful if inhaled)

CP 7.1.4 Skin irritation

Report:	KCP 7.1.4/01 [redacted]R; 2010; M-388107-01-1
Title:	Bixafen+fluoxastrobin+prothioconazole EC 40+50+100 g/L - Acute skin irritation/corrosion on rabbits
Report No.:	AT05952
Document No.:	M-388107-01-1
Guideline(s):	OECD 404 (2002); EEC Directive No. 440/2008; EPA Health Effects Test Guidelines (OPPTS 870.2500), United States, EPA 712-C-98-196 (1998)
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and Methods

The formulation BIX+FXA+PTZ EC 190, a yellow turbid liquid (batch number: 2010-000848) contained the active ingredients bixafen (BYF 00587) at the nominal concentration of 40 g/L (41.50 g/L certified by analysis), fluoxastrobin (HEC 5725 E-ISO) at the nominal concentration of 50 g/L (51.71 g/L certified by analysis) and prothioconazole (JAU 6476) at the nominal concentration of 100 g/L (102.0 g/L certified by analysis).

One day before the test, the fur was shorn on the right and left side from the dorso-lateral area of the trunk of each of the rabbits. A single application to the shorn skin of 3 female albino rabbits of 0.5 ml of the pure liquid test substance was applied to the skin of the animal under a gauzepatch. The treated skin area was approximately of 6 cm^2. After an exposure period of 4 hours, the dressing and patch were removed and the treated area was carefully washed with water.

The individual findings of the treated skin areas at the various observation times are summarized in Table 7.1.4-1.

Table 7.1.4-1: Irritant Effects on the skin (Exposure: 4 hours)

Animal		24 hours	48 hours	72 hours	Mean scores	Response	Reversible (days)
1	Erythema (redness) and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na
2	Erythema (redness) and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na
3	Erythema (redness) * and Eschar formation	0	0	0	0.0	-	na
	Oedema Formation	0	0	0	0.0	-	na

Abbreviations: No positive response: mean scores <2.3 = -
Positive response: mean scores ≥2.3 = +
na : not applicable

Findings

There were no systemic intolerance reactions.

Conclusion

Under our experimental conditions, the formulation BIX+FXA+PTZ EC 190 is not irritating to the skin.

According to the Regulation (EC) No 1272/2008, the formulation is labeled as follows:
None

CP 7.1.5 Eye irritation

Report:	KCP 7.1.5/01 [redacted]B; 2010; M-388106-01-1
Title:	Bixafen+fluoxastrobin+prothioconazole EC 40+50+100 g/L - Acute eye irritation on rabbits
Report No.:	AT05951
Document No.:	M-388106-01-1
Guideline(s):	OECD 405 (2002); EEC Directive No. 440/2008; EPA Health Effects Test Guidelines (OPPTS 870.2400); United States, EPA 712-C-98-195 (1998)
Guideline deviation(s):	not specified
GLP/GEP:	**yes**

Material and Methods

The formulation BIX+FXA+PTZ EC 190, a yellow turbid liquid (batch number: 2010-000848) contained the active ingredients bixafen (BYF 00587) at the nominal concentration of 40 g/L (41.50 g/L certified by analysis), fluoxastrobin HEC 5725 E-ISO) at the nominal concentration of 50 g/L (51.71 g/L certified by analysis) and prothioconazole (JAU 6476) at the nominal concentration of 100 g/L (102.0 g/L certified by analysis).

The test was started with one of three female albino rabbits. 0.1 ml of the pure liquid test substance was placed into the conjunctival sac of one eye after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order to prevent loss of the test compound. The other eye, which remained untreated, served as control. The eye was not rinsed for at least 24 hours following instillation. As one hour after treatment no severe irritation was observed two further rabbits were treated as described.

The individual findings of the treated eyes at the various observation times (re-classification of cornea opacity and conjunctival redness) are summarized in Table 7.1.5-1.

