

Document Title

Summary of the toxicological studies for Fluopicolide + Fluoxastrobin FS 350 (200+150 g/L)

Data Requirement(s)

Regulation (EC) No 1107/2009 & Regulation (EE) No 284/2013

Document MCP

Section 7: Toxicological studies

According to the Guidance Document SANCO/10181/2013 for applicants on preparing dossiers for the approval of a Chemical active sub-

According to the Guidance Document SANCO/10181/2013 for applicants on preparing clossiers for the approval of achemical active substance

Date

Author(s)

Author(s)

Bayer AG

Crop Science Division





OWNERSHIP STATEMENT

This document, the data contained in it and copyright therein are owned by Bayer AG and/or affiliated entities. No part of the document or any information contained in it. to any third party without the prior written authorisation of Bayer AG applor affiliated entities.

the summaries and evaluations contained in this document are based of unpublished proprietary data submitted for the purpose of the assessment undertaken by the regulatory adhority. Other registration authorities should not grant, amend, overnew a registration on the basis of the summaries and evaluation of unpublished proprietary data contained in this document unless they have received the data on which the summaries asid evaluation are based, either:

• from Bayer AG or respective affiliate; of the proprietary data symmetry of the proprietary data contained in this document unless they have received the data on which the summaries asid evaluation are based, either:

• from other applicants once the period of data projection has expired. The summaries and evaluations contained in this document are based on unpublished propretary data submitted for the purpose of the assessment undertaken by the regulatory authority. Other



Version history

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

It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined at SANCO/10180/2013 Chapter 4. How to revise an Assessment Report 2. The state of the s ersion high



Table of Contents

CP 7.1 Acute toxicity CP 7.1.1 Oral toxicity CP 7.1.2 Dermal toxicity CP 7.1.3 Inhalation toxicity CP 7.1.4 Skin irritation CP 7.1.6 Skin sensitization CP 7.1.7 Supplementary studies on the plant protection products CP 7.1.8 Supplementary studies for combinations of plant protection products CP 7.2 Data on exposure CP 7.2.1 Estimation of operator exposure CP 7.2.1 Measurement of operator exposure CP 7.2.2 Bystander and resident exposure CP 7.2.2 Measurement of bystander and resident exposure CP 7.2.2 Measurement of bystander and resident exposure CP 7.2.3 Estimation of bystander and resident exposure CP 7.2.3 Measurement of bystander and resident exposure CP 7.2.3 Dermal adsorptions CP 7.4 Available toxicological data relating to co-formulants	CP 7	TOXICOLOGICAL STUDIES ON THE PLANT P	ROTECTION PRODUCT	Page
CP 7.1.1 Oral toxicity CP 7.1.2 Dermal toxicity CP 7.1.3 Inhalation toxicity CP 7.1.4 Skin irritation CP 7.1.5 Eye irritation CP 7.1.6 Skin sensitization CP 7.1.7 Supplementary studies on the plant protection product CP 7.1.8 Supplementary studies for combinations of plant protection products				6°
CP 7.1.2 Dermal toxicity CP 7.1.3 Inhalation toxicity CP 7.1.4 Skin irritation CP 7.1.5 Eye irritation CP 7.1.6 Skin sensitization CP 7.1.7 Supplementary studies on the plant protection product CP 7.1.8 Supplementary studies for combinations of plant protection products) 67
CP 7.1.3 Inhalation toxicity CP 7.1.4 Skin irritation CP 7.1.5 Eye irritation CP 7.1.6 Skin sensitization CP 7.1.7 Supplementary studies on the plant protection product CP 7.1.8 Supplementary studies for combinations of plant protection products		Dermal toxicity		∘, °§10
CP 7.1.4 Skin irritation CP 7.1.5 Eye irritation CP 7.1.6 Skin sensitization CP 7.1.7 Supplementary studies on the plant protection product CP 7.1.8 Supplementary studies for combinations of plant protection products		Inhalation toxicity	.1 S	136
CP 7.1.6 Skin sensitization		Skin irritation		
CP 7.1.6 Skin sensitization		Eve irritation		, 70
CP 7.1.7 Supplementary studies on the plant protection product		Skin sensitization		26
CP 7.1.8 Supplementary studies for combinations of plant protection products.		Supplementary studies on the plant reatection production	rct 0 Q	O 30
CP 7.2 Data on exposure				SO.
CP 7.2.1 Operator exposure	CP 7.1.0	Data on exposure		31
CP 7.2.1.1 Estimation of operator exposure. CP 7.2.2 Bystander and resident exposure. CP 7.2.2.1 Estimation of bystander and resident exposure. CP 7.2.2.2 Measurement of bystander and resident exposure. CP 7.2.3.1 Estimation of worker exposure. CP 7.2.3.2 Measurement of worker exposure. CP 7.3.3 Dermal adsorption. CP 7.4 Available exicological data relating to co-formulant.	CP 7.2 CP 7.2 1	Operator exposure		31
CP 7.2.1.2 Measurement of operator exposure	CP 7.2.1	Estimation of operator exposure		31
CP 7.2.2 Bystander and resident exposure. CP 7.2.2.1 Estimation of bystander and resident exposure. CP 7.2.3 Worker exposure. CP 7.2.3.1 Estimation of worker exposure. CP 7.2.3.2 Measurement of worker exposure. CP 7.3.3 Dermal adsorption. CP 7.4 Available exicological data relating to co-formulant.	CP 7.2.1.1	Measurement of operator exposure Q		235
CP 7.2.2.1 Estimation of bystander and resident exposure	CP 7.2.1.2	Bystander and resident exposure.	A . O 4,	
CP 7.2.2.2 Measurement of bystander and resident exposure. CP 7.2.3.1 Estimation of worker exposure. CP 7.2.3.2 Measurement of worker exposure. CP 7.3 Dermal adsorption. CP 7.4 Available toxicological data relating to co-formulants.	CP 7.2.2	Estimation of hystande and revident exposure		25
CP 7.2.3 Worker exposure of the stimation of the stimation of worker exposure of the stimation of the stimation of worker exposure of the stimation o	CP 7.2.2.1	Measurement of hystander and resident exposure		35
CP 7.2.3.1 Estimation of worker exposure	CP 7.2.2.2	Worker exposure		35
CP 7.2.3.2 Measurement of worker exposure	CP 7.2.3	Estimation of worker exposure		35
CP 7.3 Dermal adsorption. CP 7.4 Available exicological data relating to co-formulants.	CP 7.2.3.1	Measurement of worker exposure	4	35
CP 7.4 Available exicological data relating to co-formulants.	CP 7.3	Dermal adsortations		37
	CP 7.3	Available taxicological data relating to co-formulan		61



CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Fluopicolide was included in Annex I to Council Directive 91/414/EEC in 2010 (Commission Directive 2010/15/EU, Entry into Force on June 1, 2010). The expiration of approval of Buopicolide is May 31, 2023 (Commission Implementing Regulation (EU) 2017/1527). The Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer AG (former Bayer CropScience) for the Annex Kinclusion under Council Directive 91/414/EEC are contained in the Draft Assessment Report (DAR) and its Addenda, and are included in the Baseline Dossier provided by Payer AG.

The formulation Fluopicolide + Fluoxastrobin FS 350 (200+150 g/L), abbreviation FLC+ FXA FS 350, is a flowable concentrate for seed treatment formulation (FS) containing 200 g/L of fluopicolide. This formulation is registered in Europe under the trade name Scenic Gold. FLC+ FXA FS 350 was not a representative formulation of Bayer AG for the Annext inclusion of fluopicolide under Council Directive 91/414/EEC.

Fluopicolide (AE C638206) is a fungicidal active substance developed by Bayer It is the only active substance in Europe representing a class of chemistry (pyridin limethy) benzamides with a unique mode of action via delocalization of a spectrum-like protein in the Competers fungi.

Fluopicolide is active against a wide range of Comycete fungi low dose rates against a wide range of Comycete (Phycomycetes) diseases including downy raildews (Pseudoperonospora, Peronospora, Bremia), late blight (Phytophthora). It is also effective against downy mildews and some Pythium species causing damping of at emergence time.

Fluopicolide is redistributed of the x dem and effective disease control can be achieved from foliar and seed applications. Miopicolide is used in mixture in a range of foliar formulations in potatoes, horticultural crops and industrial crops such as oilseed.

Fluopicolide has a long track record of safe use in a large number of targeted crops within industrial crops.

Fluopicolide can be formulated with other active ingredients in different types of formulations to optimise and completed activity.

The development of resistances of Oomycete's against existing, well-established fungicide groups represent a threat for European tarmers by increasing the complexity of their plant protection programs leading to severe economic impacts. With Fuopicolide, formers in EU-27 have access to a modern tool for their integrated crop projection programs, contributing to effective and sustainable management of resistance development and preserving high level of protection against Oomycete diseases.

By reducing the Oorivcete damages, applications of Fluopicolide + Fluoxastrobin FS 350 on target crops contribute to the achievement of orimum emergence ensuring yield and quality, thus securing sufficient supply of high quality oilseed for European consumer destinations and markets abroad, for the processing industry.



CP 7.1 Acute toxicity

Fluopicolide + Fluoxastrobin FS 350 (200+150 g/L) is not acutely toxic via the oral route (LD₅₀ >2000), the dermal route (LD₅₀ >2000) or the inhalation route (LC₅₀ >3.72 mg/L). FLC+FXA FS 350 is not irritating to the eyes or skin, and a mouse LLNA revealed that there was no skin sensitising potential. Overall, no classification for acute toxicity is required for FLC+FXA FS 350.

Table 7.1-1: Acute toxicity studies with FLC + FXA FS 350

Study Type				
	Species	Study Results	Classification by calculation	Reference S
Acute oral toxicity	Rat	LD ₅₀ >2000 mg/kg bw	Not classified	2015; M-53 (\$37-01 1 0 0
Acute dermal toxicity	Rat	LD ₅₀ >2000 mg/kg bw	Not classified	20 5; M-531440-01-1
Acute inhalation toxicity	Rat	4-h, 4 C ₅₀ ≥ 30 2 mg/ MAC	Not classified	\$37527-01-1
Skin irritation	Rabbit	Non-irritant	Not classified	<u>.; 2015;</u> M. 26850@1-1
In vitro eye irritation, ICET		l Moon-irritaant	I Net classified	2013
Eye irritation	Rabbit &	Non-riritant	Not classified	<u>2015;</u> \$2-523295-01-1
Skin sensitisation, LLNA	Mouse	Non-sensitising	Not classified	<u>2015;</u> <u>M-526851-01-1</u>
		Non-sensitising Non-sensitising		



CP 7.1.1 Oral toxicity

	o
Data Point:	KCP 7.1.1/01
Report Author:	
Report Year:	2015
Report Title:	Fluopicolide + fluoxastrobin FS 350 (200+150 g/L) - Active oral toxicity/study in
	the rat (Up and down procedure)
Report No:	15/049-001P
Document No:	M-531437-01-1
Guideline(s) followed in	OECD 425 (2008); Commission regulation (ECONo. 440/2008 OB.1.TRAS (2008);
study:	US-EPA 712-C-02-190, OPPTS 870.1100 (2065)
Deviations from current	none w o v o
test guideline:	
Previous evaluation:	No, not previously submed
GLP/Officially	Yes, conducted under GLP/Whicially recognised terring facilities
recognised testing	
facilities:	
Acceptability/Reliability:	Yes N N N N N N N N N N N N N N N N N N N

Executive Summary

In an acute oral toxicity test, following the up and down procedure, 5 fasted female Wistar rats, were given a single oral dose (gavage) of FLC + XA FS 350 (specification 192000928578 containing 198.7 g/L fluopicolide and 148.40g/L Fluoxastrobin) wixed with a distilled water vehicle at the limit dose of 2000 mg/kg bw, and we're observed for 14 days. There were no mortalities. Decreased activity and vocalisation was observed in 45 animals, hunched back position was noted in 45 animals, piloerection was noted in 1/5 animal. All animals recovered within approximately 24 hours post treatment.

There were no treatment related effects on body weight, and no gross pathological findings at necropsy.

In this well-conducted Study FLC +JXAJ 350 was found to be of a low order of acute oral toxicity in female rats.

In female rats Oral LD > 2000 mg/kg bw

OFCD test guidelines and was conducted to GLP. The study follows current

laterial and Methods

Materials A.

Fluoxastrobin FS 350 (200-picolide (AE €638206) – 17.0 % w/w Fluoxastrobin FIEC 5725 E-iso) – 13.1 % 2014-914396, specification 102000028578 Fluoricolido + Fluoxastropin FS 350 (200+150 g/L) Florpicolide (AE C638206) – 17.0 % w/w (198.7 g/L)

Fluoxastrobin (HEC 5725 E-iso) – 13.1 % w/w (148.4 g/L)



2. Vehicle and/or positive control

Vehicle: Distilled water

3. Test animals

Rats, female Species: Strain: CRL:(WI) 8-10 weeks Age: Weight at dosing: 192 - 204 g

Source:

Acclimatisation period:

Ssniff® SM R/M "Antoclavable complete thet for rats and mice – breeding and maintonance" produced by Ssniff Spezial diaten.

Water quality analysis performed every 3 members. Diet:

Water:

Housing: Type II polypropylene polycarbonato

Temperature: 19.1 – 23.4 % 41 – 64 %C Humidity:

15-20 aj Exchanges/hom Air changes:

Photoperiod: 12 hours dail from 6.00

В. Study design

1. In life dates: 03 to 31 March

2. Animal assignment and theatment

5. Temales No. of animals (group $\sqrt{2000}$ mg/kg bwDose(s) Exposure Once Via gavage Post exposure observation period

FLC + FXA FS 350 was tested for acute stal toxicity by dosing 8 female rats with a single oral dose of 2000 mg/kg mixed in distilled water, stirred with a magnetic stirrer up to the finishing of the treatment. The dose volume was 10 mL/kg bw. The animals were facted overnight prior to treatment. Water was still available and libituar overnight and food was returned hours after treatment.

C. Methods

1. Observations

Clinical examination of the bellaviour and general condition all rats were monitored regularly in the 6 hours after treatment and then chested daily during the 14-day observation period after dosing. All animals were weighed before treatment and on days 7 and 14.

Macroscopic examinations were carried out on all animals at sacrifice. After examination of the external appearance, the cranial, thoracic and the abdominal cavities were opened, and the organs and the tissues were observed.



II. Results and Discussion

A. Results

1. Dose-response table (LD₅₀)

The results of the study for acute oral toxicity in the fasted rat, are summarized in Table 7.1.1- Welo

Table 7.1.1-1: FLC + FXA FS 350 - Acute oral toxicity study in rats – mortality and clinical signs

Sex	Dose (mg/kg bw)	Number animals*	Duration of signals	LA 50 (mg/kg by	
Females	2000	0/5/5	₹24 h		

Number of animals which died/number of animals with inical signs/mber

2. Clinical signs

There were no mortalities. Decreased activity was been a find a saning as, vocalisation was noted in 4/5 animals, hunched back position was noted in 5/5 animals, pileerection was noted 11/5 Alimal XII animals recovered within approximately 24 hours post treatment.

3. Body weights

Body weight and body weight cain of the surviving mimals strain of rats.

4. Necropsy findings

No macroscopic findings were no

III. Conclusions

Under these test conditions the oral D₅₀ OFLC FXAFS 350 in female rats was >2000 mg/kg/bw. FLC + FXA FS 3500s concluded to be of a low order of acute oral to ricity.

Assessment and conclusion by applicants

This study was conducted to GFP and follows current OECD test guidelines.

The oral LD₅₀ of FLQ+ FXX FS 350 g/L was to be greater than 2000 mg/kg bw in female Wistar according as a gives no classical according and a gives no classical according a gives no classical according and a gives no classical according a gives no classical according and a gives no classical according a give a rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

Using the calculation method also gives no classification for acute oral toxicity.



CP 7.1.2 Dermal toxicity

	0
Data Point:	KCP 7.1.2/01
Report Author:	
Report Year:	2015
Report Title:	Fluopicolide + fluoxastrobin FS 350 (200+150 g/L) - Acute dermal toxicity study
	in rats
Report No:	15/049-002P
Document No:	M-531440-01-1
Guideline(s) followed in	OECD 402 (1987); US-EPA 712 -98-192, OPP S 870.1200 (1998);
study:	Commission Regulation (EC) 440/2008 (2008)
Deviations from current	none of the second of the seco
test guideline:	
Previous evaluation:	No, not previously submitted
GLP/Officially	Yes, conducted under GLP/Oblicially recognised testing facilities
recognised testing	
facilities:	
Acceptability/Reliability:	Yes N N N N N N N N N N N N N N N N N N N

Executive Summary:

were given a single dermat dose of FLC + In an acute dermal toxicity test groups of Wistar rate 5/sex FXA FS 350 (specification 102000028578 containing 1987 g/L fluopicolide and 148.4 g/L fluoxastrobin) 2000 mg/kg/bw, was applied unduted to shaven unbroken skin in an area of 5 x 5 cm. The skin was covered in a semi-occlusive dressing. The test item was removed by washing 24 hours after dose administration and the animals were observed for 14 days.

There were no mortalities no clinical signs of toxicity no local dermal signs, no effects on body weight and no findings at recropsy.

In conclusion LC + XA S 350 was found to be of you other of acute dermal toxicity following exposure in rats.

In rats Dermal LD₅₀ > 2000 mg/kg bw in both sexes

The study was conducted to OLP and follows the current OECD test guidelines (the use of more animals than currently recommended, and no dose range study dias no impact on the validity of the test).

A. Materials

1. Test material

Fluorastrobin (HEC 5725 E-iso) – 13.1 %, 2004-0143-96, specification 102000028578 fluoricolide + fluorastrobin FS 350 (200+150 g/L) Test substance:

Purity: Fluopi@olide, (AE C6\(\)8206) – 17.0 % w/w (198.7 g/L)

Fluca astrobin (HEC 5725 E-iso) – 13.1 % w/w (148.4 g/L)



2. Vehicle and/or positive control

Vehicle: None

3. Test animals

Species: Strain: Age: Weight at start:

Source:

Acclimation period: 5 days

Identification:

Diet:

Water:

Housing:

Temperature:

Humidity:

Air changes:

Photoperiod:

B. Study design

1. In-life dates: 31 March to 14 A

2. Animal assignment and treatment

No. of animal group size)

Dose(s) Exposure

Post exposure observation period

5 days
Cage cards and individual markings
Ssniff* SM R/M "Autodavable complete diet for rats and pace – breeding and maintenance" produced by Ssfiff Spezialdiajen
Available ad libitum.
Type II polypropytene/polycarbonate
0.1 – 24.4 °C
8 – 58 %
5-20 air exchanges/hour
-hours

or acute dential toxicity by 86sing 5 **
ag/kg undidited test substance
yal body surface) apreh on the skipte
by use FLC + FXA FS 350 was tested for acute derival toxicity by cosing 5 male and 5 female Wistar rats with a single dermal dose of 2000 mg/kg undouted test substance. The back of the animals was shorn (approximately 10% area of the total body surface) approximately 24 hours prior to the treatment. Only animals without injury or irritation on the skin were used in the test. The test substance was applied to an area dapproximately 5 x 2cm by use of a gauze pad which remained in contact with the skin during as washed off with v the 24-hour exposure period by a parch attached with adhesive hypoallergenic plaster. During this time, the entire trunk of each animal was wrapped in semi occlusive plastic wrap. At the end of the exposure period the test item was washed off with water.



