Document Title

Summary of the toxicological studies for Fluopyram + Trifloxystrobin SC 500 (250 + 250 g/L)

Data Requirement(s)

Regulation (EC) No 1107/2009 & Regulation (EU) 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 substance

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Author(s)

[redacted]

Bayer AG

Crop Science Division

OWNERSHIP STATEMENT

Version history

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

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4, 'How to revise an Assessment Report'.

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Fluopyram was included in Annex I to Council Directive 91/414/EEC in 2013 (Regulation (EU) 802/2013, Entry into Force on August 22, 2013). This Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of Fluopyram 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 I inclusion 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 Bayer.

The formulation Fluopyram + Trifloxystrobin SC 500 (250+250 g/L), abbreviation FLU+TFS SC 500, is a SC formulation containing 250 g/L of Fluopyram and 250 g/L of Trifloxystrobin This formulation is registered throughout Europe under trade names such as Luna Sensation. FLU+TFS SC 500 was not already a representative formulation of Bayer AG for the Annex I inclusion of Fluopyram under Council Directive 91/414/EEC.

CP 7.1 Acute toxicity

The acute toxicity studies have been conducted with formulation Fluopyram + Trifloxystrobin SC 500 (abbreviation: FLU+TFS SC 500) (specification 102000012886, batch 2006-004983).

FLU+TFS SC 500 is of low toxicity by the oral route of exposure in the Wistar rat and non-toxic by the dermal route of exposure in the Wistar rat. Acute inhalation exposure to FLU+TFS SC 500 in Wistar rats up to the maximal technically attainable concentration of 1742 mg/m^3 resulted in no deaths and transient signs of toxicity (bradypnea, laboured breathing patterns, motility reduced and piloerection in females). FLU+TFS SC 500 showed no potential to cause skin or eye irritation in the NZW rabbit and was shown to have no potential for skin sensitisation in the Local Lymph Node Assay.

Classification/labelling based on the toxicological studies and all submitted data:

Regulation (EC) No 1272/2008 (CLP):

- Acute Tox. 4 / H302: Harmful if swallowed (based on product data)

Table 7.1- 1: Acute toxicity studies with FLU+TFS SC 500

Study Type	Species	Results	Reference
Acute oral toxicity	Rat	LD_{50} cut off 2000 mg/kg bw	M-287410-01-1
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg bw	M-287408-01-1
Acute inhalation toxicity	Rat	LC_{50} > 1742 mg/m^3 (maximal technically attainable concentration)	M-287413-01-1
In vitro skin corrosive test	3D skin model	Non-corrosive	M-283575-01-1
Skin irritation	Rabbit	Non-irritant	M-283572-01-1
Eye irritation	Rabbit	Non-irritant	M-283570-01-1
Skin sensitisation LLNA	Mouse	Non-sensitizing	M-281763-01-1

CP 7.1.1 Oral toxicity

Data Point:	KCP 7.1.1/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 - Acute toxicity in the rat after oral administration
Report No:	AT03692
Document No:	M-287410-01-1
Guideline(s) followed in study:	OECD 423 (2001); EEC Directive 67/548 Annex V - Method B.1.tris; EPA 712-C-98-190, OPPTS 870.1100
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250 g/L
Abbreviation: FLU+TFS SC 500

Specification no.:	102000012886
Description:	Beige suspension
Lot/Batch no.:	2006-004983
Content:	Fluopyram (AE C656948): 246.1 g/L certified CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: Tap water

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu (SPF)
Age:	10 - 12 weeks
Weight at dosing:	167 - 193 g
Source:	[redacted]
Acclimatisation period:	At least 5 days
Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	The animals were group caged in polycarbonate cages on low dust wood granulate bedding.

B. Study design and methods

1. Animal assignment and treatment

Dose:	The substance was tested using a stepwise procedure, each step using three female rats according to the procedure described in OECD Test Guideline No 423. Refer to Table 7.1.1-1.
Application route/ exposure:	Single oral gavage dose
Application volume:	10 mL/kg bw
Fasting time:	Food was withheld from the animals for approx. 16 - 24 h before administration of the test compound, and they were fed again approx. 2 - 4 h after administration.
Group size:	3 females
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological result*	Occurrence of signs	Time of death	Mortality (%)
Female rats				
(1st) 2000	0 / 3 / 3	20 min - 6 h	No deaths	0
(2nd) 2000	2 / 3 / 3	35 min - 4 h	2 h - 4 h	67
(1st) 300	0 / 0 / 3	No signs	No deaths	0
(2nd) 300	0 / 0 / 3	No signs	No deaths	0
* number of animals which died spontaneously and/or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group				
LD_{50} cut-off: 2000 mg/kg bw				

B. Clinical observations

The following clinical signs were observed in animals treated with 2000 mg/kg bw.: decreased motility, uncoordinated gait, abdominal position and labored breathing.
No clinical signs were observed in animals treated with 300 mg/kg bw.

C. Body weight

There were no toxicological effects on body weight or body weight gain in the surviving animals treated with 2000 mg/kg bw and in animals treated with 300 mg/kg bw.

D. Necropsy

The necropsies performed at the end of the study revealed no particular findings in the surviving animals treated with 2000 mg/kg bw and in animals treated with 300 mg/kg bw.
In the animals treated with 2000 mg/kg bw that died during the observation period the following changes were detected: liver dark-red, spotted.

III. Conclusion

According to OECD guideline 423 the LD_{50} cut-off of FLU+TFS SC 500 is 2000 mg/kg bw.
The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): Acute Tox. 4 / H302 (Harmful if swallowed)

Assessment and conclusion by applicant:
Study meets the current guidance and the requirements in 283/2013. Regulation (EC) No 1272/2008 (CLP). The acute oral LD50 cut-off of FLU + TFS SC 500 is 2000 mg/kg bw in rats. Thus, classification as Acute Tox 4/H302 (Harmful if swallowed is required according to Regulation (EC) No. 1272/2008.