Table 7.1.5-1: Summary of irritant effect

Observations Animal 1	24h	48h	72h	Mean scores (24-48-72h)	Reversible (days)
Degree of cornea opacity	2	2	1	1.7 (+)	7
Iris	0	0	0	0.0 (-)	na
Redness conjunctivae	2	1	0	1.0 (-)	3
Chemosis conjunctivae	1	0	0	0.3 (-)	2

Observations Animal 2	24h	48h	72h	Mean scores (24-48-72h)	Reversible (days)

Degree of cornea opacity	2	2	1	1.7 (+)	7
Iris	1	0	0	0.3 (-)	2
Redness conjunctivae	2	1	0	1.0 (-)	3
Chemosis conjunctivae	1	0	0	0.3 (-)	2

Observations Animal 3	24h	48h	72h	Mean scores (24-48-72h)	Reversible (days)
Degree of cornea opacity	2	2	1	1.7 (+)	14
Iris	1	1	0	0.7 (-)	3
Redness conjunctivae	2	2	1	1.7 (-)	14
Chemosis conjunctivae	1	0	0	0.3 (-)	14

Animal 1, 1 h p.a.: test compound adhered to cornea and conjunctiva
na = not applicable
Response: Corneal opacity: mean scores <1 = (-), ≥1 <3 = (+), ≥3 = (++)
Iritis: mean scores <1 = (-), ≥1 <1.5 = (+), ≥1.5 = (++)
Conjunctival redness: mean scores <2 = (-), ≥2 = (+)
Conjunctival oedema: mean scores <2 = (-), ≥2 = (+)

Findings

There were no relevant systemic intolerance reactions.

Conclusion

Under our experimental conditions, the formulation BIX+FXA+PTZ EC 190 is irritating to eyes.

According to the Regulation (EC) No 1272/2008, the formulation is labeled as follows:
Eye irritation Cat. 2 H319 (Causes serious eye irritation)

CP 7.1.6 Skin sensitization

Report: KCP 7.1.6/01 [redacted]; 2010; M-368814-01-1
Title: Bixafen + fluoxastrobin + prothioconazole EC 40+50+100 g/L - Evaluation of potential skin sensitization in the local lymph node assay in the mouse
Report No.: SA 10126
Document No.: M-368814-01-1
Guideline(s): O.E.C.D. guideline 429 (2002)
US-EPA (OPPTS 870.2600 (2003)
Guideline deviation(s): not specified
GLP/GEP: **yes**

Material and Methods

The formulation BIX+FXA+PTZ EC 190, a yellow turbid liquid (batch number: 2010-000848) contained the active ingredients bixafen (BYF 00587) at the nominal concentration of 40 g/L (41.50 g/L certified by analysis), fluoxastrobin (HEC 5725 E-ISO) at the nominal concentration of 50 g/L (51.71 g/L certified by analysis) and prothiconazole (JAU 6476) at the nominal concentration of 100 g/L (102.0 g/L certified by analysis).

Twenty-five female CBA/J mice were allocated to 5 groups of five animals each:
- three groups received the test substance at a concentration of 25%, 50% in vehicle or 100%,
- one positive control group received 30% alpha-Hexylcinnamaldehyde (CAS N° 101-86-0, batch N°: MKAA2596) in vehicle,
- one control group received the vehicle, 1% Pluronic Acid L92® in water.

The test substance and the vehicle were applied on external surfaces of each ear (25 µl/ ear) for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations. On Day 5, the cell proliferation in the draining auricular lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices.

Findings

Table 7.1.2-1 Results of the proliferation assay:

Group Number	Test Group Name	Stimulation Index Values (SI)
1	control in 1% aqueous Pluronic Acid L92®	-
2	Bixafen + Fluoxastrobin + Prothioconazole EC 40+50+100 g/L at 25% in 1% aqueous Pluronic Acid®	3.2 (1.5)
3	Bixafen + Fluoxastrobin + Prothioconazole EC 40+50+100 g/L at 50% in 1% aqueous Pluronic Acid L92®	5.9 (2.1)
4	Bixafen + Fluoxastrobin + Prothioconazole EC 40+50+100 g/L at 100% in 1% aqueous Pluronic Acid L92®	6.6 (1.3)
5	HCA at 30% in 1% aqueous Pluronic Acid®	8.5 (3.3)

No cutaneous reactions were observed in the vehicle, reference control or treated groups.
The stimulation index values of the test substance were 3.2 (±1.5), 5.9 (±2.1) and 6.6 (±1.3) at treatment concentrations of 25, 50 and 100%, respectively.
The stimulation index value of the positive control alpha-Hexylcinnamaldehyde was 8.5 (±3.3) at a treatment concentration of 30%.
Positive lymphoproliferative responses (SI≥3) were noted for BIX+FXA+PTZ EC 190 at all concentrations tested.

Conclusion

The formulation BIX+FXA+PTZ EC 190 was found to be a sensitizing formulation in the Local Lymph Node Assay.