C. Methods

1. Observations

Clinical examinations were performed on the day of treatment, at 1 and 5 hours after the application of the test item, and once each day for 14 days thereafter. Observations included the skin and fur. eyes and mucous membranes, and also respiratory, circulatory, autonomicand central hervolos system, and somatomotor activity and behaviour patterns. Particular attention was directed to the observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep, and coma. Adverse sking reactions at the site of application were recorded following the removal of the dressing. Body weight was recorded on day 0, day 7 and day 14.

2. Necropsy

Animals were sacrificed at the end of the study and subject of a macroscopic examination including cranial, thoracic, and abdominal cavities were opened and the appearance of the tissues and organs were observed. Any gross macroscopic findings were recorded

esults and Discossion

A. Results

FLC + FX/CFS 350% acute derma Proxicity study in rats – mortality and clinical signs Table 7.1.2- 1:

Dose (mg/kg bw)	Toxicological results * Duration of signs Time of death	(14 days)
	Malerats of the second	
2000	V 10/0/5 8 N/A N/A N/A N/A	> 2000
ڎ		
2000	Ø0/5	> 2000
* Number of anima	als which died/number of animals with chinical signs/number of animals	used.

2. Clinical signs

ins noted in any animals throughout the study. There were no deat

3. Body weights

There were effects on body weight in any anima

4. Necropsy findings

did not reveal any treatment-related changes.



III. Conclusions

Under these test conditions the dermal LD₅₀ of FLC + FXA FS 350 in male and female rats was >2000 mg/kg/bw. FLC + FXA FS 350 is concluded to be of a low order of acute dermal toxicity.

Assessment and conclusion by applicant:

This study was conducted to GLP and follows OECD test guidelines (any minor deviations have no impact on the validity of the test). The dermal LD₅₀ of FLC + FXA FS 350 g/L was to be greater than 2000 mg/kg bw in male and female rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

Companion for acute dermal toxicity. Using the calculation method also gives no classification for acute dermal toxi

CP 7.1.3 Inhalation toxicity

Data Point:	KCP 7.1.3/01
Report Author:	
Report Year:	2015 Acute in Quilation toxicity study (nose-only) in the rat with fluggicolide
Report Title:	Acute invalation toxicity study (nose-only) in the rat with fluor colide.
	fluoxastrobing 350 (200+150 g/L)
Report No:	15/939-004 Py
Document No:	IM ² ₹3.753Ø ₇ .01 ₂ 1 & √
Guideline(s) followed in \(\square\$	©ECD 403 (2009); US EPA OPPTS 870.1300 (1998), EC 440/2008, Annex Part
study:	(B, B ₂) (2008)
Deviations from current	I nome of the second se
test guideline:	
Previous evaluation	Mo, not previously submitted \(\) \(\) \(\) \(\) \(\) \(\)
GLP/Officially orecognised testing	Yes, conducted under GLP Officially recognised testing facilities
recognised testing	
facilities: 🔍 🔍	
Acceptability/Reliability	Yes

Executive Summar

In an acute inholation oxicity study group of Wistar rats (5/sex), were exposed by the inhalation route to FLC + FXA FS 350 (specification 100000008578 containing 198.7 g/L fluopicolide and 148.4 g/L fluoxastrobin) in air for 4 hours to nose only at the maximum attainable concentration of 3.72 mg/L. The test term was administered as a 60% few water formulation and was administered as an aerosol achieving a MMAD of 3.84 µm with a 68D of 3.98. Animals were observed for 14 days following exposure.

One male died on day 12 of the study. All other animals survived to study termination. Clinical signs during exposore were laboured breathing in all animals, which had resolved by the end of day 1. Wet fur, ruffled für and red-bown staining resolved by day 3 and considered to be related to the restraint and exposite conditions but not toxicologically relevant. Body weight loss was seen in both sexes during the first week of the study, but all animals gained weight by the end of the study (including the animal that Gued on day 12). No gross findings were reported at necropsy with the exception of the animal which died which had an enlarged uneven spleen, discolouration of the lungs, and red liquid material h the perianal fur. The cause of death could not be determined.



In conclusion FLC + FXA FS 350 was found to be of a low order of acute inhalation toxicity following 4 hours exposure in rats.

Inhalation $LC_{50} > 3.72 \text{ mg/L}$

The study was conducted to GLP and follows OECD test guidelines.

I. Materials and Methods

1. Test material

Test substance: fluopicolide + fluoxastrobin FS 350 (200+150 CL)

Purity: Fluopicolide (AE C638206) – 67.0 % w/w

(198.7 g/L)

Fluoxastrobin (HEC 5725 \$\infty\$-iso) - 13.1 \$\infty\$ w/w \$\infty\$48.4 g/l

Batch no.: 2014-014396, specification 102000028578

2. Vehicle and/or positive control

Vehicle: Distilled water

3. Test animals

Species: Rat Strain: CRI (WI) CAge: 11 Weeks

Age: 11 weeks 40g females 40g females

Source: Wain study 357-407 g (males) and 254-271 g (demales). Acclimation period: 29 days for highling study, 33 days for main study.

Diet: Smiff® SM R/M "Autoclavable complete diet for rots and mice – breeding and

Phaintenance Toroduced by Saniff Spezial Paten

Water quality analysis performed every 9 months

Housing: Type II polypropylene/polycarbonate@

Temperature: 7.9 – 6.4 °C

Humidity: 44 – 67 %

Air changes: At least 15 air exchanges hour

Photoperiod: Phour daily from 6.00 a.m. to 6.00 p.m

B. Study design

1. In-life dates: 1. In the dates: 01 to 29 July 2005

2. Animal assignment and treatment

No. of animals (group size) 5/sex

Dose(s) S 2 2 198.7 g/L fluopicolide and 148.4 g/L fluoxastrobin

Exposure 4 hours, nose-only

Post exposure observation period 14 days

The arimals were exposed to an atmosphere of the test item for a single, continuous four-hour period, generated according to the system and flow rates determined during the technical trials. One male and female were used for a preliminary sighting study, followed by 5 males/females used in



the main test. The test item was prepared by homogenization in distilled water and used as a 60% w/w water formulation. The non-volatile component of the test material was determined and found to be 45.80%. Preliminary trials with the test substance were used to achieve the required aerosol concentration of particles with a mass median aerodynamic diameter (MMAD) of 1 to 4 µm, with a geometric standard deviation (GSD) in the range of 1.5 to 3. Particle size was measured from the animals' breathing zone using a cascade impactor (determined 3 times during the exposure perfed). The animals were exposed to the test substance under positive pressure and held in polycarbonate restraint tubes which allowed only the animals nostrils to enter the exposure port. The est item was aerosolized using a stainless-steel concentric jet nebulizer (TSE Systems GmbH, Pad Homburg, Germany), with the flow controlled by a syringe pump. Airflows and pressure were constantly monitored and controlled by a computer system to ensure uniform distribution. The test atmosphere was sampled at regular intervals (every 10 to 20 minutes) during the exposure period to determine the test atmosphere concentration.

C. Methods

1. Observations

Animals were checked hourly during exposure for clinical signs and morbidity. During the 4-day post-treatment period animals were checked for morbidity twice daily, and once taily for clinical signs. Body weights were recorded prior to treatment and on days 3,3,7 and 14

2. Necropsy

At the end of the study the animals were sacrificed and subjected to a gross purhology examination of the abdominal and horacic cavities.

, II. Results and Discussion

A. Test Atmosphere Concentration

The achieved test atmosphere is shown in the table below and meets the acceptability requirements of the OECO test guideline.

Table 7.1.3-1: JLC + FXA F 350 - acute inhalation study - exposure conditions

Parameters	Sighting Study	Main Study
Flow rate (L/min)	at least 0.5L/min	
Actual concentration (me/L) ± standard@eviation	4.08 ± 0.24	3.72 ± 0.24
Particle size (μm) MAOAD ¹	3.90	3.89
Geometric standard Deviation (GSD)	2.05	1.98
Inhalable Fraction (% Sum)	51.3	51.6
¹ Mass median aerodynamic diameter		



B. Mortality

One male in the main study died on day 12 (see table below). There were no other deaths.

Table 7.1.3- 2: FLC + FXA FS 350 - acute inhalation study in rats – mortality and clinical signs.

Sex	Mean Achieved Concentration (mg/L)	Toxicological results *	Onset and Duration of signs (day)	Time of death (day)
		Sighting stud	YO L	
Male	4.08	0/1/1	0-80	
Female	4.08	0/1/1	1	
		Mainostudy	Y . W	
Male	3.72	1/ 5 /5		
Female	3.72	0/3/5	© 00-1 °C	
Number of ani	mals which died/number of	f animals with chinical sig	ns/number of animals used	

C. Clinical Observations

In the sighting study laboured respiration (slight) to moderate phoisy respiration (slight), and decreased activity (slight) were recorded in the male animal during and after the exposure, while laboured respiration (slight) was observed in the female animal during exposure. From Day 2 to Day 8 fur loss on the left cheek was recorded in the male animal.

In the main study laboured respiration (slight to moderate) was recorded in a main also while noisy respiration (slight) was recorded in two males during the exposure. During the observation period, no clinical signs were detected except wo males having laboured respiration (slight) in Day 1.

Wet fur, ruffled fur or red-brown staining (as chromodacry or hea) occurred elsewhere in study animals from Day 0 up to Day which were considered to be related to the restraint and exposure procedures or discomfort of the amonals but not to be toxicologically significant.

D. Bodwweight

In the sighting study no body weight effects were seen in the female. In the male moderate body weight loss (8.2%) was recorded in Day 1 and body weight gain was observed from Day 7.

In the main study nanimal body weight loss (0.8-6.7 %) was recorded during the first week of the observation period in both males and females and all animals had body weight gain by the end of the observation period except the animal bound read on Day 12, but the body weight of this animal also exceeded its initial body weight at the time of its death.

E. Necropsy

No macroscopic fundings attributable to the test item were seen in the animals that survived to termination. In the animal that died on day 12 a specific cause of death could not be determined. Macroscopic fundings in the dead male were dark/red discolouration of the non-collapsed lungs, enlargement of the spleen with uneven surface and red liquid material at the perianal fur.



III. Conclusions

In this well conducted GLP study and guideline compliant study, acute inhalation LC₅₀ of FLC + FXA FS 350 g/L in the Wistar rats was greater than the maximum achievable concentration of 3.72 mg/\(\mathbb{Z}\)(4hour nose only exposure).

Assessment and conclusion by applicant:

This study was conducted to GLP and follows current OECD test guidelines.

The inhalation IC₅₀ of FLC + FXA FS 350 g/L was 3.72 mg/L male and female wistar was (four hours nose-only exposure to liquid aerosol), the highest attainable concentration.

Thus, no classification is required according to Regulation (EC) No. 1232/2008

Using the calculation method also gives no classification for wrute inhalation to

CP 7.1.4 Skin irritation

Data Point:	IKCP 7.1.4/61 & & V ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~
Report Author:	
Report Year:	2015 @ 4 6 4
Report Title:	Fluoricolide fluorastrobin FS 35 (200-030 g/b) - Acute skin Oritation study in
	rabbits & D & W Y Y Q
Report No:	425/049-906N A A A A A A A A A A A A A A A A A A A
Document No:	<u>M-524,850-Q1-I</u>
Guideline(s) followed ju	OEO 404 (2002); Compussion Regulation (EC) No 441 (2008, B.4 (2008); US-
study:	OESD 404 (2002); Compulsion Regulation (ECN) o 440 (2008, B.4 (2008); US- EPA 712 (2-98-106, OPD S 870 (2500 (1998)
Deviations from current	Prone A A A A A A
test guideline:	
	No not proviously Juhmittad
Previous evaluation:	W not picy found as a substitute of the substitu
GLP/Officially	Yes, conducted under LP/Officially recognized testing facilities
recognised testing facilities.	
Acceptability/Reliab ty:	Asses 25 20 20 20 20 20 20 20 20 20 20 20 20 20

Executive Summar®

Executive Summary

In a primary skin irritation study 3 may New Zealand rabbits were exposed via the dermal route to 0.1mL of ordiluted FLO+ FXAFS 350 (specification 102000028578 containing 198.7 g/L fluopicolide and 148.4 g/L fluoxastrobin) per animal. The test material was applied to an area of 10 x 10 cm of clipped skin by use of a ganze pad field in place in a plastic wrap. 4 hours later the dressing was removed, and the test item washed off with water. Local signs of irritation were scored 1, 24, 48 and 72 hours after treatment using the Draine scheme. There were no signs of erythema or oedema at the application sites in any of the rabbits at any of the time points.

In this study, FLC + FSA FS 350 was not irritating to the skin in rabbits according to the Draize classification system.

The study was condicted to GLP with no significant deviations from OECD test guidelines.



I. Materials and Methods

A. Materials

1. Test material

Test substance: fluopicolide + fluoxastrobin FS 350 (200+150 g/L)

Purity: Fluopicolide (AE C638206) – 17.0 % w/w

(198.7 g/L)

Fluoxastrobin (HEC 5725 E-iso) – 13.1 % w/w (148/4 g/L)

Batch no .: 2014-014396, specification 102000028578

2. Vehicle and/or positive control

Vehicle: None

3. Test animals

Rabbit (3 males Species: New Zealand Won Strain:

Age: 17 weeks Weight at start: 3.6 to 3.9 kg Source:

Acclimation period: Not stated

UNI diet for rabbits produced by Cargill Takamany Zr., H-5300 Karcag, Diet:

Madarasi road 0399, Hungary and libitum.

Water: Municipal tap water, of for human consumption, ad libiture

Individually Yoused in ASALAC approved motal with rabbit cages. Housing:

Temperature:

Humidity:

Air changes: east 15 air Exchanges/hour

5 air exchanges/hour psh. Jaily, from 6.00 a.m. to 6.00 psh. Jaily 5015 Photoperiod:

B. Study design

1. In-life dates:

2. Animal assignment and treatment

No. of a mals (group size)

Dose(s)

4 hours, comi-occlusive 4 days Exposure

Post exposure observation period

The hair was femoved from back and flanks of the rabbits with an electric clipper. 24 hours later 0.5 mL of the test item was applied undiluted by applying to a 10 x 10 cm gauze pad applied to the clipped skin and attached using adhesive hypoallergenic plaster. The entire trunk of each animal was then wrapped with plastic wrap held in place with an elastic stocking. 4 hours later the dressing was removed, and the test item was removed with water. Initially only one animal was treated. As no irritant effect was observed after I houghe test was completed with the remaining 2 animals.



C. Methods

1. Observations

Local signs of irritation were recorded 1, 24, 48 and 72 hours after treatment and scored for erythema and oedema using the Draize scoring system. The irritation was classified according to the following criteria:

P.I.I. = 0 Non-Irritant

 $0 < P.I.I. \le 2$ Mild irritant

 $2 < P.I.I. \le 5$ Moderate Irritant

5 < P.I.I. Severe Irritant

II. Results and Discussion

1. Dermal reactions

The observed dermal reactions for each animal, and the mean scores foo 24, 48 and 72 hours for each animal are provided in the Table 7.1.4-1 below:

Table 7.1.4- 1: Dermal irritation sores

Animals	Observations after patch 1h 24h 48h 72h Mean scores
Identification	removally ~ 1
Animal 1 (1864)	Erythema (redness) and eschar formation 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
, ,	Oedema formation
Animal 2 (1854)	Exphema oredness and 0 0 0 0 0 0.00 0.00
(1834)	Ocdema formation 0 0 0 0 0 0 0.00
Animal® (1844)	Brythema (reducess) and eschar formation 0.00
(10(13)	Oedema formation 0 0 0 0 0 0.00

Erythema criteria for Passification \$2.3

Oedema criteria for classification > 2

Score for erythema and oederna: 0 to irritation; 1 questionable; 2 = slight; 3 = pronounced;

 $4 = \text{severe} \ \ll$

III. Conclusions

Under these test conditions FLC* FXAFS 350 was not irritating to the skin in a guideline compliant and GLP test conducted in rabbits.

Assessment and conclusion by applicant:

This study was conducted to GLP, with no significant deviations from current OECD test guidelines.

FLO + FLOA FS 550 gal was not a skin irritant in the rabbit. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

Using the calculation method also gives no classification for skin irritancy.



CP 7.1.5 Eye irritation

D + D : +	W.CD 7.1.5/01
Data Point:	KCP 7.1.5/01
Report Author:	
Report Year:	2015
Report Title:	Fluopicolide + fluoxastrobin FS 350 (200 + 150 g/L) - Invitro eye irritation test
	isolated chicken eyes
Report No:	15/049-038CS
Document No:	<u>M-521709-01-1</u>
Guideline(s) followed in	OECD 438 (2013); EU Commission Regulation (CC) No 1272/2008 (2008); EU
study:	Commission Regulation (EC) No 152/2010 (2000), Method B 48; USEPA 712-
	C-98-195: OPPTS 870.2400 (2998)
Deviations from current	none A A A
test guideline:	
Previous evaluation:	No, not previously submitted of the subm
GLP/Officially	Yes, conducted under GLP officially recognised testing facilities
recognised testing	
facilities:	
Acceptability/Reliability:	Yes Q V V V V V V V V V V V V V V V V V V

Executive Summary:

In an in vitro eye irritation study, 30 µL of andiluted FLC + FXA FS 350 (specification 102000028578 containing 198.7 g/L fluopicolide and 138.4 g/L fluoxastrobin) was applied onto the surface of the cornea of 3 isolated chicken eyes for a period of 10 seconds then washed off with saline. The eyes were evaluated for corneal spacity and corneal thekness prior to treatment and at 30,75, 120, 180 and 240 minutes after the post-treatment rinse. Floorescent retention was measured prior to treatment and 30 minutes after the post-treatment Phse. A further 3 eyes treated with physiological saline and 3 eyes treated with a positive control underwent the same treatment and evaluation procedure to confirm the validity of the est.

In this study, FLC + FXAFS 350 was not corrosive isolated chicken eyes.

The study was conducted to TLP with no significant deviations from OECD test guidelines. The positive response in the positive control and negative response in the negative control confirmed the validity of the test

A. Materials

1. Test material

fluopicolide + fluoxastrobin FS 350 (200+150 g/L) Test substance:

Purity: Fluopic Mide (SE C638206) – 17.0 % w/w

(198Æg/L)«

Fluoxastrobin (HDC 5725 E-iso) – 13.1 % w/w (148.4 g/L)

Batch not 2914-013396, specification 102000028578



2. Vehicle and/or controls

Negative control: Physiological saline (0.9% w/v NaCl)

Positive control: Benzalkonium chloride solution 50% in water (mixed with distilled water to

achieve final concentration of 5% (w/v)

10% (w/v) solution mixed with physiological saline to achieve 2% solution Fluorescein:

The test item formed a suspension in physiological saline Solubility:

3. Test eye collection

Chicken (used for human consumpt Species:

COBB 500 Strain:

7 weeks old Age:

Weight:

Source:

TARANIS Ind. (Address: H-9600 Sárvár, Rábasomjéni út. 1295, Hungary)

Chicken headewrapied in tissue moistened with saline and stored in platic bould 5 foods and stored Storage and transport:

Vin plastic box (4-5 peads per box Q

Heads were processed within 2 hours after collec Preparation of eyes:

B. Study Design

1. In life dates

2. Animal assignment and treatment

The cornea integrity of each eye was checked by applying a small drop of 2% (w/v) fluorescein solution onto the cornea for a few seconds then rinsed off with 20 mL physiological saline. The fluoresceintreated cornea was examined with a hand-field slip lamp or slit-lamp microscope, to ensure the cornea was not damaged. Only was with undamaged cornea were used. The eye-ball was carefully removed from the arbit and placed in a seel clamp and transferred to a chamber of the superfusion apparatus, supplied with physiological saline solution dispping from a stainless steel tube, at a rate of approximately 3-4 drops/minute or 1-0.15 mL/minute Tyes were examined again with the slit lamp microscope and eyes with a high baseline fluorescein staining or corneal opacity score were rejected. The cornea thickness was measured using the death measuring device on the slit-lamp microscope and any with a thickness deviating more than 10% form the mean value for all eyes, or any eye showing other signs of damage were rejected. The selected eye were acclimatized for 45 to 60 minutes. The chambers of the superfusion apparatus were accontrolled temperature (32±1.5°C) during the acclimatization and



Test procedure

At the end of the acclimatization period, a zero-reference measurement was recorded for cornea thickness and opacity to serve as a base line (t=0) for each individual eye. The cornea thickness of the eyes should not change by more than 5% between the -45 min and the zero time. No corneal thickness changes (0.0%) were observed in the eyes. Following the equilibration period, the fluorescein retention was measured. Base line values were required to evaluate any potential test frem-related effect after treatment. All eyes were considered to be suitable for the assay. Three eyes were allocated to the treated group, three eyes to the positive control group and one eye to the negative control group.