CP 7.1.2 Dermal toxicity

Data Point:	KCP 7.1.2/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 - Acute toxicity in the rat after dermal application
Report No:	AT03690
Document No:	M-287408-01-1
Guideline(s) followed in study:	OECD 402 (1987); EEC Directive 67/548 Annex V - Method B.3; EPA 712-C-98-192, OPPTS 870.1200
Deviations from current test guideline:	The current Guideline is OECD 402 (2017). This study was performed to OECD 402 (1987). Deviations: 5 animals/sex/dose treated once, rather than testing 3 animals of single sex in a stepwise approach (animal reduction methods). This deviation has no impact on the outcome of the study and interpretation of the results.
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500

Specification no.:	102000012886
Description:	Beige suspension
Lot/Batch no:	2006-004983
Content:	Fluopyram (AE C656948): 246.1 g/L certified CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: None

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu (SPF)
Age:	9 - 13 weeks
Weight at dosing:	Males: 239 - 246 g; Females: 212 - 215 g
Source:	[redacted]
Acclimatisation period:	At least 5 days

Diet:	Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	The animals were caged individually in polycarbonate cages on low dust wood granulate bedding.

B. Study design and methods

1. Animal assignment and treatment

Dose:	Dose (mg/kg bw)		Surface area (cm²)	Range of doses (mg/cm²)
	Males	2000	16.0	29.9 - 30.8
	Females	2000	14.0	30.3 - 30.7

Application route:	Dermal, semi-occlusive dressing
Exposure:	24 hours
Group size:	5 rats/sex/group
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*	Occurrence of signs	Time of death	Mortality (%)
Male rats				
2000	0 / 0 / 5	No signs	No deaths	0
Female rats				
2000	0 / 0 / 5	No signs	No deaths	0
* number of animals which died spontaneously and/or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group				
LD_{50} > 2000 mg/kg bw				

B. Clinical observations

No clinical signs were observed.

C. Body weight

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

D. Necropsy

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

III. Conclusion

The median lethal dose of FLU+TFS SC 500 after a single dermal administration was found to be greater than 2000 mg/kg bw in male and female RccHan:WIST rats.

The study result triggers the following classification/labelling:

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

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. Acute toxicity via the dermal route is low in the rat. The LD_{50} > 2000 mg/kg bw does not trigger classification.

CP 7.1.3 Inhalation toxicity

Data Point:	KCP 7.1.3/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 - Activity ID TXGMP033- Acute inhalation toxicity in rats
Report No:	AT03716
Document No:	M-287413-01-1
Guideline(s) followed in study:	OECD 403 (1981); Directive 92/69/EEC, Annex V - Method B.2 (1992); US EPA OPPTS 870.1300 (1998); Japan MAFF, Notification No. 12 Nohsan-8147 (2000)
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500

Specification no.:	102000012886
Description:	Beige suspension
Lot/Batch no.:	2006-004983
Content:	Fluopyram (AE C656948): 246.1 g/L certified CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: The test article was aerosolized diluted with water

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu (SFP)
Age:	Approx. 2 - 3 months old
Weight at dosing:	Males: 185 - 222 g; Females: 177 - 189 g
Source:	[redacted]
Acclimatisation period:	At least 5 days

Diet:	Standard fixed-formula diet (KLIBA 3883 = NAFAG 9441 pellets maintenance diet for rats and mice; PROVIMI KLIBA SA, 4303 Kaiseraugst, Switzerland), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Animals were housed singly in conventional Makrolon® Type IIIH cages

B. Study design and methods

1. Animal assignment and treatment

Application route:	Inhalation (nose-only)
Exposure:	4 hours
Group size:	5 males and 5 females
Post-treatment observation period:	14 days
Observations:	Mortality, clinical signs, body temperature, body weight, gross necropsy

2. Generation of the test atmosphere / chamber description

Table 7.1.1-1 Technical information concerning generation of test atmospheres

	Group 1	Group 2
Target concentration (mg/m³)	0	5000
Nominal concentration (mg/m³)	Control water	14655.3
Gravimetric concentration (mg/m³)	--	832.5
Actual concentration [1] (mg/m³)	--	1742
Recovery (%)		12
Inlet Air Flow (l/m)	15	15
Exhaust Air flow (l/min)	13	13
Temperature (mean, °C)	22.6	21.7
Relative humidity (mean, %)	> 95	> 94.7
MMAD (µm)	--	2.81
GSD	--	1.84
Aerosol mass < 3 µm (%)	--	54.5
Mass recovered (mg/m³)	--	668.4

Recovery = Actual Conc x 100/ Nominal Conc.; MMAD = Mass Median Aerodynamic Diameter, GSD = Geometric Standard Deviation, -- = not applicable. 1) Actual concentration: conversion to test substance: gravimetric conc. x 100/(100-52.2)

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Actual Concentration (mg/m³)	Toxicological result*	Occurrence of signs	Time of death	Mortality (%)
Male				
(Group 1) 0	0 / 0 / 5	No signs	No deaths	0
(Group 2) 1742	0 / 5 / 5	Signs on day 0 only	No deaths	0
Female				
(Group 1) 0	0 / 0 / 5	Signs on day 0 signs	No deaths	0
(Group 2) 1742	0 / 5 / 5	Day 0 only	No deaths	0
* number of animals which died spontaneously and/or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group				
LC_{50} > 1742 mg/m³ (maximal technically attainable concentration)				

B. Clinical observations

Group 1: All rats tolerated the test without specific signs.

Group 2: Signs (bradypnea, laboured breathing patterns, motility reduced and piloerection) seen on day 0.

A battery of reflex measurements was made on the first post exposure day. All rats tolerated the exposure without abnormal reflexes.

C. Body weight

Body weight of male control and exposure rats defer significantly at begin of the study (day 0). After exposure body weight of both groups revealed a slight decrease (day 1). Comparison of body weight development during the observation period between the control and the test groups indicate no significant differences.

D. Rectal temperatures

Rectal temperature measured shortly after cessation of exposure was lower (statistically significant) in both treated groups when compared to their respective controls.

E. Necropsy

Individual gross-pathological examinations of the rats indicate at two male and female rats light-coloured areas at the lung.