According to the Regulation (EC) No 1272/2008, the formulation is labeled as follows:
Skin sensitization, Cat. 1 H317 (May cause an allergic skin reaction)

CP 7.1.7 Supplementary studies on the plant protection product

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

CP 7.1.8 Supplementary studies for combinations of plant protection products

As stipulated by Part A of Commission Regulation (EU) No 284/2013 (data requirements for plant protection products) this point shall be considered case by case. Whether or not BIX+FXA+PTZ EC 190 is recommended for tank mixing may differ from country to country within the European Union. Hence, this point will be addressed in national addenda post EU re-approval.

CP 7.2 Data on exposure

The non-dietary risk assessment is presented for fluoxastrobin using the representative formulation Bixafen + Fluoxastrobin + Prothioconazole EC 190 (40+50+100 g/L), for the use as fungicide in cereals. The formulation contains the active substance fluoxastrobin (50 g/L). Exposure is estimated using the EFSA guidance on assessment of non-dietary exposure:

> *EFSA, 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014, 2(0):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[6] on the implementation of EFSA's non-dietary exposure guidance document which notes that the EFSA guidance will apply to applications submitted from 1 January 2016. However, for the approval of active substances under Regulation (EC) No 1107/2009 an acute risk assessment is currently not required.

Endpoints relevant for risk assessment:

AOEL:

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

Dermal absorption:

> Dermal absorption was evaluated with the representative formulation (EC 190) *in vitro* using human skin. As a result of the study conducted with the representative formulation (EC 190), the following dermal absorption values are used for the risk assessment based on the critical GAP uses:
>
> - 1% for the concentrate (50 g a.s./L)
> - 9% for an intermediate dose (0.9 g a.s./L
> - 10% for a low dose (0.12 g a.s./L).
>
> For details see CP 7.3.

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

CP 7.2.1 Operator exposure

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

Table 7.2.1-1 Critical GAP for operator exposure evaluations

Crop	F/ G	Application method	Application rate (kg a.s./ha)	Spray volume (l/ha)	Dermal absorption (%)
Wheat, rye, triticale, oats	F	Field crop sprayer	0.0875	100-300	10%
Barley	F	Field crop sprayer	0.075	100-300	10%

F = field; G = greenhouse

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

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

Summary

Table 7.2.1-2: Predicted operator exposure to fluoxastrobin

Crops	F/ G	Application method	PPE	Systemic exposure (mg/kg bw/day)	% of AOEL (0.03 mg/kg bw/day)
Wheat, rye, triticale, oats	F	Vehicle mounted/ trailed boom sprayer	No[1]	0.0038	13
			With[2]	0.0004	1

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

Assessment

Exposure of operators wearing a working coverall but working with bare hands is 13% of the AOEL. Exposure of operators wearing, in addition, protective gloves during mixing/loading and when getting into contact with contaminated surfaces is 1% of the AOEL.

Conclusion

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

CP 7.2.1.1 Estimation of operator exposure

Exposure estimations are made using the EFSA guidance on the assessment of exposure of operators including the EFSA calculator[7] (version: 20 Mar 2015).

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

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

Table 7.2.1.1-1: Summary of operator exposure to fluoxastrobin

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

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate=0.0875 kg / Spray dilution = 0.875 a.s./l a.s. /ha		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 = 1	Dermal for in use dilution = 10	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0061	% of RVNAS	20.28%
	Acute systemic exposure mg/kg bw/day		0.0431	% 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		0.0038	% of RVNAS	12.78%
	Acute systemic exposure mg/kg bw/day		0.0217	% of RVAAS	

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

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

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0875 kg a.s. /ha	Spray dilution = 0.875 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 = 1	Dermal for in use diluation = 10	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0061	% of RVNAS	20.28%
	Acute systemic exposure mg/kg bw/day		0.0431	% 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		0.0004	% of RVNAS	2.34%
	Acute systemic exposure mg/kg bw/day		0.0078	% of RVAAS	

CP 7.2.1.2 Measurement of operator exposure

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

CP 7.2.2 Bystander and resident exposure

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

The critical GAP (cGAP) for resident/bystander risk assessment is presented in Table 7.2.2-1.

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

Crop	Application technique	Max. dose rate (kg a.s./ha)	Spray volume (L/ha)	Max conc. of a.s. in spray (g/L)	Max no. of appl.	Min. spray interval (days)	Dermal absorption (%)
Wheat, rye, triticale, oats	Field crop sprayer	0.0875	100-300	0.875 g/L	2	14	9%

The critical bystander and resident exposure scenario for field crop spray application with off-target drift is the use in wheat, rye, oats and triticale (2 x 0.0875kg a.s./ha in 100 L water). With this use the highest application rate is combined with the lowest water volume yielding the highest concentration of a.s. in the spray. Consequently also appropriate dermal absorption data are used.