The undiluted test item was applied in a volume of 30 μ L on the entire surface of each correct in the treated group. 30 μ L of the positive and negative control solution was applied in a similar manner to the corneas in the positive and negative control groups respectively.

After an exposure period of 10 seconds all the corneas were rinsed with 20 ml of physiological saline

Evaluation

The control and test eyes were evaluated pre-treatment and at approximately 30, 75, 120, 180 and 240 minutes after the post-treatment rinse. Corneal thickness and corneal opacity were measured at all time points. Fluorescein retention was measured on two occasions, at base line (t=0) and approximately 30 minutes after the post-treatment rinse. Haug-Streit Bern 900 sht-lamp microscope was used for the measurements. At the end of the procedures, the corneas were carefully tomoved from the eyes and placed individually into labelled containers of preservative fluid 0.0% neutral outfered formalin) for potential histopathology and stored at room temperature.

AI. Results and Discussion

A. Findings

The mean values of the treated eyes for maximum corneal thickness change corneal opacity change and fluorescein retention change are given in the table below.

Table 7.1.5-4: FLC + FXA F\$350 \(\(\) in vitro veye irritation scores \(\)

-		X X		\cup		<u> </u>	0)		•	
) <u>K</u> j	Pations S					
Treatment	75 M	Corneal ins	& welling \(\frac{2}{3} \)	lins,	Corneal	pacity	Floureso Retenti			Overall
	Mean Max. Swelling	≱ @E	Mean Max. Swelling	O ICEO Class	Mean Max. Corneal	ICE Class	Mean Flourescein Retention	ICE Class	Other Observations	ICE Class
	(%) _{\%}		(%)		Opacity		Retention			
Negative Control (saline)	0.0	1°0° (\$ 0.0 \$		0.0	I	0.0	I	None	3 x I
Positive Control (5% w/v benzalkourum chlotide)	2 A		31.29	Q, , III	3.83	IV	2.83	IV	Loosening of epithelium in 2/3 eyes at 180 and 240 mins post treatment rinse	1 x III 2 x IV
(FLC + SA FS 35)	0.0	I	0.0	I	0.0	I	0.17	I	None	3 x I



III. Conclusions

Under these test conditions FLC + FXA FS 350 was not irritating to the eye in a guideline compliant and GLP test conducted in isolated chicken eyes.

Assessment and conclusion by applicant:

This study was conducted to GLP and follows current OECD test guidelines.

Under the experimental conditions FLC + FXA FS 350 CL is not an eye irritant in crest conducted on isolated chicken eyes. Thus, no classification is required according to Regulation PEC) No. 1272/2008.

Using the calculation method also gives no classification for eye writartoy

Data Point:	KCP 7.1.5/02 A O Q Q O Q
Report Author:	
Report Year:	
Report Title:	Fluopicolide fluoxastrobio FS 350 (200+550 g/L) - Acute eye justation study in
	rabbits & O Y Y Y Y Y Y Y
Report No:	15/049-095N & & & & & & & & & & & & & & & & & & &
Document No:	M-52@295-014
Guideline(s) followed in	OFCD 405 (2012) US-EPA 712-C 98-19 OPP S 870,2400 (1998);
study:	Commission Regulation (EC) N@440/2008, B. (2008)
	prone of the state
test guideline:	
Previous evaluation:	Namot previously submitted y O & Y
<u> V</u>	
Previous evaluation: GLP/Officially	Yes, conducted under GLP/Orncially pecognised testing facilities
facilities:	
Acceptability/Reliability:	Yes o A Sy of S

Executive Summary

In a primary eye or itation study 0.1g of undiffited FLC + XA FS 350 (specification 102000028578 containing 198.7 g/L flyopic orde and 148 4 g/L flyoxastrobin) was instilled into the conjunctival sac of the left eye of 3 male New Zealand White rabbits. The eyes were examined 1, 24, 48 and 72 hours after test substance administration. Irritation was scored using the Draize scheme. There were minimal signs of redness and discharge in the first hour in all animals but this had resolved by 24 hours.

In this study, FLC FXATS 350 was not irritating to the eyes in rabbits according to the Draize classification system.

The study was conducted to GVP with no significant deviations from OECD test guidelines.



I. Materials and Methods

A. Materials

1. Test material

Fluopicolide + fluoxastrobin FS 350 (200+150 g/L) Test substance:

Fluopicolide (AE C638206) – 17.0 % w/w Purity:

(198.7 g/L)

Fluoxastrobin (HEC 5725 E-iso) – 13.1 % w/w (148.4 g/L)

2014-014396, specification 102000028578 Batch no.:

2. Vehicle and/or positive control

Vehicle: None

3. Test animals

Species: Rabbit (3 males

Strain: New Zealand

Age: 14 weeks Weight at start: 3.5 to 3.7 kg/s

Source:

Acclimation period: At least A days

At least \$\mathbb{H}\$ days \tag{\psi} \tag{\ Diet:

Õ

Madarasi road 0399, Hungary, *od libitum*.

Õ

Water: Monicipantáp water, as for human consumption, ad libitum

Housing: Andividually housed in AAALAC approved metal wire rabbit cages.

Temperature! Humidity: 27. - 60%

Air changes:

Photoperiod:

B. Study design

1. In-life dates: 28 Apri

2. Animal assignment and treatment

The pH was found to be 55, so the test rem was permitted for use in animal studies. The eyes of the animals were examined 24 hours before the fart of the study by instillation of fluorescein solution and subsequent examination with a hard slit lamp. Only those animals were accepted to the trial that did not display any changes. Initially only one mimal was treated. As the effects were non-irritant at 24 hours, two further rabbits were treated with the test item.

0.1 mg of the test substance was placed in the conjunctival sac of the left eye of each animal. The unificated eve acted as a control.

Sixty minutes (60 ± 10 min) prior to test substance application, a systemic opiate analysesic was administered subcutaneous injection. Five minutes (5 ± 1.5 min) prior to test substance application, a topical ocular anaesthetic was applied to each eye (including the control eye to ensure direct comparison



of any ocular observations). Eight hours (8 to 9 hr) after test substance application, a systemic opiate analgesic, and a nonsteroidal anti-inflammatory drug (NSAID) were administered by subcutaneous injection.

The eyes were examined 1, 24, 48 and 72 hours after application with fluorescein staining and cored according to the Draize system. Any clinical signs were also recorded. Body weight was recorded on the day of treatment and before sacrifice.

II. Results And Discussion

1. Ocular reactions

No clinical signs of toxicity. Eye irritation scores are shown in the table below. Any organ seen one hour after dosing were reversible 24 hours after treatment.

Table 7.1.5-2: FLC + FXA FS 350 – Eye irritation scores in rabbits

Animal	Time after treatment:	Øh	24h	48h	72h	Mean scores 24-72 hours	F esponse	Reversible (day)
	Corneal opacity	0	0					g n.a.
	Iritis 🔎	2 0		\$ 0 %		0.00	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	n.a.
Animal 1	Redness conjunctivae &		9 5	1	04	20 .00		1*
(19)	Chemosis conjunctivae	20		y 0	ŞÒ,	0.00	, ! Z	n.a.
	Discharge D	2 1 ₀₁) QÇ		00	Ø.00 Ž) } 	1*
	Corneal Tacity	W.	$\sqrt[\infty]{0}$	$\circ 0$	© 0	J 0.00		n.a.
	Pitis O			(A)	0.5	0.00		n.a.
Animal 2	Redness conjunctival	1	% 0	®ŏ	0 0	0.00		1*
(28)	Chemoşis onjunciyvae	0	00	0%	Q	0.00		n.a.
,	Pischarge		~0°	Ø	ð	0.00		1*
	Cornea Copacito	0 0		0)° ′ 0	0.00		n.a.
	Iritis	, O	, D	30	0	0.00		n.a.
Animal 3	Redness conjunctivae	2	× 0 ×	0	0	0.00		1*
(40)\$	Chemosis conjunctiva			0	0	0.00		n.a.
	Discharge		(°)	0	0	0.00		1*

n.a. = not applicable;

^{*} in respect of the result 1 hr post application

N	legative: S		<i>y</i>		
	QQ <1 Q "	18 < 1	R <2	OE <2	Regulation (EC) No 1272/2008 and GHS
A					
N	<u> Íild irritant: (+</u>	•)			
	CO≥1 - <3	IR ≥1 - <2	R ≥2	OE ≥2	GHS category 2B (effects reversible within 7 days)

Irritant: +



_		1		_	1
	CO ≥1 - <3	$IR \ge 1 - <2$	R ≥2	OE ≥2	GHS category 2B (effects reversible within 7 days)
	CO ≥1 - <3	IR ≥1 - <2	R ≥2	OE ≥2	Regulation (EC) No 1272/2008 (GHS) category 2
I	rreversible eff	ect/serious dar	nage: ++		
	CO ≥3	IR ≥2	R -	OE -	Regulation (EC) No 1272/2008 and GHS category 1

2. Bodyweight

Within normal range.

III. Conclusions

Under these test conditions FLC + FXA FS 350 was not irritating to the eve in a guideline compliant and GLP test conducted in rabbits.

Assessment and conclusion by applicant

The study was conducted to GLP with no significant deviations from currence ECLP test guidelines.

Under the experimental conditions FLQ+ FXQ FS 350 g/L was not an expirritary in the rabbit.

Thus, no classification is required according to Regulation (ECFNo. 1272/2008

Using the calculation method also gives not classification for eye initancy

CP 7.1.6 Skin sensitization

Data Dainti	1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1
Data Point:	1 % (P / 1.6/01
Report Autlor:	
Report Year:	2015
Report Title:	Fluopicolide + fluoxastrobin FS 350 (200 + 150 g/L) - Local lymph node assay in
~	the mouse S S S S
Report No:	15/04@037E&
Document No:	M-56851-97-1 >> S
Guideline(s) for lowed in	QCD 429 (2010), Commission Regulation (EC) No 440/2008, B.42 (2008); US-
I study.	PA 772-C-09 197, 90CSPP 970.2600 (2003)
Deviations from current	none of the second seco
test guidenne:	
Previous evaluation:	No, not previously submitted
7	
GLP/Officially	Yes conducted under GLP/Officially recognised testing facilities
recognised testing	
facilities:	
Acceptability/Reliability:	Yes 🛫 🔍

Executive Summary:

In a local symph node assay, FLC + FXA FS 350 (specification 102000028578 containing 198.7 g/L fluopicolide and 148.4 g/L fluoxastrobin) was applied at concentrations of 0, 25, 50 and 100% (w/v) in a volume of 25 μ L to the ears of female CBA/CaOlaHsd mice (5 per dose group). A positive control group was treated with 25% (w/v) α -Hexylcinnamaldehyde. The treatment was applied daily for 3



consecutive days. On day 6 the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine (3HTdR) and the values obtained were used to calculate stimulation indices (SI).

The observed stimulation index values were 2.0, 0.8 and 1.2 at concentrations of 100 % (undiluted), 50 and 25 % (w/v), respectively. As the stimulation index is below the threshold value of 3, the set item is not a skin sensitizer. A stimulation index in the positive control of 8.4 confirms the validity of the assay. Therefore, FLC+FXA FS 350 was not a skin sensitizer under the conditions of this local lymph node assay.

I. Materials and Methods

A. Materials

1. Test material

Test substance: fluopicolide + fluoxastrobin \$8 350 \(\)200+\(\)00 g/\(\)0

Purity: Fluopicolide (AE C6) 8200 – 17:0% w/w

(198.7 g/L)

Fluoxastrobin (QEC 5725 E-36) - 13.1 % Ww (148.4 g/L)

Batch no.: 2014-014396 specification 20200028578

2. Vehicle and/or positive control

Vehicle: 1% aqueous Pluronic PF 200

3. Test animals

Species: SPF female risice, 5 per dose group

Strain: CBA/CaOlaHsd

Age: 9 Weeks &

Weight a start: \$8.6 to \$3.1 Source:

Acclimation period. 14 days

Diet: Sniff SM Ray Mouse – Breeding and Maintenance, "autoclavable

Complete diet for rats/mise – Breeding and Maintenance"by ssniff

Spezialdiaten GmoH, ad libitam.

Water: Wunicipal tap Water as for human consumption, ad libitum

Housing. Individually housed in Type II. polypropylene/ polycarbonate cages

Temperature: 19.4 25.7 C

Humidity: 31 69%

Air changes: At least 15 air exchanges/hour

Photoperiod 12 hours daily, from 6.00 a.m. to 6.00 p.m.

B. Study design

1. In-life dates: 0640 12 May 2015

2. Animal assignment and treatment

Preliminary irritation test



The Preliminary Irritation/Toxicity Test used two doses (2 animals / dose) at test item concentrations of 100 % (undiluted) and 50 % (w/v) in 1% Pluronic. The preliminary experiment was conducted in a similar experimental manner to the main study, but it was terminated on Day 6 and the radioactive proliferation assay was not performed.

Based on the observation of the solubility test, the maximum achievable concentration was 100 g (undiluted).

All mice were observed daily for any clinical signs of systemic toxicity or local irrotation at the application site. Both ears of each mouse were scored for erythema. Ear thickness was also measured using a thickness gauge on Day 1 (pre-dose). Day 3 (before treatment approximately 48 hours after the first dose) and Day 6. Additional quantification of the ear thickness was performed by ear punch weight determination after the euthanasia of the experimental animals.

No mortality or clinical signs of systemic toxicity were observed. Test item precipitate minimal amount of test item precipitate was observed on the ears of the animals in the 100 % (undilited) group on Days 1-5 and in the 50 % (w/v) dose group on Days 1-3. No marked body weight loss 5 % was observed.

The ear punch weights were within the historical control range. There were no indications of any irritancy at the site of application.

The draining auricular lymph nodes of the animals were visually examined they were considered normal in both dose groups (subjective judgement by analogy with observations of former experiments).

Main test

Based on the results of the pte liminary irritation test, the 100 % (undilated) dose was selected as top dose for the main test. Treatments on the main askay were performed as follows:

Table 7.1.6-1: FLC+FXA, \$\overline{\text{FXA}}\) 350 \(\overline{\text{Local Dymph bode assay - Groups and Treatments}}\)

	No. of animals
Negative (vehicle) control (1% Pluronic) Positive control (25% HCA in 1% Pluronic)	
FLC + FXA FS 350 50	5
FLC + FXA FS 350 50 50	

Each mouse was topically desed on the dorsal surface of each ear with 25 μ L of the appropriate formulation applied using a pipette. Each animal was dosed once a day for three consecutive days (Days 1, 2 and 3). There was no treatment on Days 4.5 and 6. On Day 6 each mouse was intravenously injected via the tail voin with 250 μ L of sterile PBS (phosphate buffered saline) containing approximately μ Ci of 3HT R using a gaoge 25G x 1" hypodermic needle with 1 mL sterile syringe. Once injected the none were excised and processed individually to prepare single cell suspensions of lymph node cells. Calls were mixed with scintillation fluid and 3 HTdR incorporation was measured using a 3 HTdR incorporation was measured using a 3 HTdR incorporation was measured using a 3 HTdR incorporation was discontillation counter 4 Tri-Carb 2810 Liquid Scintillation Analyzer by Perkin Elmer), expressed as number of radioactive disintegrations per minute (DPM). Background level DPM was also measured in duplicates by adding 3 mL of 5 % (w/v) TCA solution into a scintillation vial filled with 10 mL of scintillation liquid.

3. Statistics



The results are expressed as disintegrations per node (DPN = DPM divided by the number of lymph nodes) for each animal. Stimulation index (SI = mean DPN of treated group divided by mean DPN of the appropriate control group).

The statistical analysis was performed using the SPSS/PC+ (4.0.1) software package. The heterogeneity of variance between groups was checked by Bartlett's test for the measured DPM values.

Where no significant heterogeneity was detected, a one-way analysis of variance was carried out. If the result was positive, then Duncan's Multiple Range test was used to assess the significance of intergroup differences. Where significant heterogeneity was found, the normal distribution of data was examined by Kolmogorow-Smirnow test. In the case of not normal distribution the non-parametric method of Kruskal-Wallis One-Way analysis of variance was applied. If a positive result was detected, the intergroup comparisons were performed using Mann-Whitney U-test.

A. Results

1. Clinical signs and body weight

and Discussion

Erved Slight Alone There were no deaths. No systemic toxicity was observed. Slight alope in was observed on some of the experimental animals in the 100 % (undiluted) dose group on Days 4.6. Test tem precipitate / minimal amount of test item precipitate was observed on the cars of the animals in the 100 % (undiluted) dose group on Days 1-5, and in the \$5 % (www) groups on Bays 1 and 3 and the 100 % (undilgoed) dose group three out of five animals had more than 5% body weight loss. The mean change of this group was -5.2 %. No other signs referring to systemic (exicity, were observed in this group; also, no marked body weight loss was detected at this dose in the proximinary experiment using two animals. Therefore, the dose levels used in this study are considered to be acceptable for the evaluation. No treatment-related effects were observed on the mean body weight changes of the other groups in the experiment. Prowever marked body weight loss was also defected for one animal in the 50 % (w/v) group and for one animal in the postative control group.

2. Proliferation Assay

The results of the proliferation assay are summarized in the table below. The appearance of the lymph nodes was formal in the pregative control group and in all the test item treated dose groups. Larger than normal lypon nodes were observed in the positive control group.

FEC + IOA F8-350 Local ymph mode assay - DPM, DPN and Stimulation Index

	à	
Test Group V V	√ ≪Mean DPN	Stimulation Index
Background (5% w/v FCA)	~~~ -	-
Negative control (1% Pluroph)	164.9	1.0
FLC + FXA FS 350 100% (w/x)	321.7	2.0*
FLC + FXA F\$ 350 \$0% (w)	137.1	0.8
FLC + FXA S 350 \25% (\sqrt{v})	204.2	1.2
Positive control (25% w/x in 1% Pluronic)	1386.7	8.4**
* = Significant (n@0.05 Mann-Whitney II-test versus n	egative control)	

Mañn-Wh@ney U-test versus negative control)

The test@em was a suspension, which was used undiluted or formulated in 1% Pluronic. Since there were no confounding effects of irritation or systemic toxicity at the applied concentrations, the proliferation values obtained are considered to reflect the real potential of the test item to cause lymphoproliferation in the Local Lymph Node Assay.

⁼ Significant p<0.01 Mann Whitney U-test versus negative control)



The positive control group animals showed a significant lymphoproliferative response (stimulation index value of 8.4) in this experiment. The results of the positive control group demonstrated the appropriate performance of the assay.

The observed mean DPN values for the negative and positive control were within the historical control range.

III. Conclusions

Under these test conditions FLC + FXA FS 350 was not a skin sensitizer in the assay.