III. Conclusion

The test item (liquid aerosol) proved to have low inhalation toxicity in rats. For both genders combined, the LC50 is greater than 1742 mg/m³ (maximal technically attainable concentration)

Proposed classification/labelling:

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

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. Acute toxicity via the inhalation route is low in the rat. The LC_{50} was > 1742 mg/m³. As this was the maximal technically attainable

concentration, and as there were no deaths and only transient clinical signs, no classification is warranted for acute inhalation toxicity.

CP 7.1.4 Skin irritation

Data Point:	KCP 7.1.4/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 - Acute skin irritation/corrosion on rabbits
Report No:	AT03623
Document No:	M-283572-01-1
Guideline(s) followed in study:	OECD 404 (2002); EEC Directive 67/548 Annex V - Method B.4 (1967); EPA OPPTS 870.2500; MAFF 12 Nousan No 8628 (December 06, 2000)
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500

Specification no.:	1020000112886
Description:	Beige suspension
Lot/Batch no:	2006-004983
Content:	Fluopyram (AE C656948): 246.1 g/L certified CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: none

3. Test animals

Species:	Albino rabbit
Strain:	Crl:KBL(NZW)BR
Age:	Young adult
Weight at dosing:	2.4 - 2.6 kg
Source:	[redacted]
Acclimatisation period:	At least 5 days
Diet:	Standard diet "Ssniff K-Z" 4mm (Ssniff Spezialdiaeten GmbH, Soest, Germany), 100 g per animal per day; roughage: hay, irradiated (Harlan Winkelmann GmbH, Borchen, Germany), hay pellets (ssniff Spezialdiaeten GmbH, Soest, Germany)
Water:	Tap water, *ad libitum*

Housing: Individually in cage units Metall/Noryl by EBECO

B. Study design and methods

1. Animal assignment and treatment

Dose: 0.5 mL/patch
Application route: Dermal
Exposure: 4 hours
Group size: 3 females
Observations: Clinical signs, skin effects, body weight

II. Results and discussion

A. Findings

Table 7.1.4-1 Summary of irritant effects (Scores)

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

na = not applicable

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

III. Conclusion

FLU+TFS SC 500 is not irritating to the skin of rabbits.

The study result triggers the following classification/labelling:

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

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The product does not provoke skin irritation and the results do not trigger classification.

Data Point:	KCP 7.1.4/02
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 (Profect: AE C656948) - Evaluation of corrosive properties by using an artificial 3D-skin model
Report No:	AT03577
Document No:	M-283575-01-1
Guideline(s) followed in study:	OECD 404; EPA 40 CFR part 160 (1989) MAFF 12 Nousan No 8628 (December 06, 2000); Equivalent to US EPA OPPTS 870.2500 SUPP
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500

Specification no.: 102000012886
Description: Beige suspension
Lot/Batch no: 2006-004983
Content: Fluopyram (AE C656948): 21.1% w/w
CGA 279202 (Trifloxystrobin): 21.1% w/w
Stability of test compound: Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: None

3. Test system Reconstructed human epidermis EST-1000 (CellSystems, St. Katharinen, Germany).

B. Study design and methods

Test system: The tissue equivalents were shipped in 24 well cell culture plates on Agarose supplemented with maintenance medium (Kit contents EST-1000; CellSystems, Cat- No.CS-1001). Inserts were of 0.63 cm^2 size. All tests were performed in triplets for each concentration and each time point (3 min or 60 min).

Concentration: The test item was applied at a 100% concentration, i.e. 50 µL per insert.

Application of the test material and incubation: For testing of chemical induced corrosivity the EST-1000 inserts were exposed to 50 µL of the test item for 3 min (RT) and 60 min in the incubator (3 inserts per period of incubation time), respectively. 0.9% NaCl (50 µL) treated epidermal models were used as negative controls (determination in triplicates).

Determination of cell viability (MTT):	After the incubation period the inserts were washed carefully in PBS and MTT reduction was performed. For viability testing the inserts were placed in new 24 well plates containing 300 µL of MTT solution (37°C,1mg/ml in MTT-assay medium). The tissues were incubated for about 2 hours under cell culture conditions (5% CO_2, 37°C, max humidity). The extraction of blue formazan was performed in Isopropanol (24 well plates, 2 ml per insert) on a vertical shaker (at least 60 min). For determination of cell viability the absorption of the Isopropanol-extracts was measured in duplicates at 570 nm in an automatic reader (EL808, Bio-Tek; 96 well format, 200 µL). Data acquisition and evaluation were done with "KC4" (software by Bio-Tek).
Reliability Check:	Reliability of the test was confirmed before by interlaboratory Validation.
Evaluation criteria:	Substances are classified as corrosive, if the cell viability of the EST 1000 is decreased by more than 50% after 3 min of incubation to the test item, or if the cell viability is less than 15% after 60 min of exposure to the test item.

II. Results and discussion

A. Findings

FLU+TFS SC 500 was not detected as positive (exceeding the LD_{50} value and the 15% viability value, respectively) by the EST-1000 model after an incubation period of 3 min or 60 min.

Table 7.1.4-1 Summary of results

Compound	Cell viability after 3 min [%]	Cell viability after 60 min [%]	Classification*
FLU+TFS SC 500	92.50	95.73	Non-Corrosive Negative Control
Negative control	100.00	100.00	
* Classification was done in accordance with the existing guideline and internationally accepted protocols, i.e. evaluation of LD_{50} values after 3 min and/or less than 15% viability after a 60 min incubation period.			

III. Conclusion

FLU+TFS SC 500 was not characterised by a significant impact on cell viability after the 3 min and after the 60 min period.

Thus, FLU+TFS SC 500 should not be labelled as corrosive to skin.

Assessment and conclusion by applicant:

FLU+TFS SC 500 does not provoke skin corrosion and the results do not trigger classification.