Separate calculations for the use in barley – due to lower application rates – are therefore covered and not presented in this dossier.

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

Summary

Table 7.2.2-2: Predicted systemic exposures to fluoxastrobin

Target group	Scenario	Total systemic exposure (mg/kg bw/day)*	% of AOEL (0.03 mg/kg bw/day)
Resident-child	Spray drift	0.0021	7
	Vapour	0.0011	4
	Surface deposits	0.0003	1
	Entry into treated crops	0.0023	8
	All pathways	0.0043	14
Resident-adult	Spray drift	0.0005	2
	Vapour	0.0002	1
	Surface deposits	0.0001	<1
	Entry into treated crops	0.0013	4
	All pathways	0.0016	5

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

Assessment

Mean estimates over all pathways for adult and child resident exposure to fluoxastrobin are 5% and 14% of the AOEL, respectively.

Conclusion

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

CP 7.2.2.1 Estimation of bystander and resident exposure

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

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

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

Table 7.2.2.1-1: Summary of resident exposure to fluoxastrobin

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0875 kg a.s. /ha	Spray dilution = 0.875 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 = 1	Dermal for in use diluation = 9	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	
Resident - child	Spray drift (75th percentile) mg/kg bw/day		0.0021	% of RVNAS	7.10%
	Vapour (75th percentile) mg/kg bw/day		0.0011	% of RVNAS	3.57%
	Surface deposits (75th percentile) mg/kg bw/day		0.0003	% of RVNAS	1.07%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0023	% of RVNAS	7.64%
	All pathways (mean) mg/kg bw/day		0.0043	% of RVNAS	14.36%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day		0.0005	% of RVNAS	1.59%
	Vapour (75th percentile) mg/kg bw/day		0.0002	% of RVNAS	0.77%
	Surface deposits (75th percentile) mg/kg bw/day		0.0001	% of RVNAS	0.31%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0013	% of RVNAS	4.24%
	All pathways (mean) mg/kg bw/day		0.0016	% of RVNAS	5.18%

CP 7.2.2.2 Measurement of bystander and resident exposure

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

CP 7.2.3 Worker exposure

The EFSA guidance on assessment of non-dietary exposure is used. The critical GAP (cGAP) for worker risk assessment is presented in Table 7.2.3-1.

Table 7.2.3-1 Critical GAP for worker exposure evaluations

Crop	F/ G	Re-entry activity	Application rate (kg a.s./ha)	Number of applications	Min. spray interval (days)	Dermal absorption (%)
Wheat, rye, triticale, oats	F	Crop inspection	0.0875	2	14	10%

F = field; G = greenhouse

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

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

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

Summary

Table 7.2.3-2: Predicted worker exposure to fluoxastrobin

Crops	F/ G	Re-entry activity	Clothing scenario	Systemic exposure (mg/kg bw/day)	% of AOEL (0.03 mg/kg bw/day)
Wheat, rye, triticale, oats	F	Crop inspection	No clothing	0.0189	63
			Arms, body, legs covered	0.0021	7

Assessment

Exposure of naked workers to fluoxastrobin (wearing no clothing) is 63% of the AOEL. Exposure of workers wearing one layer of work clothing is 7% of the AOEL.

Conclusion

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

CP 7.2.3.1 Estimation of worker exposure

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

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

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

Table 7.2.3.1-1: Summary of worker exposure to fluoxastrobin

Substance	Fluoxastrobin	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.0875 kg a.s. /ha	Spray dilution = 0.875 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 = 1	Dermal for in use dilution = 10	Oral = 100	Inhalation = 100	
RVNAS	0.03 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0189	% of RVNAS	62.84%
	Working clothing mg/kg bw/day	0.0021	% of RVNAS	7.04%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

CP 7.2.3.2 Measurement of worker exposure

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

CP 7.3 Dermal adsorption

The extent of dermal absorption of Fluoxastrobin formulated as an EC 190 (Bixafen + Fluoxastrobin + Prothioconazole EC 190) formulation was investigated *in vitro* using human skin. A summary of the study is given in the following along with the mean values based on the study results and following application of the new EFSA[8] guidance rules. A conclusion and recommendation regarding the dermal absorption of Fluoxastrobin formulated as a spray dilution of an EC 190 is given below.