Assessment and conclusion by applicant:

The study was conducted to GLP, with no significant deviations from current OECD test guidelines. Under the experimental conditions FLC + FXA ES 350@/L was not a skin sensitive in the local lymph node assay. Thus, no classification is required according to Regulation (EC) No. 1292/2008. Using the calculation method also gives no classification for skin sensitization

The product contains 1,2-Benzis friazol-9(2H)-one and 5-chloro-2-methyl isothing one and 2-methyl-2H isothiazol-3-one both of which are classified as skin sensitisers (#1317) but at levels below the specific concentration limits for classification. These both trigger that the product label should contain the phrase EVH208 'contains 12 Benzisothiazol-3(24) -one and 5-chloro-2-methyl-4-isothiazolin-3-one and 2 meth 2-2H is othiazol-3-one, may produce an altergic reaction'.

Supplementary studies on the plant protection product **CP 7.1.7**

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the source substance (s) of other components in FLC + FXA FS 350 that would require further investigations.

upplementary studies for combinations of plant protection products **CP 7.1.8**

No such studies are necessary since FLC FXA FS 350 is not intended for use in combination with other plant protection products.



CP 7.2 Data on exposure

The safe use FLX + FXA FS 350 to operators during treatment and sowing of seeds has been demonstrated when appropriate PPE is worn. An assessment of worker, resident and bystander exposure is not required as no such exposure is expected during normal use of the product. A combined exposure assessment of both active substances also demonstrated safe use for operators at the first tier and therefore further investigations into combined exposure were not required. A summary of the exposure assessments is presented below, and more detailed calculations are provided in appendix 2

The product information and toxicological reference values used in the assessment are presented in table 7.2-1 below.

Table 7.2-1: Product information and toxicological reference values for the exposure assessment

Product name and code	FLC+FXA FS 350
Formulation type	FS & S & S & S & S & S & S & S & S & S &
Category	Fungicide applied as seed treatment
Active substance(s) (incl. content)	Fluopicolide 200 g/L 2
AOEL systemic	0.07 mg/kg by/d S S O 0.03 mg/kg/fw/d S
Inhalation absorption	
Oral absorption	190%
Dermal absorption	Concentrate: 0.21 % Concentrate: 0.07 % Dilution: 3.59 % (56 g a.s./L) Dilution: 0.73 % (37.5 g a.s./L)
, \$\frac{1}{2}	Dilution: 3,9 % (5,6 g a.s./L))
, "Y	(Based on product (formulation)) (Based on product (formulation))

CP 7.2.1 Operator exposure

CP 7.2.1.1 Estimation of operator exposure

A summary of the exposure prodels sed for estimation of operator exposure to the active substance during application of LC+1XA FS 350 according to the critical use(s) is presented in table 7.2.1-1. The GAP is presented in appendix 1.

Table 7.2.1-1: Exposure prodels for intended uses

Critical use(s)	Oilseed ape (max. 1 Loroduct 100 kg seed)	
Model(s)	Seed ROPEX S	

As stated on the label, FC+FXA FS \$50 is available in pack sizes of 5 to 1000 L. Therefore, the exposure assessment for operators has been conducted with reference to selected pack sizes of 200 and 25 L.

200 L pack size

The input parameters for the estimation of operator exposure (200 L pack size) are presented in table 7.2.12 for suopicorde and table 7.2.1-3 for fluoxastrobin.



Table 7.2.1-2: Input parameters considered for the estimation of operator exposure for fluopicolide (200 L packaging)

Formulation type:	FS		Application technique:		ercial seed
Application rate (AR):	0.2	kg a.s./dt seed		treatme Loading	nt g/sowing()
Seed treated per day:	40	Tonnes/day	Product container size	200	L & S
				Ĉ	(for whole day treatment arge (containers are (assumed)
Amount product handled	400	L/day	Number of loading operations	20	op@ay
Dilution rate:	1	Undiluted (worst case)	Number of calibration operations		Søp/day
Dermal absorption (DA):	0.21	% (concentr.)	Duration of bagging	8,5	hours/day
	3.9	% (dilution)	Nomber of cleaning operations	l (Op/day O
Inhalation absorption (IA):	100	% Q' \\			
Body weight (BW):	60	kg/person			
AOEL	0.07	mg/kg w/d	Duration of loading sowing	100	hours/day

Table 7.2.1-3: Input parameters considered for the estimation of operator exposure for fluoxastrobin (200L pack size)

	_	V		\sim	
Formulation type:	F		Application technique:		ercial seed
	0.15	10 a.s./dt/seed		treatme Loading	nt g/sowing
Amount product handled	400	L/day	Product container size	200	L
					(for whole day treatment large containers are assumed)
Seed treated per day	* 40	tonnes of	Number of loading operations	2	op/day
Dilution rate:	1	Undikuted (wast case)	Number of Calibration operations	1	op/day
Dermal absorption (PA):)0.07	(concentr.)	Duration of bagging	8	hours/day
	0.73	% (dilation)	Number of cleaning operations	1	op/day
Inhafation absorption (IA)	₹00 k				
Body weight (BW):	6Q [©]	kg/person	Duration of loading/ sowing	10	hours/day
AOEL A	9 .03	mag/kg bw/d			

The outcome of the exposure assessment for the 200 L pack size is presented in table 7.2.1-4 below, detailed calculations are presented in appendix 2.



Table 7.2.1-4: Estimated operator exposure 200 L packaging

		Fluopicolide		Fluoxastrobin	
Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL	Total absorbed dose (mg/kg/day)	% of systemic a
Commercial seed treatment Application rate: 1 L product/100 kg seed (200 g fluopicolide/100 kg seed, 150 g fluoxastrobin/100 kg seed)					
Seed	Standard clothing*	0.0725	3 03.52	0.0467	\$\text{Q\$5.59}\$
TROPEX Body weight: 60 kg	with RPE: mask during cleaning	0.0245	34.95	0.0107	\$\frac{1}{2} 35. 50
Seed sowing Application rate: 1 L product/100 kg seed (200 Fluopiconde/100 kg seed, 150 fluoyastrobin/100 kg seed)					
Seed TROPEX Body weight: 60 kg	Standard clothing**	0.0035899	Ø5.13 Q	0.0034189	9.40 J

Operator wearing one layer of work cothing and additional chemical protective foves during all siks except bagging and RPE during cleaning of the equipment

For the 200 L pack size, the acceptable operator exposure level AOEL is not exceeded when normal workwear is worn, and additional oppropriate PPE is

25 L pack size

The input parameters used for the exposure assessments for Duopic Aide and fluoxastrobin with a 25 L pack size are presented in tables 7.2 1-5 and 7.2.1-6 below. Input parameters considered for the estimation of operator exposure for fluopicolide

Table 7.2.1-5; (25 L packaging)

Formulation type:	₩S	\$. 6° x	Application technique:		ercial seed
Application rate (AR):	0.2	kg a.s./At seed		treatme: Loading	nt g/sowing
Seed treated per day	40	Tonnes/day	Product container size	25	L
Amount product handled	400	L/dagy S	Number of loading operations	16	op/day
Dilution rate:	1		Number of calibration operations	1	op/day
Dermal absorption (DA):	0.\$1 3 9	% (Concentry)	Duration of bagging	8	hours/day
	§.9	%(dilution)	Number of cleaning operations	1	op/day
Inhalation absorption (IA):		%			
	€0	kg/person			
AGEL	0.07	mg/kg bw/d	Duration of loading/ sowing	10	hours/day

Operator wearing one layer of work clothing



Table 7.2.1-6: Input parameters considered for the estimation of operator exposure for fluoxastrobin (25 L pack size)

Formulation type:	FS		Application technique:	Commercial seed	
Application rate (AR):	0.15	kg a.s./dt seed		treatme Loadin	ent g/sowing©
Amount product handled	400	L/day	Product container size	2 5	L & S
				, Q)	(for whole day treatmen Darge & containers are assumed)
Seed treated per day:	40	tonnes	Number of loading operations	160	op@ay
Dilution rate:	1	Undiluted (worst case)	Number of calibration operations		Sp/day
Dermal absorption (DA):	0.07	% (concentr.)	Duration of bagging	8,5	hours/day
	0.73	% (dilution)	Nomber of cleaning operations	9	op/dato
Inhalation absorption (IA):	100	% Q' \\			
Body weight (BW):	60	kgperson	Deration of loading/ sowing	90 S	hours day
AOEL	0.03	mg/kg low/d			

The outcome of the exposure assessment with a 25 L pack size is presented in table 7.2.1-7 below. Detailed calculations are presented in appendix

Table 7.2.1-7: Estimated operator exposure 25 packaging

		Fluop	icoside		strobin
, Q	Gevel of PPE	Cotal absorbed dose (mg/kg/day)	AOELS O	(mg/kg/uay)	% of systemic AOEL
Commercial see Application rate	ed treatment e: 1 L product/190 kg s		olide/100 kg seed,	150 g fluoxastrobi	n/100 kg seed)
Seed	Standard clothing	0.07890	° 112,78	0.0513	170.95
TROPEX Body weight: 60 kg	with RFB: mask during cleaning	0.0309	4 .21	0.0153	50.95
Seed sowing Application rate: : 1 L product/100 kg seed (200 g fluor) colide/100 kg seed, 150 g fluoxastrobin/100 kg seed)					
Seed TROPEX Body weight: 60 kg	Standard clothing	0.5035899	5.13	0.0034189	11.40

Operator wearing one layer of work clothing and additional chemical protective gloves during all tasks except bagging and ROE during cleaning of the equipment

For the 25 L pack size, the acceptable operator exposure level (AOEL) is not exceeded when normal workwear is worn, and additional appropriate PPE is worn during cleaning tasks.

^{**} Operator wearing one layer of work clothing



CP 7.2.1.2 Measurement of operator exposure

Not required as assessments demonstrated safe use using the accepted models.

CP 7.2.2 Bystander and resident exposure

CP 7.2.2.1 Estimation of bystander and resident exposure

The following definitions and assumptions for bystanders and residents may be applied.

Bystanders and residents are not involved in application or handing plant protection products or the professional handling of treated crops. The question arises whether it is processary to divinguish between bystanders and residents in terms of the potential for exposure and health risks. However, because the circumstances of this exposure could differ with respect to amount, frequency, and duration, this seems to be reasonable.

Bystanders may inadvertently be present within or directly adjacent to an area for a short period of time, typically a matter of minutes, where supplication of a plant protection products in progress or has recently taken place. They may be coposed to plant protection products mainly via the desmal route from spray drift and by inhalation of drifting spray droplets. Handheld application is considered to be worse case compared to field crop sprayer.

Residents may live or work near areas of the application of plant protection products (e.g. standing, working, or sitting in a garden in the wicinity of the application). They may be exposed to plant protection products mainly via the dermal route from spray drift deposits and by inhalation of vapour drift (depending on the vapour pressure of the active substance). For infants and too dier's exposure might also occur orally (e.g. through hand to-mouth transfer and/or object-to-mouth transfer).

Treatment of seeds with FLC + FSA FS 350 is performed in professional plants where no residents or bystanders are present. Further, no other (uninvolved persons are glowed to enter the plant. Therefore, bystander exposure to LC + FXA FS 350 during seed treatment is not relevant. A detailed calculation resident or bystander exposure is considered to be not precessary and has thus not been conducted.

CP 7.2.2.2 Measurement of by stander and resident exposure

Since no exposure of residents of bystanders is expected a study to provide a measure of bystander exposure was not necessary and was therefore not carried out.

CP 7.2.3 Worker exposure

The only intended use of LC + XA FQ 350 the treatment of seeds prior to sowing. During sowing, the seeds are immediately covered by soil. Consequently, no re-entry tasks are required that could result in exposure to the worker. Therefore, a worker exposure assessment for FLC + FXA FS 350 is not required and has not been conducted.

CP 7.23.1 Estimation of worker exposure

Not considered to be necessary as no worker exposure is expected.

CP 7.2.9.2 Measurement of worker exposure

Not considered to be necessary as no worker exposure is expected.



Combined exposure

As the product is a mixture of 2 active substances a combined exposure assessment is required. At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from tables 72.1-4 and 7.2 1.7 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 7.2.3-1: Acute risk assessment from combined exposure

Application scenario	Active Ingredient	Estimated exposure / AQCL
Operators – Seed treatment Standard clothing* 200 L packaging 2 loading operations per day	Fluopicolide Fluoxastrobin Cumulative risk Operators (141)	0352 6 9 0 1.5559 2,5911
Operators – Seed treatment with RPE: mask during cleaning 200 L packaging	Fluorastrobin Cumulative risk Operators (HI)	0,3539 0,7054
Operators – Seed sowing Standard clothing**	Floopicolide Fluoxastrobin Cumulative risk Operators (HI)	0.513 0.114 0.627
Operators – Seed treatment Standard clothing 25 L packaging 16 loading operations per day	Fluogastrobin	1.1278 1.7095
Operators Seed treatment with RPE mask during Cleaning	Cumulative risk Operators (HI) Fluopicolide Fluoxastrobar	2.8373 0.4421 0.5095
16 loading operations per day	Cimulative rist Operators (41) Fluor Colide	0.9516
Operators – Seed sowing Standard clothing**	Proposition of the control of the co	0.513 0.114
	Cumutative risk Operators (HI)	0.627

Operator wearing one layer of work lothing and additional chemical protective gloves during all tasks except bagging

The Hazard Index is < 1, if the operator uses the appropriate PPE during seed treatment and during sowing of treated seeds. I.e. During seed treatment the operator is wearing one layer of work clothing and additional chemical protective gloves during all tasks except bagging and RPE during cleaning of the treating equipment. During sowing of treated seeds the operator is wearing one layer of work clothing. Thus combined exposure to all active substances in FLC + FXA FS 350 is not expected to present a risk for protected operators, workers, bystanders, and residents. No further refinement of the assessment is required.

^{**} Operator wearing one layer of work@fothing



CP 7.3 Dermal adsorption

A summary of the dermal absorption rates for fluopicolide in the fluopicolide + fluoxastrobin F\$\sqrt{350}\$ (200+150 g/L) (also named FLC+FXA FS 350) formulation is presented in the following table

Dermal absorption rates for fluopicolide in FLC+FXA FS 350 **Table 7.3-1:**

	fluopicotide
	Value (% of Gose applied)
Concentrate	Q _{0.21} %, A A A
Dilution	% 50.g/V 50.g/V
(dilution factor)	

Justification for proposed values – Fuopicolide — Justification for proposed dermal absorption rates for fluopicolide are based or an in viro human skin dermal absorption study using the FLC+FXA ES 350 formulation. The study results are summarized in the following table. A full summar of the study is described in detail below.

Summary of the results of subportted dermal absorption studies for Fluopicolide **Table 7.3-2:**

Table 7.3	-2:	Summary of the	esults of subport	tted dermal ab	sorption studies	forFluopicolide
Test	Concent	rate Spray dintio (diffition) factors (3.9%) (1.11)	Formalation in study	Fustifi@tion representatis formulation Forod	provided on of the forcurrent luck	Reference
In vitro (Human)	0.2108	3.9% (Lin 4)	FLC+FXA	Not required	537	2015; N
Ŕ						
				\$ \$ 5		
É				Z Z		
A .	(V)					
S						
Ö		~				



Comparative dermal absorption, in vitro using rat and human skin

Data Point:	KCP 7.3/01
Report Author:	<u>Ø</u>
Report Year:	2015
Report Title:	FLC+FXA FS 200+150: [14C]-fluopicolide - In vitro dermal absorption study
1	using human skin
Report No:	SA 15160
Document No:	M-537120-01-1
Guideline(s) followed in	OECD 428 2004); OECD Environmental Health and Safety Publications Series on
study:	testing and Assessment N° 28 (2004).
	EFSA Panel on Plant Protection Products and their Residues (PR), EFSA
	Journal 2012
Deviations from current	none & & & & & & & & & & & & & & & & & & &
test guideline:	
Previous evaluation:	No, not previously submitted
GLP/Officially	Yes, conducted under GLP Officially recognised testing facilities
recognised testing	
facilities:	
Acceptability/Reliability:	Yes O V V V V V V
Material and methods	
Human skin:	Source: Xenometrix Hégenheim, France.
	Number and sex: Adonors Temal®
9	Source: Xenometrix, Hégenheim, Ffance. Number and sex: Adonors, femal@ Anatomical region: Abdomen Thickness: 366.2 to 477.0 µm.
4	Thiologics: 266 2 to 0770 the
Tank Madadah	Till Capress. 3600.2 to 427.0 page.
Test Material:	
Non-radiolabelled:	Batch: MOY 627, O S
0 ~ \	Purity ≠ 99.2% w/w
Radiolabelled	[phenyl-U-OC]-fluopicoliste & O
*(')	
	Batch: KML 9969. Specific activity: 5.50 MBq/mg.
£\$ ['] . @	Dad Paurity of the Parmylo Pan. 00 20/
, , , , , , , , , , , , , , , , , , ,	Radiopurity of the Cormulation: 98.5%.

Material and methods

Formulation:

The formulation used in this experiment was the Fluopicolide + Flucia Strobin FS 200+150 formaliation (specification N° 102000028578) containing fluopicolide at a concentration of 200 g/L. It was used at two rominal concentrations of Monicolide: neat, 200 g/L and 50 g/L.

A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was assed to study the absorption of the test substance (exposure area of 1 cm² skin). A diffusion celleonsisted of a donor chamber and a receptor chamber between which the kin was positioned. The receptor fluid was Eagle's medium supplemented with bovine servo albumin and gentamycin (50 mg/L) at a pH of approximately 7.4. The Reptor chamber was warmed by a constant circulation of warm water which manufained the receptor fluid at 32 ± 2 °C (close to the normal skin temperature). The eceptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity:

Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter



probe (Tewameter TM300) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment:

The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately $10 \, \mu L/\text{cm}^2$ exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.

Sampling:

The receptor fluid passing through the receptor chamberowas collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the Quration of the experiment (24 loours) At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffer safine) using precision suipes (b) intech Sciences from Kimberley-Qark professional), in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (2/4 hours after application), the treatest skin and the skin adjacent to the treatment site (surrounding swabs) were wabbed Each skin sample was tapestripped to remove the stratum conteum. This involved the application of Monaderm adhesiye tape (Monadovin, Monaco) for 5 seconds by fore the tape was carefully removed against the Girection of hair growth. This procedure was continued until a 'shiny' appearance of the pidern's was eviden which indicated that the stratum Forneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay

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

Findings:

Fluopicolide 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: Distribution of radioactivity at 24 hours after dose application of [14C]- fluopicolide in a FS 350 formulation at the rates of 200 g/L to human skin samples (All cells).