CP 7.1.5 Eye irritation

Data Point:	KCP 7.1.5/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 & trifloxystrobin SC 250 & 250 (AE C656948 + TFS SC 250+250 G) - Acute eye irritation on rabbits
Report No:	AT03624
Document No:	M-283570-01-1
Guideline(s) followed in study:	OECD 405 (2002) EEC Directive 67/548 Annex V - Method B.5. (1967) EPA OPPTS 870.2400 MAFF 12 Nousan No 8628 (December 06, 2000)
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500
Specification no.: 102000012886
Description: Beige suspension
Lot/Batch no: 2006-004983
Content: Fluopyram (AE C656948): 246.1 g/L certified
CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound: Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: None

3. Test animals
Species: Rabbit
Strain: Crl:KBL(NZW)BR
Age: Young adult animals
Weight at dosing: 3.0 - 3.6 kg
Source: [redacted]
Acclimatisation period: At least 5 days
Diet: Standard diet "Ssniff K-Z" 4mm (Ssniff Spezialdiaeten GmbH, Soest, Germany), 100g per animal per day; roughage: hay, irradiated (Harlan Winkelmann GmbH, Borchen, Germany), hay pellets (ssniff Spezialdiaeten GmbH, Soest, Germany)
Water: Tap water, *ad libitum*
Housing: Individually in cage units Metall/Noryl by EBECO

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.1 mL in one eye/animal
Application route:	Instillation into the conjunctival sac
Rinsing:	After 24 hours
Group size:	3 females
Observations:	Clinical signs, eye effects, body weight

II. Results and discussion

A. Findings

There were no relevant systemic intolerance reactions.

Table 7.1.5-1 Summary of Irritant Effects (Scores)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	na
	Chemosis conjunctivae	0	0	0	0.0	--	na
2	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	1*
	Chemosis conjunctivae	0	0	0	0.0	--	na
3	Corneal opacity	0	0	0	0.0	--	na
	Iritis	0	0	0	0.0	--	na
	Redness conjunctivae	0	0	0	0.0	--	1*
	Chemosis conjunctivae	0	0	0	0.0	--	na

* In respect of the result 1 h post application

Na: not applicable

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

III. Conclusion

FLU+TFS SC 500 is not irritating to the eyes of rabbits.

The study result triggers the following classification/labelling:

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

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The product does not provoke eye irritation and the results do not trigger classification.

CP 7.1.6 Skin sensitization

Data Point:	KCP 7.1.6/01
Report Author:	[redacted]
Report Year:	2006
Report Title:	AE C656948 and trifloxystrobin SC 250 & 250 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No:	SA 06266
Document No:	M-281763-01-1
Guideline(s) followed in study:	OECD guideline 429 (2002)
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: AE C656948 + Trifloxystrobin SC 250+250
Abbreviation: FLU+TFS SC 500

Specification no.: 102000012886
Description: Beige suspension
Lot/Batch no.: 2006-004983
Content: Fluopyram (AE C656948): 246.1 g/L certified
CGA 279202 (Trifloxystrobin): 245.8 g/L certified
Stability of test compound: Guaranteed for study duration; expiry date: 24 October 2007

2. Vehicle: 1% aqueous Pluronic Acid

3. Test animals

Species: Mouse
Strain: CBA/J
Age: At least 8 weeks
Weight at dosing: 21 - 23 g
Source: [redacted]
Acclimatisation period: At least 5 days
Diet: Certified rodent pellet and irradiated diet: AO4C-10, S.A.F.E. (Scientific Animal Food and Engineering, Route de Saint Bris, Augy, France), *ad libitum*
Water: Filtered and softened tap water, *ad libitum*
Housing: Housed individually in suspended, stainless steel, wire-mesh cages

B. Study design and methods

1. Animal assignment and treatment

Dose:	0% - 25% - 50% - 100%
Application route:	Topically applied onto the dorsal surface of both ears
Application volume:	25 µL/ear
Exposure:	Three consecutive days (d0, d1, d2)
Group size:	5 females/group
Observations:	On day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices. Clinical signs (daily), body weight (at beginning and termination of study).

II. Results and discussion

A. Findings

No mortality was observed during the study. All animals treated at concentration of 100% had depilation around the ears. No cutaneous reactions were observed at the treated sites for the negative control or FLU+TFS SC 500 treated groups.

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

Results of the proliferation assay are summarized in the following table:

Table 7.1.6-1 DPM, DPN and Stimulation Index Values for all Groups

Test Group Name	DPM	Number of lymph nodes	DPN	Stimulation Index
Control 1% aqueous Pluronic Acid	3304	10	330	-
FLU+TFS SC 500 25% in 1% aqueous Pluronic Acid	3915	10	392	1.2
FLU+TFS SC 500 50% in 1% aqueous Pluronic Acid	3276	10	328	0.99
FLU+TFS SC 500 100% (undiluted)	3362	10	36	1.0

Negative lymphoproliferative responses (SI<3) were noted for FLU+TFS SC 500 at all concentrations tested.

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

FLU+TFS SC 500 was found to be a non-sensitizing formulation in the Local Lymph Node Assay.

III. Conclusion

FLU+TFS SC 500 is not sensitising in the local lymph node assay on mice.

The study result triggers the following classification/labelling:

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

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. No sensitizing potential was noted, and the results do not trigger classification.

CP 7.1.7 Supplementary studies on the plant protection product

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the active substance(s) or other components in Fluopyram + Trifloxystrobin SC 500 (250 + 250 g/L) that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since Fluopyram + Trifloxystrobin SC 500 (250 + 250 g/L) is not intended for use in combination with other plant protection products.

CP 7.2 Data on exposure

Evaluations of the exposure of operators, bystanders, residents and re-entry workers to Fluopyram when used in the FLU+TFS SC 500 formulation are provided in the following sections.

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

Product	FLU+TFS SC 500						
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.						
Active substance(s) (incl. content)	**Substance Concentration** [g/L or g/kg]	**AOEL$_{systemic}$ (RVMAS)** [mg/kg bw/d]	**AAOEL$_{s}$ (RVAAS)** [mg/kg bw/d]	**Inhalation absorption [%]**	**Oral absorption [%]**	**Dermal absorption***	
						Concentrate **[%]**	Dilution **[%]**
Fluopyram (FLU)	250	0.05	-	100	100	0.083	18
Trifloxystrobin (TFS)	250	0.06	0.3	100	60	0.14	16

**For more information please refer to CP 7.3*

Selection of representative use and justification

The critical GAP(s) used for the exposure assessment of the plant protection product is/are shown in A list of all intended uses within the zone/ EU is given in Part B, Section 0.