Report:	KCP 7.3/01 [redacted] B; 2014; M-486361-01-1
Title:	The in vitro percutaneous absorption of radiolabelled fluoxastrobin in the concentrate bixafen+ fluoxastrobin+ prothioconazole EC 190 formulation and two iIn-use spray dilutions through human skin
Report No.:	34838
Document No.:	M-486361-01-1
Guideline(s):	OECD Guideline for the testing of Chemicals. Skin Absorption In Vitro Method Guideline 428 (April 2004). OECD Environmental Health and Safety Publication Series on Testing and Assessment N° 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004). EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption. EFSA Journal 2012: 10(4); 2665.
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods

Human skin:	Source: [redacted], UK. Number and sex: 10 donors, 1 male, 9 female. Anatomical region: Breast & Abdomen. Thickness: 320 to 400 µm.
Test Material:	
Non-radiolabelled:	Batch: AE 1228646 00 1B99 0001. Purity = 99.5% w/w.
Radiolabelled:	[methoxyiminotolyl-ring -UL-^{14}C]-fluoxastrobin. Batch: KML 9568. Specific activity: 3.7 MBq/mg. Radiopurity of the formulation: >98%.
Formulation:	The formulation used in this experiment was the BIX+FXA+PTZ EC 190 formulation (specification number 1020000123924 containing bixafen (40 g/L), fluoxastrobin (50 g/L) and prothioconazole (100 g/L). It was used at nominal concentrations of Fluoxastrobin of 50 g/L, 0.95 g/L and 0.12 g/L.

[8] 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.

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:

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

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

The study results are presented in Table 7.3-1.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- Fluoxastrobin in an EC 190formulation at the rates of 50 g/L, 0.9 g/L and 0.12 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 (50 g/L)		Dilution: Intermediate dose (0.9 g/L)		Dilution: Low dose (0.12 g/L)	
Species	Human (n=10)		Human (n=9)		Human (n=10)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (total)[a]	94.72	2.70	87.74	5.20	86.56	4.37
Surface Dose (1st two tape-strips)	0.22	0.10	1.77	1.00	1.85	1.00
Donor chamber	0.34	0.14	1.20	1.12	1.24	0.93
Total % non-absorbed	**95.28**	**2.68**	**90.72**	**3.45**	**89.66**	**3.75**
SKIN COMPARTMENT						
Skin [b]	0.30	0.20	2.19	0.93	2.64	1.17
Stratum corneum [c]	0.40	0.11	3.60	2.38	3.73	2.22
Total % at dose site	***0.70***	***0.27***	***5.79***	***2.78***	***6.37***	***3.09***
RECEPTOR COMPARTMENT						
Total % directly absorbed [d]	***0.09***	***0.04***	***0.55***	***0.23***	***1.08***	***0.47***
STUDY: Total % Potentially Absorbable [e]	0.79	0.28	6.16	2.65	7.34	3.08
TOTAL % RECOVERY	**96.08**	**2.92**	**97.06**	**2.01**	**97.11**	**2.36**
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	No		No		No	
standard deviation >25%	Yes		Yes		Yes	
recovery <95%	No		No		No	
adjusted: Total % Potentially Absorbable[f]	**1**		**9**		**10**	

[a]: sum of radioactivity found in swabs at 8h and 24h.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[c]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
[f]: values considered for the adjusted Total % Potentially Absorbable according to EFSA are in ***bold Italics***

SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a.: not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:

The dermal penetration through human dermatomed skin of [^{14}C]-Fluoxastrobin in the EC 190 formulation was investigated at the lowest spray dilution concentration of 0.25 g/L.

The mean percentage of Fluoxastrobin in the EC 190 neat formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours was 0.79% for human skin. Applying the new EFSA guidance this value adjusts to 1%.

The mean percentage of Fluoxastrobin in the EC 190 formulation intermediate dose spray dilution that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours was 6.16% for human skin. Applying the new EFSA guidance this value adjusts to 9%.

The mean percentage of Fluoxastrobin in the EC 190 formulation low dose spray dilution that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a

period of 24 hours was 7.34% for human skin. Applying the new EFSA guidance this value adjusts to 10%.

According to the new EFSA guidance[9] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Neither of these criteria was met and therefore the application of the guidance results in the following values for [^{14}C]-Fluoxastrobin in the BIX+FXA+PTZ EC 190 formulation:

- 1% for the high dose (50 g/L)
- 9% for the intermediate dose (0.9 g/L)
- 10% for the low dose (0.12 g/L)

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document JCP for BIX+FXA+PTZ EC 190).

[9] 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.