	Γ	C						
Donor N°	X2015/4-4	X2014/8- 28	X2015/2- 13	X2014/7 -7	X2015/7- 19	X2014/1 21-12	Group (Homan D = 6 🔊
Sex	Female	Female	Female	Female	Female ₄	Female	K'N'	
Cell N°	H01	H02	Н03	≽Н04	H05	Н06	MEAN	SP
Skin wash 8h	98.05	97.86	88.40	98.51	Ø9.46	98@3	96.72	2 √4.12
Skin wash 24h	0.0144	0.0029	0.0484	0.0532	0.0473	00 844	©0.06	D 0.07
Surrounding swabs 24 h	0.0060	0.0039	002494	0.0043	6 0114	Q0.0018	0,05	Ø .10
Total swabs	98.07	97.86	& 88.69	98.57	√ 99. 5 2	28.24	96.82	4.03
SC 1	0.0589	0.0092	0:2389	0.0488	0.0761	9 .0493	<i>"(/)</i> "	0,08
SC 2	0.0048	0.063/1	Ø.0806	0.0081	0.0228	0.0078	0.02	0.03
Total SC 1 + SC 2	0.0637	0,0123		0,0569	0.0989	Ø571	$\bigcirc 0.10$	0.11
Donor chamber	ND	L ND	0,5772	$\sqrt[3]{0.0266}$	30. 0397	S NO	. 0,21	0.31
TOTAL NON- ABSORBED	980\$	♥* \$\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	89059	\$ \$98.65	99.66	98.30	√y √y 97.03	3.70
Skin	(CA)	(0.00 K	© 0.278	0.023	0.024	0.037	0.06	0.11
Surrounding skin	°>> 0.004	0.004	1.545	Q :018	0.006	20 .004	0.27	0.63
Total skin	\$ 00\(\text{017}\)	Ø 0.010	V.823	0.043	9 .050	(***) (********************************	0.33	0.73
SC3	√ 0.002	0 ,002	0.050	Q6 07	0.020	0.011	0.015	0.018
SC4	0.002	& 0.00£	9 084	0.004	© 6609	0.005	0.018	0.033
SC5	ר.001	n.d	0.087	0.003	©0.011	0.003	0.018	0.034
SC6	S pri	n.d	0,035	€ .002	0.009	0.005	0.008	0.013
SC7	2003	z nQt	0.040	0.006	0.009	0.001	0.010	0.015
SC8	0.00	n.d	© 0.0Q	0.004	0.014	0.002	0.018	0.031
SC9	9	O na	<u> </u>	3 0.002	0.006	0.003	0.007	0.012
SC10	n.s.) jn.s	0.360		0.010	0.002	0.064	0.149
SC11		v n.s.	y , Mn.s	n.s	0.006	0.002	0.001	0.002
SC12	n.s.		n.s	n.s	0.010	0.004	0.002	0.004
SC13	o ne	n.s	n.s	n.s	0.002	0.002	0.001	0.001
SC14	\ \Qn.s.	n:Q		n.s	0.003	0.001	0.001	0.001
SC15	n.ş.	, On.s	n.s	n.s	0.004	0.002	0.001	0.002
TOTAL SC3+ a	0.017	0.003	0.774	0.029	0.111	0.044	0.16	0.30
TOTAL DOSESTES	0.033	0.013	2.597	0.072	0.161	0.064	0.49	1.03
Receptor fluid (0 - 12h)	0.029	0.036	0.197	0.043	0.043	0.027	0.06	0.07
Receptor fluid								
(0 - 24h)	0.052	0.060	0.268	0.079	0.073	0.050	0.10	0.08



	Е	Distribution of radioactivity (% dose applied)							
Donor N°	X2015/4-4	X2014/8- 28	X2015/2- 13	X2014/7 -7	X2015/7- 19	X2014/1 1-12	Group I H N=		
Sex	Female	Female	Female	Female	Female	Female	K N	¥1 0	
Cell N°	H01	H02	Н03	H04	Н05	УН06	MEAN	, SD	
%Ratio receptor 12h/24h	54	61	74	54	549,	53	59%	\$.	
Residual Rec Fluid	n.d	n.d	0.0085	🕲 n.d	n.d	n.d	// -	6 00	
Receptor chamber	n.d	n.d	0.3192	™" n.d	n.d	√¶.d	30.05	0.130	
TOTAL DIRECT	0.0523	0.0598	0.5960	0.0792	0.0726	0.0503	0.15	0.22	
POTENTIAL (dose site+ receptor)	0.0856	0.0727	© ' (L) 3.1934	0.1515	© 0.23 3 5	0,1945	° ~ 0.64	V 1.25	
POTENTIAL (skin+ receptor)	0.0689	0.0700	©′° -,2 <mark>9</mark> 4189×			& 0.0709	; Ø48	Ø.95	
TOTAL RECOVERY	98.22	9 7.95	92.78	, ∮8.8 0	99,89	98.4 1	<i>\$</i> 97.7 <i>;</i>	2.5	
	Ev	valuation ac	cording to I	EFSA Gui	& n > ~				
	Absorption > 7% within half of study duration? Not include SC values except SC1 & 2)								
					No correcti	<u> </u>	,		
				o 4	Mean (%	dose site	+%rece	ptor) +	
Total % Potentially Ab	sorbable ad	justed@acco	rding to RFS	SA (2017)	(SD)*1) =Q*	<u>.9%</u>			

a: tape-strips excluding numbers & 2 which are considered to non-assorbed

SD: standard deviation

n.d.: below limit of detection; n.s.: sample n.a: not applicable.

In the above table, the presented metors do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spheadsheet program.

In the study report the Cell H03 was excluded from the reported cells due to "low recovery". Futhermore, looking at the cumulative absorption profile of all the cells it shows that cell H03 can be considered as an outlier compared to other cells as shown in the graphs below.



Figure 7.3-1: Cumulative Absorption Profile after dose application of [14C]-fluopicolide in an FS 350 formulation at the nominal rate of 5 g/L to human skin (All cells)

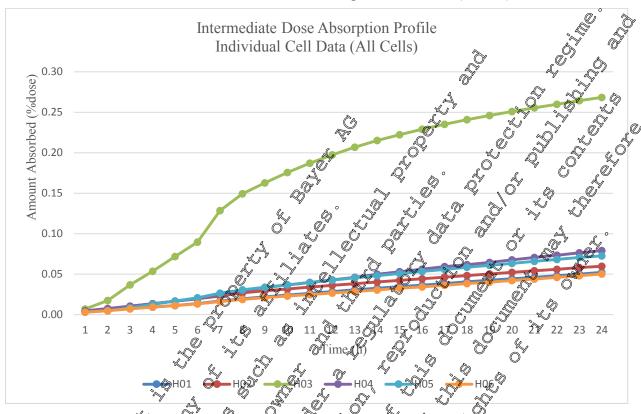


Figure 7.3-2: Cumplitative Absorption Profile after dose application of [14C] fluopicolide in an FS

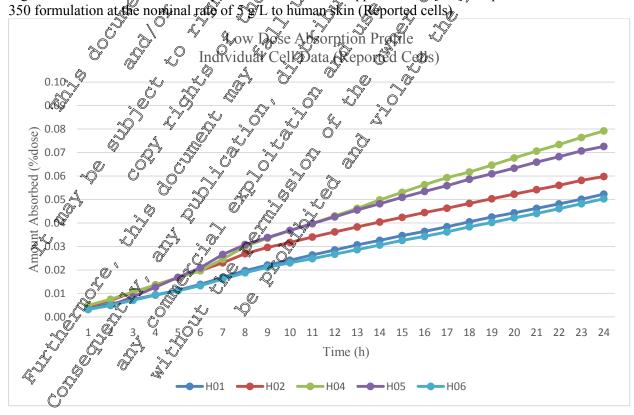




Table 7.3-4: Distribution of radioactivity at 24 hours after dose application of [14C]- fluopicolide in a FS 350 formulation at the rates of 200 g/L to human skin samples (Reported cells).

	1					r	
	Distril		, Ø				
Donor N°	X2015/4-4	X2014/8- 28	X2014/7 -7	X2015/7- 19	X2014/11-	Group Hu >> N= K N° :	500
Sex	Female	Female	Female	Female	Female	K IV	- 1. 2
Cell N°	H01	H02	H04	_{Р∞} Н05	1106	MEĂN	SD A
Skin wash 8h	98.05	97.86	98.51	99.46	Ø 98.05	@198.39) 0×65
Skin wash 24h	0.0144	0.0029	0,0532	0.047\$	0.1844	0.06	20 .07
Surrounding swabs 24 h	0.0060	0.0039	0 .0043	0.0114	@ ⁰ 0.001&	0.01	© 0.00
Total swabs	98.0700	97.8618	98.5673	29.5172	98,2407	98.45	0.65
SC 1	0.0589	0.0092	©0488	O.0761	3 .0493	% .05	\$ 0.02
SC 2	0.0048	0.0031	~0.008)×	20,0228	0.00	√ 0.01 ⁴	Q Q (V)
Total SC 1 + SC 2	0.0637	0.0123	020569	0.0989		E 9Ç 06	00.03
Donor chamber	ND		30.0266	0.9397	NO NO	\$0.03	0.01
TOTAL NON- ABSORBED	%.13	97.87	98.65	- 0	98.30		0.69
Skin	0.0	9 .006	(*) 0.02 %	0.024	0.097	ۇي 0.02	0.01
Surrounding skin	9 .004	0.00	979 18	\$\^\0.026	3 .004	0.01	0.01
Total skin	∂0.01 ₹	9 .010	0.043	y 00050	0.021	0.03	0.02
SC3	\$ 0.0002	0.002	0.607	0.020	9 ,011	0.008	0.007
SC4	Ø.0029	0.001	Ø.004	0.009	3 0.005	0.004	0.003
SC5	© 0.001	n.d.	Ø 0.003	0 .011	0.003	0.004	0.004
SC6	n.d	n.d	0,002	© 0.00°	0.005	0.003	0.004
SC7 S	0.003	Ş n.d	0.006	20,009	0.001	0.004	0.004
SC8	0.008	n.	0.004	0.014	0.002	0.006	0.006
SC9	n.s.	n.d	0.002	0.006	0.003	0.002	0.002
SC10	ins.	n.sc	0.002	0.010	0.002	0.003	0.004
SC11 S	n.s.	0 11.80 0 77.8	n.s	0.006	0.002	0.001	0.002
SC12	a ns	n.s	n.s	0.010	0.004	0.00	0.00
SCY3	m.s.		n.s	0.002	0.002	0.00	0.00
SC14	Ø n.s.	Žn.s	n.s	0.003	0.001	0.00	0.00
SC15	ŋ.s.	n.s	n.s	0.004	0.002	0.00	0.00
TOTAUSC 3	0.017	0.003	0.029	0.111	0.044	0.04	0.04
TOTAL DOSE SICE	0.033	0.013	0.072	0.161	0.064	0.07	0.06
Receptor fluid	0.029	0.036	0.043	0.043	0.027	0.04	0.01
Receptor fluid							
(0 - 24h)	0.052	0.060	0.079	0.073	0.050	0.06	0.01



	Distril	Group Human HD				
Donor N°	X2014/8- X2014/7 X2015/7- X2014/11- Gr X2015/4-4 28 -7 19 12					
Sex	Female	Female	Female	Female	Female ?	K N° = 1.2
Cell N°	H01	H02	H04	Н05	H06 🔊	MEAN SDS
%Ratio receptor 12h/24h	54	61	54	59	53	6 3 3
Residual Rec Fluid	n.d	n.d	n.d	n.d	n.d	n.d.
Receptor chamber	n.d	n.d	n.d	n.d	\$ n.d	n.d n.a
TOTAL DIRECT	0.0523	0.0598	030792	0.0726	0.0503	0.06 0.01
POTENTIAL (dose site+ receptor)	0.0856	0.0727	© ' 0.1 5 15	9.233	0,1,145	0.133
POTENTIAL (skin+ receptor)	0.0689	0: 0 700	©.1224	0.1229	0.0709	0.09
TOTAL RECOVERY	98.22	Ø 97 ,95 √	98280	√ 99.8 €	98.41	98.65
Total % Potentially Ab a: tape-strips excluding numbers		()		FSA (2017)	Mean (%d + (SD*1.2)	ose site +%receptor) 70.21%
n.d.: below limit of detection in the above able, the presente differences resulting from the difference resulting from the differenc	d means do not see of the preads	always calculate	e exactly from	(A . A	Sindividual data	. This is due to rounding-up



Table 7.3.5: Distribution of radioactivity at 24 hours after dose application of [14C]- fluopicolide in a FS 350 formulation at the rates of 50 g/L to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)							W. S.
Sex	Female	Female	Female	Female	Female	Female	Group H	D)
		X2014/1	X2015/1	X2014/8-			K N°	26 S
Donor N°	X2015/4-3	1-2	-12	1	X2015/8-7	X2014/7-8		
Cell N°	H07	H08	H09	H010	H11	ິ້H12	MEAN?	SD
Skin wash 8h	91.36	102.93	132.20	101.50	92067	90.7	10139	9 k 36
Skin wash 24h	0.01	0.10	0.01	0.00	0.11	€ 14	0.06	Q0.01
Surrounding swabs 24 h	0.0010	0.0012	0.0040	0.0027	0,0085	0.0049	0.00	0.001
Total swabs	91.37	103.02	3 2.21	© 10150	92.79	99.86	101.96	91.37
SC1	0.104	1.293	A 0.088	0.115	0,761	©0.452	0′ _{0.47} ©	0.1004
SC2	0.099	0.357	20,020	0.00%	% .167,	0.034	Q .¥2	49 .099
Total SC1 + SC2	0.20	a.65	V 0.11	9.12	\$ Q.25°	\$0.54	0.59	0.20
Donor chamber	n.d.	Q n.g	øg.d.	n.d	on.d.	nð.	n.ed.	n.a.
TOTAL NON-			0				&	
ABSORBED	914.57	104.67	132.32	101.62	93,52	<u>⊘</u> 91.40	102.55	15.59
Skin	№ 0.11	0.138	0 7.08	0.04	₹0.36	9 42	0.20	0.16
Surrounding skin		000 008	00.016	0.003	0.010	\$ 9 .023	0.01	0.01
Total skin	0.12	0.19	0.90	ॐ 0.04₂	0.37	0.44	0.21	0.16
SC3	0.010	0.308	0.009	0.005	0.080	0.062	0.079	0.116
SC4	Q. © 06	©.123	0.058	© .007	0,978	0.031	0.044	0.047
SC5	n.s _×	0.06	6 010	ngs.	29.060	0.023	0.027	0.030
SC6	, in.s.	6.187	§ 0.00€	n.s.	0.055	0.052	0.050	0.072
SC7	yn.s.	0.019	0.905	n.s.	0.040	n.s.	0.011	0.016
SC8	n.S.	07917	0.004	y Ang.s.	0.016	n.s.	0.006	0.008
SC9	n.s.	~~°0.01₹	0.006	n.s.	0.015	n.s.	0.006	0.008
SC10	n.s.	0.997	· Ø.008,	un.s.	0.010	n.s.	0.009	0.014
SC11	y n.s.	n.s.,	0.00	n.s.	0.135	n.s.	0.023	0.055
SCK W	n.s.	y n.Q,	1 2 3 3 3 3 3 3 3 3 3 3	n.s.	n.s.	n.s.	0.001	0.003
Total SC3+	0.62	%.77	0.07	0.01	0.49	0.17	0.26	0.31
TOTAL ODOSE			* — <u>— </u>					
SITE &	0.13	<i>∪</i> 0°.986	0.17	0.05	0.86	0.61	0.46	0.40
Receptor fluid (0 - 12h)	\$ 0275	0.233	0.071	0.167	0.492	0.667	0.32	0.22
Receptor fluid (0 - 24h)	0.281	0.298	0.128	0.173	0.616	0.796	0.38	0.27
%Ratio receptor 12h/24h	98	78	55	96	80	84	82	15



	D	Distribution of radioactivity (% dose applied)							
Sex	Female	Female	Female	Female	Female	Female	Group Human HD		
Donor N°	X2015/4-3	X2014/1 1-2	X2015/1 -12	X2014/8- 1	X2015/8-7	X2014/7-8	N= K N	= 6 ©	
Cell N°	Н07	H08	Н09	H010	H11	A 12	MEAN	Ş I	
Residual Rec Fluid	0.012	0.009	0.017	0.007	0.023	0.020	0.012	009	
Receptor chamber	0.135	4.927	n.d.	2 93	0.72	1.650	©.135	4.92	
TOTAL DIRECT	0.43	5.23	0.14	0.47	3.36	2.49	1,68	1594	
POTENTIAL (dose site+ receptor)	0.56	6.19	032	0.52	222	© 3.07	2. k 5	0	
POTENTIAL (skin+ receptor)	0.55	5.42	©0.24	© 0.51	7 1.74		1.89	2.00	
TOTAL RECOVERY	92.1	110,8	<u> </u>	102,1	Q 95.9	945	0″ © 1 04 .7	25.3	
	Eval	luatien/ac	C Y		dance (2010	V ay	Ō,	0	
Ab	Absorption >75% within half of study duration? Yes (exclude \$\vec{\pi}\$ values)								
		Z Z Z Z	lean Recov		No@orrecti	on needed	<u> </u>		
Total % Potentiall	y Absorbab		. 🐟 .	g to EFSA	0/18		ptor) + (SD*1) =	

SD: standard deviation; N: number of kin cells used for calculation

n.d.: not detected (below the limit of detection); n.g.: not applicable

In the above table, the resented means of not ways calculate exactly from the presented addividual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:

skin of CC]-fluopicolide in the fluopicolide FS 350 The dermal penetration through human dermatorned formulation was investigated at Oree nominal concentrations corresponding to the neat product (200 g /L) and to two representative spray dilutions of 39

Concentrate

The mean percentage of fluopicolide in the FLC FXA FS 350 formulation that was considered to be potentially absorbable for the near formulation applying the EFSA guidance (2017) to the study data was 0.21%

The mean percentage of Tuopic lide in the FEC+FXA FS 350 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 3.9%.

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for Quopicolide in the FLC+FXA FS 350 formulation:

- For the neat formulation (200 g/L)
- % for the intermediate dose (50 g/L)



Assessment and conclusion by applicant:

An acceptable study yielding valid conclusions.

and the state of t A summary of the dermal absorption rates for fluoxastrobin in the fluopicolide + fluoxastrobin (8 20 + 150 (FLC+FXA FS 350) formulation is presented in the following table The state of the s



Table 7.3-6: Dermal absorption rates for fluoxastrobin in FLC+FXA FS 350

	Fluoxastrobin ©	
	Value (% of dose applied)	, and a
Concentrate	0.07%	
Dilution (dilution factor)	0.73% @ 7.5 g/L	

Justification for proposed values - Fluoxastrobin

The proposed dermal absorption rates for flooxastrobin are based on anon vito human skin dermal absorption study using the FLC+FXA FS 350 formulation. The study results are summarized in the following table. A full summary of the study is described in detail below.

Table 7.3-7: Summary of the results of submitted designal absorption studies for Flooxastrobin

Test	Concentrate	Spray dilution Formulation Justification Reference
		Tullulwa lactor)
		representativity of
		Q Q Current product \
		Current product
In vitro	0.07%	0.73% FLC+FXX Not required 2016; M-548487-01-1
(Human)	0.07%	(sin 4) S 350 S Tequised S 48487-01-1

Comparative dermal absorption, it vitre asing rat and human skin

Data Point:	KCP 7.3402 5 5 6 5 6
Report Author:	
Report Year:	2016
Report Title:	FLO + FXQ FS 200 + 150 formulation: [14C]-fluoxastrobin - In vitro dermal
	Dsorption study using human skin
Report No:	SA 15902 AV ON O
Document No:	<u>M-538487-04-1</u>
Guideline(s) followed	QECD 428 2004 DECE Environmental Health and Safety Publication Series on
study.	testing and Assessment No 28 (2004); EFSA Panel on Plant Protection Products
	and their Residues (POR), EFSA Journal (2012)
Deviations from current	nope of the second seco
test guideline:	
Previous evaluation.	No, not previously submitted
GLP/Officially recognised testing	Yes conducted under GLP/Officially recognised testing facilities
facilities:	
Acceptability/Reliability:	Yes

Material and methods

Human skin: Source: Xenometrix, Hégenheim, France.



Number and sex: minimum of 6 donors, female.

Anatomical region: Abdomen. Thickness: 357.2 to 496.0 µm.

Test Material:

Non-radiolabelled: Batch: EDCI000205.

Purity = 99.5% w/w.

Radiolabelled: [chlorophenyl-UL-¹⁴C]-fluoxastrobin

Batch: KML 10000.