Table 7.2-2: Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	Crops and situation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, bystander or resident exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind (incl. application technique ***	Max. number (min. interval between applications) a) per use b) per crop/ season	Max. application rate kg as/ha a) a.s. 1 b) a.s. 2	Water L/ha min / max			Operator	Worker	Bystander	Resident(s)
2	Grape (VITVI) (BBCH 53-73)	F	spraying (broadcast, overall) HCTM	a) 2 (7 d) b) 2 (7 d)	a) 0.05 b) 0.05	500 – 750	14	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874				
5	Lettuce (LACSA) (BBCH 12-49)	G	spraying, LCHH, high-tech soil-less greenhouse	2 (7 d)	a) 0.8 b) 1.6	500-1000	3	Operators [Dutch model, Southern Greenhouse Model, Trolley Model, EUROPOEM 2, BfR Model], Workers (EFSA Model, EFSA Journal 2014;12(10):3874)				

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Justification

The chosen use no. 2 covers the representative use in the scope of operator, resident/bystander and worker exposure.

For the chosen use no. 5 the greenhouse indoor applications, no EU-harmonised model is currently available. Therefore, all known indoor exposure model are applied in this risk assessment for this representative use.

1. ECPA Greenhouse model
2. Dutch Greenhouse model (Van Golstein Brouwers, Y.G.C., Marquart, J. and Van Hemmen, J.J. (1996). Assessment of occupational exposure to pesticides in agriculture. Part IV. Protocol for the use of generic exposure data. TNO Nutrition and Food Research Institute, The Netherlands. TNO Report V 96.120)

3. Joint development of a new Greenhouse Agricultural Operator Exposure Model for hand-held application (Draft, submitted to EFSA). 75th centile and 95th centile. More information can be found here: https://mobil.bfr.bund.de/cm/350/joint-development-of-a-new-greenhouse-agricultural-operator-exposure-model-for-hand-held-application.pdf
4. AEPLA Trolley Study (exposure values cited in: Evaluation criteria for the estimation of the exposure of operators, workers, residents and bystanders to plant protection products, Ministerio de Sanidad, Servicios Sociales E Igualdad, Version 02; Nov. 2020) – **Spanish requirement**
5. EUROPOEM 2 Model (exposure values cited in: Evaluation criteria for the estimation of the exposure of operators, workers, residents and bystanders to plant protection products, Ministerio de Sanidad, Servicios Sociales E Igualdad, Version 02;Nov. 2020) – **Spanish requirement**

CP 7.2.2 Operator exposure

CP 7.2.2.1 Estimation of operator exposure

A summary of the exposure models used for the estimation of operator exposure to the active substance(s) during application of FLU+TFS SC 500 according to the critical use(s) is presented in the following table. Detailed calculations are presented on page 31 ff.

Table 7.2-3: Exposure models for intended uses

Critical use(s)	0.2 L / kg product/ha for Grapes 0.8 L / kg product/ha for Leaf vegetables and fresh herbs (greenhouse)
Model(s)	***Outdoor*** *Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874* ***Indoor*** *For the greenhouse indoor applications, no EU-harmonised model is currently available. Therefore, all known indoor exposure model are applied in this risk assessment:* *1. ECPA Greenhouse model* *2. Dutch Greenhouse model ([redacted] (1996). Assessment of occupational exposure to pesticides in agriculture. Part IV. Protocol for the use of generic exposure data. TNO Nutrition and Food Research Institute, The Netherlands. TNO Report V 96.120)* *3. Joint development of a new Greenhouse Agricultural Operator Exposure Model for hand-held application (Draft, submitted to EFSA). 75th centile and 95th centile. More information can be found here: https://mobil.bfr.bund.de/cm/350/joint-development-of-a-new-greenhouse-agricultural-operator-exposure-model-for-hand-held-application.pdf* *4. AEPLA Trolley Study (exposure values cited in: Evaluation criteria for the estimation of the exposure of operators, workers, residents and bystanders to plant protection products, Ministerio de Sanidad, Servicios Sociales E Igualdad, Version 02; Nov. 2020) – Spanish requirement* *5. EUROPOEM 2 Model (exposure values cited in: Evaluation criteria for the estimation of the exposure of operators, workers, residents and bystanders to plant protection products, Ministerio de Sanidad, Servicios Sociales E Igualdad, Version 02; Nov. 2020) – Spanish requirement*

The outcome of the estimation is presented in the following table(s).

Table 7.2-4: Estimated operator exposure, Fluopyram, Grapes

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Upward spraying, Vehicle-mounted Application rate: 0.05 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.00681	13.6
	with PPE[3]	0.00273	5.46

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered, In addition gloves during mixing and loading and when handling contaminated surfaces during application

Table 7.2-5: Estimated operator exposure, Trifloxystrobin, Grapes

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Upward spraying, Vehicle-mounted Application rate: 0.05 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.00617	10.3
	with PPE[3]	0.00251	4.19

[1] AOEL (RVNAS) of TFS: 0.06 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered, In addition gloves during mixing and loading and when handling contaminated surfaces during application

Table 7.2-6: Estimated acute operator exposure, Trifloxystrobin, Grapes

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL[1] (RVAAS)
Outdoor, Upward spraying, Vehicle-mounted Application rate: 0.05 kg a.s./ha			
EFSA Operator Model (95th quantile regression)	no PPE[2]	0.0195	6.5
	with PPE[3]	0.0122	4.06

[1] AAOEL (RVAAS) of TFS: 0.3 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered, In addition gloves during mixing and loading and when handling contaminated surfaces during application