Specific activity: 3.77 MBq/mg. Radiopurity of the formulation: >99%.

Formulation:

this experiment was the suopicolide The formulation used and 30) formulation specification N° Fluoxastrobin FS 350 (200 + 10200008578) containing flux astrobin at a concentration of 150 g/L. It was used at two nominal concentrations of flooxas bin: neat, 150 g/L and 37,5 o

Test system:

A flow-through diffusion cell system Franz's cell prodifice, Gallas, France) was used to study the absorption of the rest substance exposure area of 1 cm skin). A diffusion cell consisted of a donor chamber and receptor chamber between which the skill was positioned. The receptor and was Eagle medium supplemented with 5% boving serum a Dumin and gentamycin (50 mg/L) at a pH of 9.43 to 7.45. The receptor chamber was warmed by a constant virculation of warm water which maintained the receptor fluid at 32 ± 200 (close to the pormatisk in temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whils in the receptor chamber by means of a magnetic bar.

Skin integrity

Before dose application, the integrity of the kin samples was assessed by measuring the frans-epidermal water coss (TEWL) from the tratum corneum. An evaporimeter probe (Tewameter TM200) was placed securely on the top of the donor chamber and the appount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm2 were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

Treatment:

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

apling: A A

The receptor fluid passing through the receptor chamber was collected in glass vials head in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween §On PBS (phosphate buffer saline) using natural sponge swabs, in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the



application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The clip common that it is a strip of the clip common that it into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. With surrounding skin and tape-stripped treated skin were retained for analysis.

Radioassay:

The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation & ktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method, Efficiency correlation curves, were prepared for each scintal ation cocktail and were regularly checked by the use of [14C-Findings:
Fluorastrobin was demonstrated to be sufficiently soluble in the receptor fluoriton applied and fask of back diffusion.

Measurements of the homogeneity of the two scone platitions of formulation applied indicated that it was acceptable.

The study results are presented in the following Tables. n-hexadecane standards. The scintillation counter was recalibrated when an eviation



Table 7.3-8: Distribution of radioactivity at 24 hours after dose application of [14C]- fluoxastrohin in a FS 350 formulation at the rate of 150 g/kg to human skin samples (All cells).

		Distribution	n of radioac	tivity (% do	ose applied)	ð	Ĉ.	
	X2015/4-	X2014/1	X2015/5-	X2015/8-	X2014/8-	X2014/7-	Group H	Hundava D
Donor N°	7	1-10	1	10	23	15	NÉ NÉ	
Sex	Female	Female	Female	Female	Female	Female *		'= I 🍣
Cell N°	H01	H02	Н03	H04	H0\$	Н06€	MEAN	ŠD.
Skin wash 8h	94.19	99.27	94.98,4	100.42	Q 89.18°	9 0.97	ر گ4.84°	4.03
Skin wash 24h	0.2287	0.0036	0.0030	0.0012	y 0.8 <u>9</u> 18	0.1828	y 021	Ø.32
Surrounding swabs 24h	0.1601	n.d.	∭n.d.	0.0023	0.0074	or.d.	~~0.03	© [▼] 0.06
Total swabs	94.58	99.27	94.98	100.43	90.01	91.150	95.07	_4√18
SC 1	0.9662	0.1172	0.0053	0.008	0(0)751 ×	0.0092	0.19	0.38
SC 2	0.0647	0.00\$	& 0.0024	0.0024	©0.00 <u>6</u>	n.d.	$\sqrt[\infty]{0.01}^{\mathbb{C}}$	0.03
Total SC 1 + SC 2	1.03	0.12	0.01	0.01	0.02	0.00	\$\tag{9.20}	0.41
Donor chamber	0.3284	© 0.02%6°	On.d.	9 0.0701	Ø.2835©	~ 0 2 900	% 0.17	0.15
TOTAL NON- ABSORBED	95.94	\$\frac{\circ}{\chi}\geq 9.42 \land{\chi}	94299	¶00.51	20.32	91, 4 5	95.44	4.10
Skin	0.4934	△, 0.0112°	0.0025	0.0098	© 0.0088	0 0020	0.09	0.20
Surrounding skin	\$0.8380°	0.0198	Q, 0.0023	20. 0058	0.0374	£0.0034	0.15	0.34
Total skin	§ £33	0.03	0.00	9 0.00 <u>2</u>	√y 0.05.©	0.01	0.24	0.54
SC3	<i>#</i> 1250	0.0099	n.d.	0.0022	© 0.0014	n.d.	0.0231	0.0501
SC4	0.0983	Ø.0018₄	»p.d.	\$0.0014	Q\$041	n.d.	0.0176	0.0396
SC5	Œ9396 g	Ö 0.00	n.d.C	v 0:0013	3 0.0015	n.s.	0.0088	0.0172
SC6	$n \stackrel{\circ}{>} n$	Q 0059	5 [™] 0.003⁄2	0.0015	n.s.	n.s.	0.0035	0.0022
SC7	n.s.	0.0044	n.d.	O OS.	n.s.	n.s.	0.0007	0.0000
SC8	n.se	, Gald.	n.d	n.s.	n.s.	n.s.	0.0000	0.0000
SC9	OS.	Ø.001 <u>0</u> Q	n.s.	n.s.	n.s.	n.s.	0.0010	0.0000
SC10	"Q n.s. A	0.0024	n.\$	n.s.	n.s.	n.s.	0.0024	0.0000
SC11 👟	T nes	n.d.	D nys.	n.s.	n.s.	n.s.	0.0000	0.0000
SC12	n.s.	0.0017	n.s.	n.s.	n.s.	n.s.	0.0017	0.0000
SC13	△ n.s.	Q. 0011	n.s.	n.s.	n.s.	n.s.	0.0000	0.0000
TOTAL SC 3	0363		0.003	0.006	0.007	n.d.	0.05	0.10
TOTAL POSE SIJE	1.59	0.06	0.01	0.02	0.05	0.01	0.29	0.64
Receptor fluid () (0 - (2h)	0.024	n.d.	n.d.	n.d.	n.d.	n.d.	0.0037	0.0091
Receptor And (0 - 24h)	0.0679	n.d.	n.d.	n.d.	0.0147	n.d.	0.0138	0.0272
%Ratio receptor 12h/24h	33.0	100.0	100.0	100.0	0.0	100.0	72	44



		Distribution	n of radioac	tivity (% do	se applied)		Community
	X2015/4-	X2014/1	X2015/5-	X2015/8-	X2014/8-	X2014/7-	Group Human HD © 8
Donor N°	7	1-10	1	10	23	15	N=6 K N°≠1
Sex	Female	Female	Female	Female	Female	Female	
Cell N°	H01	H02	H03	H04	H05	A 106	MEAN 50 1.010
TOTAL DIRECT	2.49	0.00	0.00	0.00	0.02	0.01	0.42 1.012
POTENTIAL (dose site+ receptor)	4.09	0.06	0.01	₹0.02	9,67	0.02	4.65 J.65
POTENTIAL (skin+ receptor)	3.82	0.03	0.00	0.02	0.07	Ø.02	0.66
TOTAL RECOVERY	100.0	99.5	95.0	· 100,50	90.4	Q 93 5	96.15 \$\frac{1}{2}\fra
		Evaluation	n acerding	% EFSA G	ρ · ν		
	Absorption >	>75% within	half of stud	y dûration?	No. (includ	le S C values	excep SC1 (2)
_			Recoy	4 < 95 %?	Nocorrect	ion negaed	
Total % Potent		. O	0 ,	× (2017)	^y = 2.4%		eceptor) + (SD*1)
SD: standard deviation n.d.: below limit of det		(V		G W			% <u>,</u>
SD: standard deviation n.d.: below limit of det In the above table, the p rounding-up differences							



Cell H01 was excluded as the values for the stratum, corneum, skin and direct absorption were clear outliers compared to the other cells as measured by the modified Z-score test.

In general, finding the "Outliers" in a data set can be done by calculating the deviation for each number, expressed as either a "Z-score" or "modified Z-score" and testing it against certain predefined in restord. Z-score typically refers to number of standard deviation relative to the statistical average. The Modified Z-score applies the median computation technique to measure the deviation. Mathematically the Modified Z-score can be written as:

where MAD stands for Median Absolute Deviation Any number in a data set with the absolute value of a modified Z-score exceeding 3.5 is considered in "Outlier".

Table 7.3-9: Modified Z-score result for the stratum corneum (SC3+), skin and direct absorption results for FXA following application of [C]- Hoxastrobin in the FLC+FXAFS 350° formulation at the rate of 150 g/L to human skin samples (Alf cells).

			, <u>() </u>	
Cell N°	SC3+ (%do@) 0.263	,	m@n-value	mod Z store 34.6
H01	0.263	OUTIONER	-0.2565	® 0/34.6.
			-0.2365 -0.0205 -0.0035	© 2×8
H02	0. 02 /7 💪 🖏	NO RMA	0 .02050	© 2×8
H03	Ø:003 V	ORM Ø Ľ	© 0.003 S	% % -0.5
H04	0.003	NORMAL	e U.UUggus	
H05	0.007	NO@MAL	-0.0005 ×	<u>ش</u> 0.1
H06	0.007	NORMAL MORMAL	×0.0065	-0.9
			&, . · · ·	Š
	Spin (%dose)		Omean-walue	^r mod Z score
H01	l 0/1 1/34 _	ODTLIER,	-1.305	44.0
H02	Spin (%idose)	NORMAL	-1.305 \$\sqrt{-0.005}\$ 0.025	0.2
HU3		NORMÂL	© 0.0 25	-0.8
Н	l & .0 0.0 2 % &	NORMAL	₽° 0,005	-0.2
H 05		MORMAL	₹0 .025	0.8
`≯H06	0.01	NORMAL	0.015	-0.5
			0′	
*	Direct (4dose)	& <u>3</u>	mean-value	mod Z score
H01	1.78	OUTLIER NORMAL	-2.485	335.2
H02		NORMAL	0.005	-0.7
H0 3		NORMAL	0.005	-0.7
Ĥ 9 4		N@RMAL	0.005	-0.7
△ H 05		ORMAL	-0.015	2.0
₩ H06	0.01	NORMAL	-0.005	0.7

Furthermore, the value for the receptor damber was anomalously high suggesting an experimental error such as contamination of the sample.



Table 7.3-10: Distribution of radioactivity at 24 hours after dose application of [14C]- fluoxastrobin in a FS 350 formulation at the rate of 150 g/kg to human skin samples (Reported cells).

	Distril	nution of vo	dioactivity (9/ dose ann	liad)		
Donor N°	X2014/11- 10	X2015/5-	X2015/8- 10	X2014/8- 23	X20147-	Group H HJ N=	Iuman Y
Sex	Female	Female	Female	Female	Female	K S	= 1.20
Cell N°	Н02	Н03	H04		H06	MEAN!	≯SD Ø
Skin wash 8h	99.27	94.98	100.42	89,18	90.97	94,96	494
Skin wash 24h	0.0036	0.0050	9.0012	0.8218	© 0.18\$8	₹ 9.20	0.35
Surrounding swabs 24h	n.d.	n Ø	© y 9024 _≪	0.0074	n.d.C	0.002	0.003
Total swabs	99.27	24.98	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	2 0.01	91.15	9 5.17	2.67 ⁴
SC 1	0.1172	\$0.0053\square	0,0088	0.0150	×0,0092	Ų 0,03 [®]	0.05
SC 2	0.0055	0.0024	0.0024	0,0062	O not.	6 5003	0.003
Total SC 1 + SC 2	0,12	0.01	0.01	0.02	9.01	S 0.03€	0.05
Donor chamber	0@296	© n. 0 °.	0.0711	0.2835	0.2900	Ø,13	0.14
TOTAL NON ABSORBED	9932	y 	100.61	90.32	\$ 	©° § 95.34	4.58
Skin	9 9 9 1 12 2	0.00\$5	Ø.00985	0,0086	0.002	0.007	0.004
Surrounding skin	0.0198	© ,0023 ₂	\$ 0.0 65 8	0.0374	0.40034	0.014	0.015
Total skin	9.03	0:00	0.02	© g:95	0.01	0.02	0.02
SC3	0.009	on.d.	2, 0.0 02 2	0.0014	n.d.	0.003	0.004
SC4	0.00018	nd.y	0.0014	0.0041	n.d.	0.001	0.002
SC5 D	20 0017	n.d.	\$0.00 <u>1</u> 3\$	0.0015	n.s.	0.001	0.001
SC6	0.00\$9	6.0032	0.0015	n.s.	n.s.	0.004	0.002
SC7	0.0014	Z r.J.	n.s.Q	» n.s.	n.s.	0.001	0.000
SC8 V O	n d	On.d.	n.s.	n.s.	n.s.	n.d.	n.a.
SC9	0.0010	Q ns	n.s.	n.s.	n.s.	0.001	0.000
SC10	Q ,0024	U Sn.s.	n.s.	n.s.	n.s.	0.002	0.000
SCV1	nod.	n,s	n.s.	n.s.	n.s.	n.d.	n.a.
SC12	Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø Ø	z, <u>"n</u> ,s.	n.s.	n.s.	n.s.	0.002	0.000
SC13	0.00	n.s.	n.s.	n.s.	n.s.	0.000	0.000
TOTAL SC 3+	6 6.027	0.003	0.006	0.007	n.d.	0.01	0.01
TOTAL DOSE SIDE	0.06	0.01	0.02	0.05	0.01	0.03	0.02
Receptor fluid							
(0 - JQh)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
Receptor fluid		_	_				
(0 - 24h)	n.d.	n.d.	n.d.	0.0147	n.d.	0.003	0.007



	Distrib	oution of ra	dioactivity (% dose app	lied)	Group Humar
Donor N°	X2014/11- 10	X2015/5- 1	X2015/8- 10	X2014/8- 23	X2014/7- 15	HD N= 5
Sex	Female	Female	Female	Female	Female	$\mathbf{K} \mathbf{N}^{\circ} = 1 2^{\circ}$
Cell N°	H02	Н03	H04	Н05	но б	MEAN SD
%Ratio receptor 12h/24h	100.0	100.0	100,0	0.0	100.0	×80 × 4
TOTAL DIRECT	0.00	0.00	0.00	0.02	0.01	0.01 0.0
POTENTIAL (dose site+ receptor)	0.06	0.01	0.02	0.07	© 0.02	\$0.04 0.04
POTENTIAL (skin+ receptor)	0.03	0.06	© 0.02 ×	2 0:07	0.02	0.03
TOTAL RECOVERY	99.5	\$\int\delta 5 0\cdot\$) 100.5	90,4	0°	95.37 4.5
RECOVERT		affon a de or o	ling to EFS?	\\ // 4		
					No. Sincl	ud SC Qvalue
	Absorption >	>75% within			except SC1	(% 2) ×
	<u>~~~</u>		Recoy	ery <95%?	No correct	ion peeded
Total % Potentially A : standard deviation : below limit of detection to the above table, the presented nding-up differences resorting	s.: no sample; means do note; from the use	n.a.: not appl dways calcula of the spreads	icable, te exactly from	n the presented	0.07%	ata. This is due to
Total % Potentially A						



Table 7.3-11: Distribution of radioactivity at 24 hours after dose application of [14C]- fluoxastrohin in a FS 350 formulation at the rate of 37.5 g/L to human skin samples (All cells).

]	Distribution	of radioact	ivity (% dos	se applied)	ð	Group I	
	X2014/8-	X2014/7-	X2015/2-	X2015/3-	X2015/8-	X 2014/1	Group	D
Donor N°	14	18	11	1	8	1-3		
Sex	Female	Female	Female	Female H10	Female	Female &		
Cell N°	H07	H08	Н09	2	H ₂ Q,	H12 Ø	MEAN	SD
Skin wash 8h	102.62	27.54	-	>	(105.85 ₀	109.50	91.6%	31.5
Skin wash 24h	0.03	5.85	0.03	0.01^	y 0002	© 0.26°	1203	2 .36
Surrounding swabs 24 h	0.0044	0.06	00.07	0.0028	0.020	\$.02	\$\times 0.03	0.03
Total swabs	102.65	33.45	10126	105.50	105.88	\$107.78	9 2 75	29.15
SC 1	0.04	0.12	€ 20.01	© 0,62) 03	0.04	0.04
SC 2	0.00	, Ø.3 7	0.06	8 0.01	© Q 0 2	\$\int 0.016	^{D'} 0 0 08	0.15
Total SC 1 + SC 2	0.04	Q* _Q 0.49	©0.06	\$ 0202	0.02	9.04	%) %, 0.11	0.19
Donor chamber	0.08	© 0.25	\$ 0. 9	0.59 ¢	\$ 12,000 \$ 12,000	0.33	0.37	0.37
TOTAL NON- ABSORBED	102.76	Å 34≥20	302.31	10611	%, 105,90°	108.14		29.01
	0.02	S 0 8		\$ 100 11	©01		93.24	
Skin Surrounding skin	\$\int_0002^3\\ \sigma^0.02^3\\ \sigma^001	1.36	© 0,\$6 ~0.54 √	0.02	©01 \$\frac{1}{2} 0.01	0.10	0.34	31.06 0.54
Total skin	0.03	73.50	(O 0.70)	<i>≫</i> 0.03 ₄	0.02	0.18	13.08	31.56
SC3	n.d.	Ø9.1409	0.0)34	0.0024	Ø 0042	0.0099	0.028	0.055
SC4	© n.d. 2	© 0.2 2 91	0.0029©	0.0014	≫ 0.0012	0.0108	0.042	0.095
SC5	ns.	Ø 10637 (n.s.	& 0.001£	0.0013	0.0040	0.018	0.031
SC6	An.s.	<u> 0.1068</u>	n.s.	0.0023	n.s.	0.0090	0.037	0.055
SC7	n.sc	0,6310	n.©	00013	n.s.	0.0070	0.020	0.027
SC8	Ôs.	n.s.S	n.s.	0.0031	n.s.	0.0052	0.004	0.001
SC9	n.s. A		n.§.	n.d.	n.s.	0.0053	0.003	0.000
SC10 📞	N ncs	n.s.	D ny.s.	n.d.	n.s.	0.0050	0.003	0.000
TOTAL SC 3+	n.d.	0.5915	0.0163	0.0121	0.0067	0.0562	0.114	0.235
TOTAL DOSE	0.03	78.09 78.09	②,″ 0.72	0.04	0.02	0.24	13.19	31.80
Receptor of fluido (0 - 12h)	20.0039	0.1906	0.0824	n.d.	0.0896	0.0025	0.0614	0.0756
Receptor fluid								
(0 - 24h)	0.0030	0.3666	0.1088	n.d.	0.1297	0.0025	0.1018	0.1421
%Ratio receptor 12h/24h	100	52	76	100	69	100	83	20



]	Distribution	of radioact	ivity (% do	se applied)		Group l	Human		
Donor N°	X2014/8- 14	X2014/7- 18	X2015/2- 11	X2015/3- 1	X2015/8- 8	X2014/1 1-3	Croup i Li N=	D °		
Sex	Female	Female	Female	Female	Female	Female	K N	¥1 0		
Cell N°	H07	H08	Н09	H10	H11	7112	MEAN	, SD		
Residual Rec Fluid	n.d.	0.0209	n.d.	n.d.	n.d. a	n.d.	\$0.0035\$	0.0085		
Receptor Chamber	n.d.	0.2340	n.d.	n.d.	o.d.	0.3 6 78	951003 J	Ø.1610		
TOTAL DIRECT	0.00	0.62	0.4	<i>©</i> ° > 0.00^	\(\int_{\infty}\)\(\infty}\)\(\int_{\inf	0.370	021	2 0.24		
POTENTIAL (dose site+ receptor)	0.03	<i>78.71</i>	4 0.82°	© 5 0.04	2 0.15	0.61	L A	\$\frac{1}{3}\frac{1}{2}\llogram 00		
POTENTIAL (skin+ receptor)	0.03	78,J	% 0.81 ×	© 0,03	0.15	Ø.55	\$\times 13.28^{\tilde{\			
TOTAL RECOVERY	102.8	\(\sqrt{\partial}\) \(\sqrt{\partial}\) \(103.1	\times 1062\times	006.1	1087	106.63	3.78		
	*	Evaluatio	n according	To EFSA G	uidance		&			
No due to variability and mean lower limit contidence value of 62%. (include SC values except SEV & 2)										
				ery \$35%?	No corecti	ion needed				
Total % Poter		patoke adjust	ed aecordin	g o EFSA (2017)	Mean (%d 45%	Øse site +%ı	receptor) +	(SD*1)		

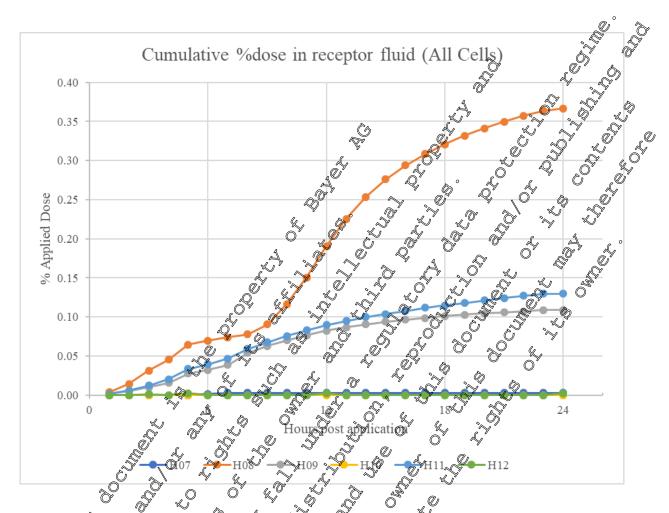
n.d.: below limit of detection; n.s.: no sample; n.d.: not applicable.

In the above table, the presented means to not aways calculate exactly from the presented individual data. This is due to rounding any differences resulting from the use of the spreadsheet program.

Cell H08 was excluded as the values for the swallong and the skin were clear outliers compared to the other cells. Furthermore the absorption frofile was also clearly different to the remaining cells as shown in the following figure



Figure 7.3-3: Cumulative Absorption Profile showing the different absorption profile of cell H08



The results excluding cell H08 are presented in the following table of

Table 7.3-12:

Distribution of radioactivity at 24 hours after dose application of [14C]- fluoxastrobin at the rate of 37.5 g/E to human skin samples (Reported cells).

Q	Dist	ribution of a	adioactivity	odose app	olied)		
Donor N° A	X2004/8- ^		X 2015/3	X2015/8- 8	X2014/11- 3	-	uman LD
Sex S	Female	Female	Eemale	Female	Female	N= K N° = 1.2	3
Cell No.	J J 10 7 %	~ D'	~ Н10	H11	H12	MEAN	SD
Skin wash 8h	102.62	Ø01.17	105.49	105.85	107.50	104.52	2.57
Skin wash 24h	9 .03	0,02	0.01	0.02	0.26	0.07	0.11
Surrounding swabs 24	0.0004	0.07	0.0028	0.02	0.02	0.02	0.03
Total swabs	102.65	101.26	105.50	105.88	107.78	104.61	2.62
SC S	0.04	0.01	0.02	0.005	0.03	0.02	0.01
SC 2	0.00	0.06	0.01	0.02	0.01	0.02	0.02
Total SC 1 + SC 2	0.04	0.06	0.02	0.02	0.04	0.04	0.02



						1	1
Donor chamber	0.08	0.99	0.59	0.00	0.33	0.39	0.40
TOTAL NON ABSORBED	102.76	102.31	106.11	105.90	108.14	105.05	&2.46
Skin	0.02	0.16	0.02	0.01	0.10	0.06	0.06
Surrounding skin	0.01	0.54	0.01	0.01	0,50%	0.13	\$\tag{\partial}{\partial}\$\tag{\partial}\$\tag{\partial}\$
Total skin	0.03	0.70	0.03	0.02	40.18	039	© 0.29©
SC3	n.d.	0.0134	0.0024	© 0.0042	\$\int_0.0099	×0.006×	0,506
SC4	n.d.	0.0029	0.0014	0.0012	0.0108	, © 0.003	
SC5	n.s.	n.s.	0.0016	0.00	. 0.004 Q	ρ.002	0.00
SC6	n.s.	n.s.	Ø.0023	n.s.	0.0090	0.006	
SC7	n.s.	n.s.		n.sc.	9.00704	0.004	0.004
SC8	n.s.	n.s.	00031	©	0.0052	% .004_4	0.001
SC9	n.s.	(*) (*) (*)	n.d	n.s. A	0.9053		3 0.004
SC10	n.s.	Q n.s.	₹ Z u l.d.			\$,003	0.004
TOTAL SC 3+	n.d.	0.0169	0.0121	0.0067	0.0562	\$0.01 8	0.022
TOTAL DOSE SITE	0.03	%	© 0.904	0.03	0.24	0.21	0.30
Receptor fluid		\$ 0.08\$	40"	~~ _@~		O	
(0 - 12h)	0,0030	O 0.08\$4	n.d. [©]	0.0896	0:0025	© 0.04	0.05
Receptor fluid						*	
(0 - 24h)	0.0030	2 0.1088	Ş n.d≼	, 0.1 <u>9</u> 97	0.0025	0.05	0.06
%Ratio receptor 12h/24h	100	76	700		3 100	88.96	15.29
Residual Rec Flord	, Pa.d.	o n.d.	n.d.	n.d.	n.d.	0.00	0.00
Receptor Chamber	n.d	n.d.	n.d.	© n.do	0.3678	0.07	0.16
TOTALOTRECT	0.000	0.14,	, O.00 °		0.37	0.12	0.15
POTENTIAL S			0.04	A.			
(dose site+ receptor)	0.08	0.82 %	0.04	0.15	0.61	0.33	0.36
POTENTIAL (skin+ receptor)		\$\times_\	(a) 0.03°	0.15	0.55	0.31	0.35
TOTAL ORDERY	102:8	103A	706.2	106.1	108.7	105.38	2.46
W S	<i>ž</i> 4.	0 0 i		FSA Guidan			20.0
<i>n</i>	10° C1	″————————————————————————————————————	h half of stud		Yes (exclude	SC values)	
	1			very <95%?	No correction		
Total & Potentially	A beart Que	odiusted co			Mean (%s $(SD*1.2) = 0$	kin +%re	ceptor) +
Total so role mitally	Aznani hanie	aujusteu ac	coruing to L	15A (2017)	(3D 1.2) = 0	1.13/0	

SD: standard deviation

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.

n.d.: below imit of detection; n.s.: no sample; n.a.: not applicable.



Conclusion:

The dermal penetration through human dermatomed skin of [14C]-fluoxastrobin in the FLC+FXA FS 350 formulation was investigated at two nominal concentrations corresponding to the neat product (150 g/L) and to one representative dilution of 37.5 g/L.

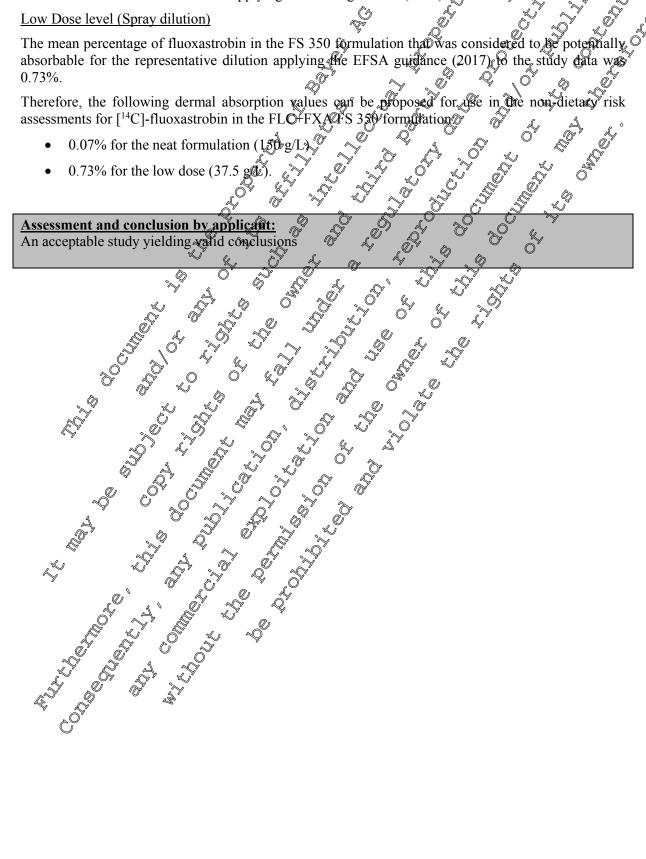
Concentrate

The mean percentage of fluoxastrobin in the FS 350 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 00%

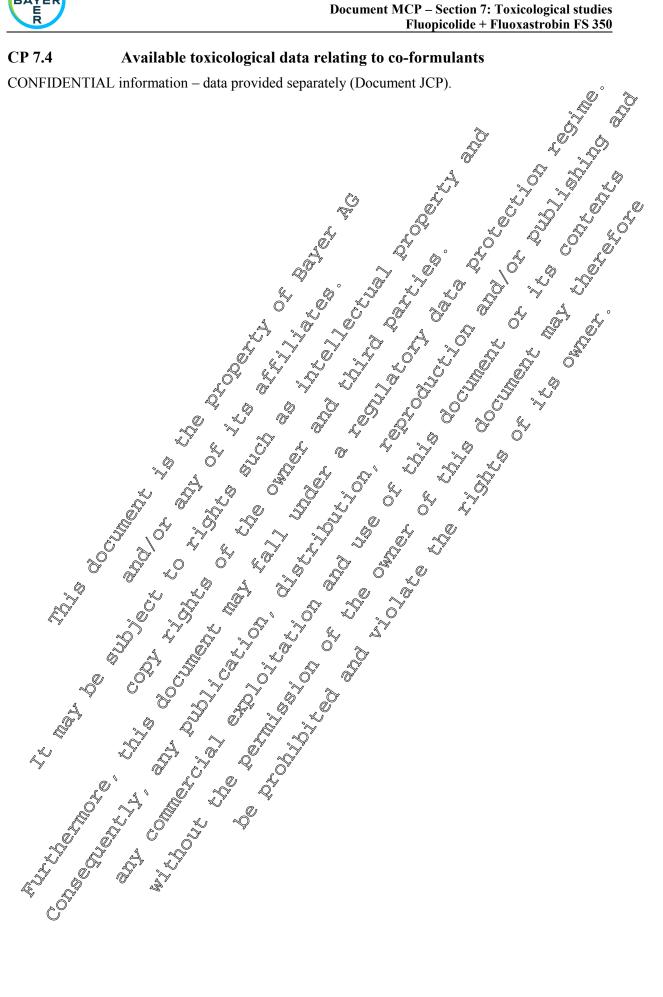
Low Dose level (Spray dilution)

The mean percentage of fluoxastrobin in the FS 350 formulation that was considered to be potentially absorbable for the representative dilution applying the EFSA guidance (2017) to the study data

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for [14C]-fluoxastrobin in the FLO+FXAPFS 350 formulation.









Appendix 1 Critical GAP for this assessment

						Fiuopiconae + Fiuoxastrobin	F 5 5 5 5 0
A 12 3	1.0-11	-1 4	CAD 6 41 '			Application Appli	
Appendix	I Critica	ai (GAP for this assess	men	t		
Table of su	pported	use	s for this renewal.				
						Baye Coler Lion Militar	
Crop and/	Country			F	ormulation	Application P Application PHI R	Remarks:
or situation		G or I	Group of pests controlled			Method / Tinfing Growth kind G	
		1		Type	Conc.	Method / Tinking / Growth Number Interval between ga. \$100 kg seeds kg seeds a ga. \$100 kg seeds kg seeds a ga.	
					of a.s.	kind trage of crop & min max applications min	
(a)		(b)	(c)	(d-f)	(i)	$(\mathbf{f}_{-}\mathbf{h}) = \begin{pmatrix} \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} & \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} \\ \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} & \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} \end{pmatrix} \begin{pmatrix} \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} \\ \mathbf{s}_{-}\mathbf{a}_{\mathbf{k}} \end{pmatrix} \begin{pmatrix} \mathbf{s}_{-}s$	(m)
Rape, winter	EU	F	Plenodomus lingam	FS	FLC: 200 g/L	See Operatment BOCH 00	
			(LEPTMA),		FXA: 150 g/L	FXA: 3.75 - 9 OF SICH STREET REPRODUCTION OF THE STREET S	
			(PEROPA),		* . **.		
			Alternaria brassicae			to the fix the transfer of the fixed of the transfer of the tr	
			(ALTEBA), Rhizoctonia spn.				
			(RHIZSP)		102		
FLC: Fluopico	olide		· \$	a4	^J O., 4		
FLX: Fluoxas n.a: not applic	strobin Pable			(O)	(_K ,O		
n.a. not applic	Zaore		* # "				
				×0°	i nto		
))			
			\$. 1		The Carlot of the Fifth	
				6,1			
			at c	, r	TOTAL		
			The same	20			
	6		, , §	•			
		•		Q	The state of		
				1			
				. 4			
		N		LC?	~ ~		
	1	Ć,		,,,,,,	ne "		
				K	YE OF		
S. S		.e		, C	we "		
		ラ -			¥		
	Co						
			<i>%</i> -			kind Wage of copies min and applications min with max min max (1) Southwattern 1980 H 00 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -	



Appendix 2 Spreadsheets for exposure calculations

2.1 Estimation of operator exposure during seed treatment, fluopicolide 200 L packaging, standard clothing

										.0
TASK	Potential Dermal Exposure (mg/op)*	Exposure (mg/op)*	Inhalation Exposure (mg/op)*	Frequency of operation **/ day	additional RPE yes/no		Estimated Actual Dermal Exposure (mg/day)	Exposure (mg/day)	Inhalation Exposure Worst case (mg/day)	
Calibration	6.51	2.85	0.276	1	no	6.5115	2.8456	0.2762		, O' 67 49
Mixing / Loading	1.0384	1.038	0.026	2	no	2.0769	2.0769	0.051 2	, V 1	
Bagging (mg/hr)	1.84	0.698	0.0054	8	no	14.7200	5.5840		0.4320	
Cle aning	174	16.67	3.2	1	no	1074,3514	16.6728	3.2000		
Dermal absorption/Inhaltion ab	sorption		Calibration			n/a	3.90%	Q' 100%	0	
Task specific absorbed dos		bw/day)	Mixing/loading Bagging Cleaning Calibration Mixing/loading Bagging Cleaning	,		n/a n/a U V	© 0.00185 0.0000 0.0000 0.0000 0.0000 0.0000	0.00460 0.00085	4	
Total absorbed dose (mg/kg # standard clothing of the open	g bw/day)	a larvan af re	ouls alathina da	min a (Maalaa an d	& coldision as	es Salinea ala	0.07	25(<u>)</u>	J.0002	
# standard clothing of the oper * exposure during bagging mg/ ** frequency during bagging in SCENARIO VARIABLES	hour		% of AOEL MoS	103.52		0.07 6.4	wes except for the my/kg bw/day/	ragging 7	î Î å	
SCEAARIO VARIABLES Given a.i. concentration = Given dilution factor = Given average bodyweight = Given Dermal absorption Concentrate Dilution Given Inhalation absorption =	200 1 60 0.21 3.9	kg % %		Enter varia		4//18		77,177		

2.2 Estimation of operator exposure during seed treatment, fluoricolide 200 Loackaging, standard clothing + RPE during cleaning

	Š	NO.	e* >	~ ~	¥ %	V (
	Total	Stimated		Frequency of	PPE#\$	Total			Inhalation
TASK	Potential	Actual		operation **/	UGOof	Potential	Estimated	. W	Exposure
I ASK	Derma	Dermal ~	Inhalati	May	additional	Decraal	Actual Dermah	Cultalation	Worst
	Exposure	& //	Exposure		O*RPE	Exposure		Exposure	case
	(mg/op)*	(prig/op)*	(\$00@\$p)*	0	yes/no		mg/day)	(mg/day)	(mg/day)
Calibration	6.51	2.85	0.276		no\(\int\)^v	6. 541. 5	√ € 3 456	0.2762	
Mixing / Loading	4.0384	12638			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	\$\tag{2}.0769	2.0769	0.0512	
Bagging (mg/hr)	1.84	√ 9.698	0.0054		J no	14.7200	5.5840	0.0432	0.4320
Cleaning	1,74	16.67	~ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	<i>1</i> 0"	veQ"	174.3914	16.6728	0.3200	
Dermal absorption/Inhanion a	bsorption	۸ 0		*		A			
4		8	Calibration			n/a	3.90%	100%	0%
4		,	Mixing loading			n/a	0.21%	100%	0%
<i></i>		Q	Bagging			n/a	0.21%	100%	0%
	-7/	¥ .	Cleaning		~O″	n/a	3.90%	100%	0%
Task specific absorbed do	se (mg/kg	bw/day) 🔟	. <i>~</i>	a i	2 X				
	*		Calibration	0	~(C)"		0.00185	0.00460	
7		<i>\@</i> '	Mixing/loading	g . 🌂			0.00007	0.00085	
	7,0	-	Bargging	(1		0.00020	0.00072	
		\	Skaning ~	¥ Q'			0.01084	0.00533	
Total absorbed dose (mg/)	<u> </u>	v 8			0.02		0.0002
# standard clothing of the ope	rators is on	ie layer	ork clothing du	ıring all aks and	l in addition p	rotective glo	ves except for b	agging	
* avnacura during hearing me	/how //		0/ of act	24.05		0.07	manuflen breefdore		

^{*} exposure during begging mg/hotis / % of AQEL 34.95 0.07 mg/kg bw/day

** frequency during agging in hours/day / MoD 262 6.4 mg/kg bw/day

Enter variables in red colour

SCENARIO FARIABLES	,
Given a.i. concentration	2 <i>6</i> 77 /2/1
Given dilution factor =	
Given and age body ight =	"0"60 kg
Given Dermal absorption	7
Concentrate	0.21 %
Dilution	<i>3.9</i> %
Given Inhalation absorption =	<i>100</i> %



2.3 Estimation of operator exposure during loading/sowing of treated seeds, fluopicolide

SOWING SEED										0
	Tot	tal	Estimated							
	Pot	tential	Actual						9	
	De	rmal	Dermal	Inhalation			^	~	Ó) . "O"
	exp	posure	exposure	exposure				r	1. W.	٥
	(mg	g/day)	(mg/day)	(mg/day)					. **	
							1			
Loading / Sowing (x10 hrs)		14.79	7.33	0.200	\gg_{Λ}	, , , , , , , , , , , , , , , , , , ,)"			
				√	9					
				y y		Q		, Ø		
				a. Y					Q ć	
Total exposure (mg/kg bw/day)		0.25	0.122	Ø.003		\mathbb{Q}'	, L) , 1.	Ű	
				~~			-Q,"	, Ö	Ĉ	9) Y
			,	₹	- O'		m ·			, G
			Dermak⊄	Inhalation	TotaD		U ,		**************************************	S
Systemic Exposure (mg/kg bw/d	lay)		0.00025658	√ ¥0.003	0:0035899	6 × C			4	e o
			4		7, .0			\bigcirc^{ν}		
%AOEL	5.13			"						
· ·		(a)		@)"	4		Y	Ø '		<i>₽</i> ,

Route of exposure Total Dermal Actual Dermal Total Inhalation	Specific exposure	Working duration per	Expos Fesu [ms/perso	ure later la	posure result /kg/w/day/ 0.25, 9 0.032	**xbsorbed dose [mg/kg bw/day]
exposure	[mg a.s./hour]	day	[mg/perso	markay] [mg	/kg Bw/dag)	[Ilig/kg Uw/day]
Total Dermal	1.479	10 hours	$\left = \right $ 14.7		¥0.25,\$	
Actual Dermal	0,733 x	a 10 hours	7.3		0.003	0.00025658
Total Inhalation	0.02	1 Phours	0.20		4 002	0.003
Ô	To To	tal systemic expo	osure S			0.0035899
		%XOEI®				5.13
			~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~			
Ky .				/		
, i						
) Î			
			y			
¥ .						