Table 7.2-7: Estimated operator exposure, Fluopyram

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Indoor, Downward spraying, Handheld Application rate: 0.2 kg a.s./ha			
ECPA Greenhouse Model, Low Crop standard	no PPE[2]	0.00514	10.3
	with PPE[3]	0.001709	3.4
ECPA Greenhouse Model, Low Crop, intensive contact with treated crop	no PPE[2]	0.20546	410
	with PPE[4]	0.006091	12.2
Dutch Greenhouse model, Handheld	no PPE[2]	0.1233	247
	with PPE[3]	0.01533	31
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, normal crop	no PPE[2]	0.05645	112
	with PPE[3]	0.00114	2.3
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, normal crop	no PPE[2]	0.2617	523
	with PPE[3]	0.01192	23.8
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, dense crop	no PPE[2]	0.4505	901
	with PPE[4]	0.00284	5.7
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, dense crop	no PPE[2]	1.0526	2105
	with PPE[4]	0.00637	12.7
AEPLA Trolley Study	no PPE[2]	0.019596	39.2
	with PPE[3]	0.006710	13.4
EUROPOEM 2 Model, high crop	no PPE[2]	0.034042	68.1
	with PPE[3]	0.021156	42.3
EUROPOEM 2 Model, low crop	no PPE[2]	0.017258	34.5
	with PPE[3]	0.006885	13.8

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing and loading and when handling contaminated surfaces during application
[4] with PPE: Impervious clothing + gloves, both mandatory when intensive contact is assumed

Table 7.2-8: Estimated operator exposure, Trifloxystrobin

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Indoor, Downward spraying, Handheld Application rate: 0.2 kg a.s./ha			
ECPA Greenhouse Model, Low Crop standard	no PPE[2]	0.00474	7.9
	with PPE[3]	0.001683	2.8
ECPA Greenhouse Model, Low Crop, intensive contact with treated crop	no PPE[2]	0.18318	305
	with PPE[3]	0.005957	9.9
Dutch Greenhouse model, Handheld	no PPE[2]	0.11	183
	with PPE[3]	0.014	23
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, normal crop	no PPE[2]	0.05031	83.8
	with PPE[3]	0.00111	1.8
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, normal crop	no PPE[2]	0.2381	388
	with PPE[3]	0.01074	17.9
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, dense crop	no PPE[2]	0.409	668
	with PPE[4]	0.00276	4.6
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, dense crop	no PPE[2]	0.9359	1560
	with PPE[4]	0.00586	9.8
AEPLA Trolley Study	no PPE[2]	0.004812	8
	with PPE[3]	0.002618	4.4
EUROPOEM 2 Model, high crop	no PPE[2]	0.008104	13.5
	with PPE[3]	0.005919	9.8
EUROPOEM 2 Model, low crop	no PPE[2]	0.004487	7.5
	with PPE[3]	0.002698	4.5

[1] AOEL (RVNAS) of TFS: 0.06 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered, in addition gloves during mixing and loading and when handling contaminated surfaces during application
[4] with PPE: Impervious clothing + gloves, both mandatory when intensive contact is assumed

Table 7.2-9: Estimated acute operator exposure, Trifloxystrobin

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AAOEL[1] (RVAAS)
Indoor, Downward spraying, Handheld Application rate: 0.2 kg a.s./ha			
New Greenhouse AOEM – 95th centile (draft), Handheld, LCHH, normal crop	no PPE[2]	0.08853	29.5
	with PPE[3]	0.00182	0.6
New Greenhouse AOEM – 95th centile (draft), Handheld, HCHH, normal crop	no PPE[2]	1.02285	341
	with PPE[3]	0.06158	20.5
New Greenhouse AOEM – 95th centile (draft), Handheld, LCHH, dense crop	no PPE[2]	0.6233	208
	with PPE[4]	0.0049	1.6
New Greenhouse AOEM – 95th centile (draft), Handheld, HCHH, dense crop	no PPE[2]	3.8080	1269
	with PPE[4]	0.07011	23.4

[1] AAOEL (RVAAS) of TFS: 0.3 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing and loading and when handling contaminated surfaces during application
[4] with PPE: Impervious clothing + gloves, both mandatory when intensive contact is assumed

Conclusion

The operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) of FLU and TFS as well as the AAOEL of TFS will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).
Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of FLU+TFS SC 500.

Operator exposure calculations (KCP 7.2.1.1)

Table 7.2-10: Operator exposure, Fluopyram, Grapes, no PPE / with PPE

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution** = 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Grapes, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval** = 7 days
Percentage Absorption	Dermal for product = 0.083%	**Dermal for in use dilution** = 18%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.0199	% of RVNAS[1]	39.8%
	Acute systemic exposure mg/kg bw/day		-	% of RVAAS[2]	-%
Mixing and Loading		**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered	PPE = None	Soluble bags = No
Application		**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered	PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day		**0.00681**	% of RVNAS[1]	**13.6%**
	Acute systemic exposure mg/kg bw/day		-	% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day		**0.00273**	% of RVNAS[1]	**5.46%**
	Acute systemic exposure mg/kg bw/day			% of RVAAS[2]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 7.2-11: Operator exposure, Trifloxystrobin, Grapes, no PPE / with PPE

Substance	Trifloxystrobin	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution** = 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Grapes, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval =** 7 days
Percentage Absorption	Dermal for product = 0.14%	**Dermal for in use dilution** = 16%	**Oral =** 60%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.06 mg/kg bw/day		RVAAS[2]	0.3 mg/kg bw/day	

Operator Model		Mixing, loading and application AOEM		
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.0178	% of RVNAS[1]	29.7%
	Acute systemic exposure mg/kg bw/day	0.0391	% of RVAAS[2]	29.7%
Mixing and Loading	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered	PPE = None	Soluble bags = No
Application	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered	PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	**0.00617**	% of RVNAS[1]	**10.3%**
	Acute systemic exposure mg/kg bw/day	0.0195	% of RVAAS[2]	6.5%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	**0.00251**	% of RVNAS[1]	**4.19%**
	Acute systemic exposure mg/kg bw/day	0.0122	% of RVAAS[2]	4.06%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Operator exposure, Fluopyram & Trifloxystrobin, Lettuce, ECPA Greenhouse Model

Table 7.2-12: Normal Crop:

Data entry screen & summary calculation sheet — GREENHOUSE MODEL v_2.1

Product:	FLU+TFS SC 500		75th percentile
Formulation:	Liquid		
Body weight [kg]:	60		
Active substance(s):	Fluopyram	Trifloxystrobin	Add substance
Concentration [g/l or kg]:	250	250	
Inhalation absorption [%]	100	100	
Dermal absorption [%]			Remove substance
Concentrate:	0.083	0.14	
Dilution:	18.0	16.0	
AOEL [mg/kg bw/day]	0.05	0.06	

Scenario 1:	Low crop, standard		
Application rate [l or kg product/ha]:	0.8		Add application scenario
Dose [kg a.s./ha]:	0.2		
Work rate [ha/day]:	1.00		
PPE during mix/loading:		PPE during application:	
Respiration:	None	Respiration:	None
Hands:	Gloves	Hands:	Gloves
		Head:	None	Remove application scenario
		Body:	Coverall

Scenario 2:	High crop, standard		
Application rate [l or kg product/ha]:	0.6		
Dose [kg a.s./ha]:	0.15	0.18	
Work rate [ha/day]:	3.00		
PPE during mix/loading:		PPE during application:	
Respiration:	None	Respiration:	None
Hands:	Gloves	Hands:	Gloves
		Head:	None
		Body:	Coverall

Summary

Predicted systemic exposure as a percentage of the AOEL: Greenhouse Model

75th percentile

Active substance	Protection	Systemic exposure [mg/kg bw/day]	AOEL [mg/kg bw/day]	% of AOEL
Low crop, standard				
Fluopyram	None	0.00514	0.05	10.3
	With	0.001709		3.4
Trifloxystrobin	None	0.00474	0.06	7.9
	With	0.001683		2.8
High crop, standard				
Fluopyram	None	0.02108	0.05	42.2
	With	0.009753		19.5
Trifloxystrobin	None	0.01893	0.06	31.6
	With	0.008857		14.8

Table 7.2-13: Dense Crop:

Data entry screen & summary calculation sheet — GREENHOUSE MODEL v_2.1

Product:	FLU+TFS SC 500		75th percentile
Formulation:	Liquid		
Body weight [kg]:	60		
Active substance(s):	Fluopyram	Trifloxystrobin	
Concentration [g/l or kg]:	250	250	
Inhalation absorption [%]	100	100	
Dermal absorption [%]			
Concentrate:	0.083	0.14	
Dilution:	18.0	16.0	
AOEL [mg/kg bw/day]	0.05	0.06	

Add substance / Remove substance

Scenario 1:	Low crop, intensive contact with treated crop		
Application rate [l or kg product/ha]:	0.8		
Dose [kg a.s./ha]:	0.2	0.2	
Work rate [ha/day]:	1.00		
PPE during mix/loading:		PPE during application:	
Respiration:	None	Respiration:	None
Hands:	Gloves	Hands:	Gloves
		Head:	None
		Body:	Impervious clothing

Add application scenario / Remove application scenario

Scenario 2:	High crop, intensive contact with treated crop		
Application rate [l or kg product/ha]:	0.6		
Dose [kg a.s./ha]:	0.15	0.15	
Work rate [ha/day]:	1.00		
PPE during mix/loading:		PPE during application:	
Respiration:	None	Respiration:	None
Hands:	Gloves	Hands:	Gloves
		Head:	None
		Body:	Impervious clothing

Summary

Predicted systemic exposure as a percentage of the AOEL: Greenhouse Model

75th percentile

Active substance	Protection	Systemic exposure [mg/kg bw/day]	AOEL [mg/kg bw/day]	% of AOEL
Low crop, intensive contact with treated crop				
Fluopyram	None	0.20546	0.05	410.9
	With	0.006095		12.2
Trifloxystrobin	None	0.18318	0.06	305.3
	With	0.005957		9.9
High crop, intensive contact with treated crop				
Fluopyram	None		0.05	
	With	0.003992		8.0
Trifloxystrobin	None		0.06	
	With	0.003778		6.3

Table 7.2-14: Operator exposure, Fluopyram, Dutch Model

OPERATOR EXPOSURE — **DUTCH GREENHOUSE MODEL**

form: FLUZ+TFS SC 500
a.s.: Fluopyram
Application including mixing and loading

Parameter		Value	Unit	References, comments
MANUAL SPRAYING in greenhouses				
AR	Application rate	0.2	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Inhalation Exposure (without PPE)		**0.2**	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	1		Non-powered mask filtertype 2: (most conservative): 10; more advanced PPE: see note* (Dutch model)
Inhalation Exposure (with PPE)		**0.2**	mg a.s./ day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Dermal Exposure		**40**	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	10		Gloves + coverall: 10 (Dutch model)
Dermal Exposure (with PPE)		**4**	mg a.s./ day	DE(PPE) = (1/PPE factor) x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	18	%	
	AOEL	3.0	mg a.s./ day	based on 70 kg bw

Internal exposure	Without PPE [mg a.s. / day]	With PPE [mg a.s. / day]	
Inhalation	0.2000	0.2000	IE(int) = IE x (IA/100)
Dermal	7.2000	0.7200	DE(int) = DE x (DA/100)
Total	**7.4000**	**0.9200**	**sum**
% AOEL			
Inhalation	6.7	6.7	%AOEL = 100 x IE(int) / AOEL
Dermal	240	24	%AOEL = 100 x DE(int) / AOEL
Total	**247**	**31**	**sum**

* NOTE: The above mentioned model is for spraying in greenhouses. For dusting of carnations the surrogate values should be changed: inhalation should be 20 mg/kg instead of 1, and dermal should be 300 mg/kg instead of 200.