2.4 Estimation of operator exposure during seed treatment, Fluoxastrobin 200 L packaging, , standard clothing

					PPE"						
	Total	Estimated		Frequency of		Total			Inhalation		Ø. °
TO A COLC	Potential	Actual		operation **/	Use of	Potential	Estimated		Exposure	1	
TASK	Dermal	Dermal	Inhalation	operation ^^/	additional	Dermal	Actual Dermal	Inhalation	Worst		. 4
	Exposure	Exposure	Exposure	aay	RPE	Exposure	Exposure	Exposure	case		
1	(mg/op)*	(mg/op)*	(mg/op)*		yes/no	(mg/day)	(mg/day)	(mg/day)	(mg/day)	^ .	
Calibration	4.88	2.13	0.207	1	no	4.8836	2.1342	0.2071			e [©] b
Mixing / Loading	0.7788	0.779	0.019	2	no	1.5576	1.5576	0.0384		8	
g / Louding	0.7700	0.777	0.01)	-		1.5570	1.5570	0.0501		,	
Bagging (mg/hr)	1.84	0.698	0.0054	8	no	14.7200	5.5840	0.0432	0.4320		
Cleaning	131	12.50	2.4	1	no	130.7635		2.4000		K 4	
Dermal absorption/Inhaltion	absorption						V.73%		_@	ľ Ĉ	
1			Calibration			n/a	ı 19 7.73%	100%	-Q	Q)	
			Mixing/loading	3		n/a	0.07%			₩.	
			Bagging Cleaning			n/a	0.07%		0%	\bigcirc	% ,O' ;\
Task specific absorbed d	oco (ma/ka	hw/dov)	Cicaring			n/a n/a n/s	0.73%	100%	D, 070		r. O (V
rask specific absorbed d	ose (mg/kg	Dw/day)	Calibration			M	0.00026	0,00345			Y
			Mixing/loading	,		Qn"	0.00002	0.00064			Q Q
			Bagging	,		. *	6.00007	. 000072		~ ~\	
			Cleaning		(L ,	© 0.00152	₹0.04000	*		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Total absorbed dose (mg	/kg bw/day)				0) 7	@i 0,84	000072 0.04000	0.0001		. 4
# standard clothing of the op	perators is or	ne layer of w	ork clothing du	ring all tasks and	l in addition p	rotective					
* exposure during bagging r	ng/hour		% of AOEL	155.59		M	mg/kg bw/dd/y	Q,		° ~ 0)'
** frequency during bagging	g in hours/day	y	MoS	137	×2,19	6.4	mg/kg bw/day	~		~~ ·	
SCENARIO VARIABLE	S		-	-	(,	~	~~ <u>`</u>			, 0	
Given a.i. concentration =	150	g/l		Enter var	bles in re	d/colour		4	0		
Given dilution factor =	1			.O.	' , ¥	, ×	<u>`</u>	y «	Ĵ		
Given average bodyweight:	60	kg		-0 _A		. \$. O			
Given Dermal absorption				4	<i>~</i>		***		***		4 1
Concentra				Q."		æ.			0		\$
Dilutio			1	* (Ò a	Q		(O)			Y
Given Inhalation absorption	= 100	%		7)	i a)°	\$ (V" .	Ď*	0" 20 (4 .
			~~	· ~ /		4	NY JE	- ~	≪ ⊿	(C) ^p	<u>"</u> "

2.5 Estimation of operator exposure during seed treatment, Fluoxastrobin 200 L packaging, , standard clothing + RPE during cleaning

Total Espirated Frequency of V	Y Total 🖔			Inhalation
TASK TASK	Potentia	Estimated		Exposure -
TASK Dermal Dermal Inhalation with additional	Dermal	A gy al Dermal	Inhalation	Worst
Exposure Exposure Exposure	E@posure	Exposure	Exposure	case
(mg/op)* (mg/op)* (mg/op)* yes/no	(mg/day) 🖔	(mg/day)	(mg/day)	(mg/day)
Calibration	4.8836	2.1342	0.2071	
Mixing / Loading 0.5788 0.779 0.019 2	√J Ø1.5576	1.5576	0.0384	
Bagging (mg/hr) 0.698 0.9054	14.7200	5.5840	0.0432	0.4320
Cleaning 331 1230 2.4 7 1 0	130.7635	12.5046	0.2400	
Cleaning 131 130 2.4 7 1 Ses	n/a	0.73%	100%	0%
Mixing fooding	n/a	0.07%	100%	0%
Bagging	n/a	0.07%	100%	
Task specific absorbed dose (mg/kg bw/kgy) Mixing Touring Clearing Mixing Touring Alibration Mixing Fading Bagging	n/a	0.73%	100%	0%
Task specific absorbed dose (mg/kg bw/lly)				
Talibration Talibration		0.00026		
Mixing Codding		0.00002		
Bagging O'		0.00007		
Total absorbed dose mg/kg wyday)		0.00152		
Total absorbed dos (mg/kg tow/day)		0.01	.07	0.0001

SCENARIO VARIABLES	
Given as concentration =	150 V
Giver dution factor =	
Given average Godyweight =	60 kg
Given Derman absorption	
Concentrate	0.07 %
Dilution	<i>0.73</i> %
Given Inhalation absorption =	100 %

Enter variables in red colour



2.5 Estimation of operator exposure during loading/sowing of treated seeds, fluopicolide, 200 L packaging

SOWING SEED						1	Absorbed dos [mg/kg bw/da
		Total	Estimated			-	
		Potential	Actual				
		Dermal	Dermal	Inhalation			
		exposure	exposure	exposure		S. V.	4 .5
		(mg/day)	(mg/day)	(mg/day)	کے		\$ 2\$
				∂a.			
Loading / Sowing (x)	l 0 hrs)	14.79	7.32	0.200	W .		
			L			L V	
				L	Š		
Total exposure (m	g/kg bw/dow)	0.25	© 0.122	0,003	y Q	Q' \0	o T
Total exposure (III	g/kg bw/day)	0.23	, Pa°	0,403		D D	
		C				\$ 1.	4
		A	Definal 🔍	Inhalation	Total		
Systemic Exposure	(mg/kg bw/day)		// * /	©.003	0:0034189	py 👟 .	
-			Y L				
%AOEL	11.40						, Ö
	Q	,0		# \$\text{\$\text{\$\phi\$}\$\	0,		
	Specific	Working	lg 5	#Unosuk		Expassire &	
Route of	.1.3		ner	result	* . •	**************************************	Absorbed do
exposure	exposure (, dur ægon Alav		mg/person/	da Cill Ima	kg bw day]	[mg/kg bw/da
	[mg u,s.exour]			14.79	W //	y kg o whaty	
Total Dermal	1,479 x	Ø 10 h@ui	s 🎏 .	, O'14.7 %	, <u>u</u>	.0035	
Actual Dermal	0.733	Hou	·s\$\disp\' = \disp\	7,33	O ^r	0.122	0.00008553
Tatal Inhalation®		10 10 10		\$0.2000		0.003	0.002
	1 00.02 % X	10 nour		₩ 0.200°		0.003	0.003
, Q,	To To	tal systemic	exposure	7,33 50.200	<i>V</i>		0.0034189
	1,479 x x 2 0.733 x x 2 0.02 x x x x x x x x x x x x x x x x x x x	AOÎ	L		~		11.40
					,		
				1			
Q			0°	Ž,			
				F			
•							
, W							
		~ ~ C)				
"							
		~					
	P						
Ö							



					PPE#				
	Total	Estimated		Frequency of		Total			Inha © ion
TASK	Potential	Actual		operation **/	Use of	Potential	Estimated		Ex Ssure
IASK	Dermal	Dermal	Inhalation	day	additional	Dermal	Actual Dermal	Inhalation	orst
	Exposure	Exposure	Exposure	auy	RPE	Exposure	Exposure	Exposure @	case
	(mg/op)*	(mg/op)*	(mg/op)*		yes/no	(mg/day)	(mg/day)	(mg/day)∜	(mg (y)
Calibration	6.51	2.85	0.276	1	no	6.5115	2.8456	2762	
Mixing / Loading	1.0384	1.038	0.026	16	o no	16.6149	16.6149	0.409	
Bagging (mg/hr)	1.84	0.698		8	no	Q,7200	5.5 Q 0	0.0432	4320
Cleaning	174	16.67	3.2		no L	174.3514	A5.6728	3.2000	
Dermal absorption/Inhaltion a	bsorption	•	•	O V			Q, (A .	
_	_		Calibration	<i>Q</i> \$\text{7}		°√ n/a	3,90%	∫ √100%	~ 0%
			Mixing/loading	, o	.j	"≪″ n/aչ	(<i>)</i>	°≫100%	V 0%
			Bagging C)"		∜ _m@	ž 🖟 📆 Ž. Ž1%	100%	0%
			Cleaning 4		7, 0	Ø√a	3.90%	√ 10 0 %	4 0%
Task specific absorbed dos					, &	4			
			Calibration	Y'	NO.	Ky ?	O.00185	0,00460	
			Mixang/loading			, X	<i>j" ∯</i> 00058	0.00683	D ~
			Bagging (. Š .	Ş" m	, Q	© 00020	0.00072	
		4	Cleaning &	**************************************			₩ 0.010 %	0.05333	
Total absorbed dose (mg/k	kg bw/day)	- Q	<u> </u>	ping all tasks and			Ø,07		0.0002
standard clothing of the ope	erators is on	e layer of w	ork clothing dr	yng all tasky and	I in Addition p	rotective glo	es except for t	agging	1
exposure during bagging mg	g/hour		%of AOEL	°©112.78		₩ 0.07 ©	mg/kg w/day	O [*]	1
** frequency during bagging	in hours/day	/~ <u> </u>	MoS N	- \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	. 4	36.4	mg@sg bw/day]
SCENARIO VARIABLES		<u> </u>	ı 🔊 ,		\$	4 J . ~			
Given a.i. concentration =	200	g/l 🔏		Enter varia	bley in re	d coloux			
Given dilution factor =	\swarrow 1	Q"	Q O	\(\text{O} \)		/ &,			
Given average bodyweight =	60	NQ .	.		,	O	&"		
Given Dermal absorption	y L				Q.	J. (N n		
Concentrate		% ~				Ÿ :S	7		
C: IIII: 189:	1 3.9	% V		47 %	🔊				
Given innalation absorption =						. 0			
." ا		, Q	4 %						
						A 10			
Š)				2				
			. ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~						
W	, O	Õ .		"O _A ()* [*]				
	O ~C								
1	O'	~Q"	551	ð, <u>e</u>					
(O)	Ò		O' X	,					
				~O*					
. W		. ~	W.						
Y			Q, ŝ	Za Za					
	10	4	W 4						
	4	O A	Ş Q'						
			, W						
, O ×	Ů Š	\swarrow	~Q~						
		a W							
	Õ								
	Ŏ *								
		5							
		5							
		Š.							
Fotal absorbed dose (mg/k) standard clothing of the ope exposure during bagging mg frequency during bagging b		9							



during cleaning	-		-	•		_	-		
					PPE#				@1° %
	Total	Estimated		Frequency of		Total			Intention
TASK	Potential			operation **/	Use of	Potential	Estimated	4	Exposure 6
TASK	Dermal	Dermal	Inhalation	day	additional	Dermal	Actua Dermal		Worst
		Exposure	Exposure	,	RPE	Exposure	Expessire	Exposure	case
	(mg/op)*	(mg/op)*	(mg/op)*		yes/no	(mg/day)	(m@day)	(mg/day)	(n' Gay)
Calibration	6.51	2.85	0.276	1	no	6.5115 4	2.8456	© 0.2762	
Mixing / Loading	1.0384	1.038	0.026	16) no	16.65.49	16.6149	0.4996 0.4996	
Bagging (mg/hr)	1.84	0.698		@\Y	no	Á 4.7200	5,5,840 	Q 0.0432	0.4320
Cleaning	174	16.67	3.2	Tring all tooks and	yes	√ 174. 25 √14	¥6.6728	-	
Dermal absorption/Inhaltion a	bsorption					~@'	~ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		
			Calibration	u. To		√y n/a	/ (b) 3 399 %	×100%	J 0%
			Mixing/loading)		√ n/á	0,21%	100%	0%
			Bagging) A	″00.21%		₽ 2%
			Cleaning			n/a	3.90%		<i>®</i> ⁸ %
Total absorbed dose (mg/k# standard clothing of the ope * exposure during bagging ing ** frequency during bagging ing ** Given a.i. concentration = Given dilution factor = Given Dermal absorption Concentration Given Inhalation absorption Given Inhalation	se (mg/kg	bw/day)		~" ~"	Ö		, O' , & ,	So r	
			Calibration 2	~'(Q' -		0′ 🔣	0.60185	9/00460	
			Muxing/loading			<i>ૺ</i>	9.00058	0.00683	
		A	Bagging	~_{\text{A}} \%	J' ~		₹0.0002#	0.00072	
T-4-1-hh-1-1(/l-	- 1(1)	Q,	Cleaning		ĮŠ'	.0	0.010824	0.09533	
# standard clothing of the ope	g bw/day)	- 10 ml of 12	الله و سنطاع السور	Ome all tooks and	U) Ling (Adition of		9.03	009 °	0.0002
# standard clothing of the ope	rators is on	e layer or w	ork clothing du	ring all tooks and	i in addition a	rojective gio	ves except for t	aggang (1
** fraguency during bagging mg	ynour 'n bourg/dox	, ^W	Mos C	44.21	, 4	× 6.4	mg/kg bw/day		
SCENADIO VADIARI ES	n nours/day		INIOS			0.4	Augusty DW/Q		ı
SCENARIO VARIABLES		4	1 [©] 4						
Given a.i. concentration =	200	g/1	i de la constant de l	Entervaria	ibres in re	d colour	, 6)		
Given dilution factor =	1		J [*]		, ^y Oʻ		1. J.		
Given average bodyweight =	7) 60	kg		J J	On	0	**		
Given Dermal absorption	, 0 y		. W	, <u>,</u>			<u>V</u>		
Concentrate	0.21	%.\(\sigma^*	Q. ~				y		
Oilution	3.9	8 (_			
Given Inhalation absorption =	100	%	Ĭ ~		0~	_ Q			
`. Q	<i>√</i> ,	4 1	4		Q1				
	õ					¥			
	" <i>©</i> ,	(O)		″o,	J' ,_O				
) L	,		47 4	1				
J.	g · S			~~ O'	^ .				
	\Rightarrow			Ĭ "					
Q _I	ON TO		Ò Ö		7				
	Ò, c								
.4	8	~O*	5Q (
	Ĉo	S.							
		Q .							
4 n	Ş' 4								
			Q, 5	Ş"					
- 4	10	"Č"	a. 1.)					
	a \								
		ji L	,						
		, √ 1	~0						
		Š	¥						
	4 .								
		2							
, Ő									
Ũ									



2.8 Estimation of operator exposure during seed treatment, fluoxastrobin, 25 L packaging, standard clothing

					PPE#				<i>@</i> ,
	Total	Estimated			112	Total			In Cation
m., arr	Potential	Actual		Frequency of	Use of	Potential	Estimated		Exposure O
TASK	Dermal	Dermal	Inhalation	operation **/	additional	Dermal	Actua Dermal	Inhalation	Worst
	Exposure	Exposure	Exposure	day	RPE	Exposure	Exposure	Exposure	case
	(mg/op)*	(mg/op)*	(mg/op)*		yes/no	(mg/day)	(mg day)	(mg/day)	(mgyay)
Calibration	4.88	2.13	0.207	1	no	4.8836	2.1342	0.2071	
Mixing / Loading	0.7788	0.779	0.019	16 N	no no	12 4 §12	12.4612	0.3092	
Bagging (mg/hr)	1.84	0.698	0.0054	ring all looks and	no L	94.7200 	5/\$ 38 40	0.0432	\$\text{0.432}\text{(\$\frac{\text{C}}{\text{7}}}\text{\text{2}}
Cleaning	131	12.50	2.4		no	130.1635	12.5046	2.4000	
Dermal absorption/Inhaltion a	bsorption								~~
			Calibration	Z Š	, D	" n/a	<i>J</i>	× 100%	& " 0%
			Mixing/loading)"@`		NO NO	√ %°07%	100%	0%
			Bagging		7) Q.	Ø≯a	0.07%	5 10 9	2 %
m 1	, -		Cleaning		, ». ¥	n/a	0.73%	JO 5%	20 0%
Task specific absorbed dos	se (mg/kg	bw/day)	C-18.	7 67		Zy" ?	0	Socar-	
			Calleration /		~~ ~ ~		0.00026	0.00345	D
		ā	onexing/loagaing		S 0		Ø.00015	0.005 12 0.00672	
			Cleaning Cleaning	, ×		7	J*U.UUU₩	9.04000 9.04000	
Total absorbed does (ma/l	a hw/dov)	4	Cleaning			10 ×	O U.UU452	9,U4UUU 13	0.0001
# standard clothing of the ope	ratore is on	e laser of w	ork clothing du	ring all tasks and	Lin addition in	ratective glo	ves event for h	a modina	0.0001
* evnocure during bagging mo	/hour	c jayya or w	% of A ONE	170 95	Tall addition of	On 3	malka bw/day	O Balling	1
** frequency during bagging in	n hours/day		MoS &	170.93	, 4	6.4	hadka bw/day		
SCENARIO VARIARLES	1 \	0	WIOS S		_ 0	% (y 0.∓			1
G: : : : : :	150	n 🕰.		Entalloria		d colour			
Given a.i. concentration =	150		Q O	Ellesyaria		u colour	~		
Given dilution factor =			V @	\$ \$,"	O _x	4		
Given average bodyweight		Kg 🔊			"W		Nn		
Given Dermal absorption	0,00	W 4 .		Y 2~ Y	. S		7		
Concentrate	0.07	%~\		.,4					
Pilution	0.73	Ö(Øn.			
Given Inhalation absorption	y' 1000.	1% (h)	l . « * *		0	45			
	\swarrow),	<i>\(\mathbb{O}\)</i>	~			
		Ş				1			
Ky' .	% %	Y) 4,							
~) / 4		~ O.	&					
	21	Q"		<i>y</i> 0	8				
Q	Ø. **		, O 📉		Q"				
Q	,Oy (Õ ~	9 ,0"	~~O,	Ď*				
~Q	0,	Q'		ð .,O					
~Q (01 ×						
	, <i>©</i>			~ n					
		Q _							
	,								
	J J								
Fotal absorbed dose (mg/k) # standard clothing of the ope * exposure during bagging in ** frequency during bagging in SCENARIO VARIABLES Given a.i. concentration = Given dilution factor = Given Dermal absorption Concentrate Other Dermal absorption Concentrate Given Inhalation absorption									



2.9 Estimation of operator exposure during seed treatment, fluoxastrobin, 25 L packaging, standard clothing + RPE during cleaning