** Note: Alleen voor gasvormende/gasvormige middelen en gronsontsmettingsmiddelen mag een hogere factor dan 10 als volgt worden voorgeschreven; Aangedreven volgelaatsmasker met filtertype 2: factor 20; Aangedreven volgelaatsmasker met filtertype 3: factor 40

LET OP: Voor DARs bovenstaande in z'n geheel in DAR kopieren. Voor NL aanvragen alleen de internal exposure en % AOEL getallen without PPE overnemen in C-stuk; daarna nog wel % AOEL omzetten in Risk Index (delen door 100) en aanpassen aan juiste decimale

Table 7.2-15: Operator exposure, Trifloxystrobin, Dutch Model

OPERATOR EXPOSURE — **DUTCH GREENHOUSE MODEL**

form: FLUZ+TFS SC 500
a.s.: Trifloxystrobin
Application including mixing and loading

Parameter	Value	Unit	References, comments
MANUAL SPRAYING in greenhouses			
AR Application rate	0.2	kg a.s./ha	summary of intended uses
A Area treated	1	ha/ day	Dutch model
Inhalation Exposure			without PPE
SV Surrogate Exposure Value	1	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Inhalation Exposure (without PPE)	**0.2**	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)			with PPE
PPE-factor	1		Non-powered mask filtertype 2 (most conservative): 10; more advanced PPE see note** (Dutch model)
Inhalation Exposure (with PPE)	**0.2**	mg a.s./ day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure			without PPE
SV Surrogate Exposure Value	200	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Dermal Exposure	**40**	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)			with PPE
PPE-factor	10		Gloves + coverall: 10 (Dutch model)
Dermal Exposure (with PPE)	**4**	mg a.s./ day	DE(PPE) = (1/PPE factor) x DE
Internal exposure			
IA Inhalation Absorption	100	%	
DA Dermal Absorption	16	%	
AOEL	3.6	mg a.s./ day	based on 70 kg bw

Internal exposure	Without PPE [mg a.s. / day]	With PPE [mg a.s. / day]	
Inhalation	0.2000	0.2000	IE(int) = IE x (IA/100)
Dermal	6.4000	0.6400	DE(int) = DE x (DA/100)
Total	**6.6000**	**0.8400**	**sum**
% AOEL			
Inhalation	5.6	5.6	%AOEL = 100 x IE(int) / AOEL
Dermal	178	18	%AOEL = 100 x DE(int) / AOEL
Total	**183**	**23**	**sum**

* NOTE: The above mentioned model is for spraying in greenhouses. For dusting of carnations the surrogate values should be changed: inhalation should be 20 mg/kg instead of 1, and dermal should be 300 mg/kg instead of 200.

** Note: Alleen voor gasvormende/gasvormige middelen en gronsontsmettingsmiddelen mag een hogere factor dan 10 als volgt worden voorgeschreven: Aangedreven volgelaatsmasker met filtertype 2: factor 20; Aangedreven volgelaatsmasker met filtertype 3: factor 40

LET OP: Voor DARs bovenstaande in z'n geheel in DAR kopieren. Voor NL aanvragen alleen de internal exposure en % AOEL getallen without PPE overnemen in C-stuk; daarna nog wel % AOEL omzetten in Risk Index (delen door 100) en aanpassen aan juiste decimale

Operator exposure, Fluopyram, New Greenhouse AOEM (draft) – 75th Centile

Table 7.2-16: Normal Crop:

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	%DA (conc.)	%DA (dil.)	BW (kg)	AOEL (mg/kg wb/day)
Fluopyram	1	0.2	0.2	0.083%	18.0%	60	0.05

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	formulation type	Hand wash			
0.2	liquid	normal	total hand	1951 µg	
			protected hand	12 µg	
Outdoor ML model, no new data for body			total body	1151 µg	
		normal	protected body	6 µg	
			head	15 µg	
			inhalation	2 µg	

Exposure (mg/kg bw/day)

ML Tank	No PPE	With PPE
	0.00087	0.00003

A GH-LCHH

relevant factors			Quantile Regression 75	Percentile 75
TA (kg)	dense culture	protection		
0.2	normal culture	normal	total hand	1323 µg
			protected hand	0 µg
			total body	17207 µg
			protected body	167 µg
			head	0 µg
			inhalation	47 µg

Rain trousers only available in dense culture

A LCHH	No PPE	With PPE
	0.05638	0.00111

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	dense culture	protection			
0.2	normal culture	normal	total hand	6399 µg	
			protected hand	28 µg	
			total body	80018 µg	
			protected body	2140 µg	
			head	457 µg	
			inhalation	73 µg	

Rain coat only available in dense culture

A HCHH	No PPE	With PPE
	0.26163	0.01189

Total MLA		
LCHH	No PPE	With PPE
	0.05645	0.00114
% of AOEL	112.9	2.3
HCHH	No PPE	With PPE
	0.26272	0.01192
% of AOEL	525.4	23.8

Table 7.2-17: Dense Crop: 0.2 L/ha

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	%DA (conc.)	%DA (dil.)	BW (kg)	AOEL (mg/kg wb/day)
Fluopyram	1	0.2	0.2	0.083%	18.0%	60	0.86

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	formulation type	Hand wash			
0.2	liquid	normal	total hand	1951 µg	
Outdoor ML model, no new data for body			protected hand	12 µg	
		normal	total body	1151 µg	
			protected body	6 µg	
			head	15 µg	
			inhalation	2 µg	

Exposure (mg/kg bw/day)

	No PPE	With PPE
ML Tank	0.00907	0.00003
A LCHH	0.45038	0.00281
A HCHH	1.00558	0.00634

Total MLA	No PPE	With PPE
LCHH	0.4504	0.0028
% of AOEL	900.9	5.7
HCHH	1.0060	0.0063
% of AOELs	2105.2	12.5

A GH-LCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	dense culture	rain trousers			total hand	1322 µg
					protected hand	4 µg
					total body	1480 µg
					protected body	186 µg
					head	67 µg
					inhalation	125 µg

Rain trousers only available in dense culture

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	dense culture	rain coat	total hand	6570 µg		
					protected hand	481 µg
			total body	343265 µg		
			protected body	743 µg		
			head	694 µg		
			inhalation	107 µg		

Operator exposure, trifloxystrobin, New Greenhouse AOEM (draft) – 75th Centile

Table 7.2-18: Normal Crop:

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	%DA (conc.)	%DA (dil.)	BW (kg)	AOEL (mg/kg wb/day)
Trifloxystrobin	1	0.2	0.2	0.140%	16.0%	60	0.06

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	formulation type	Hand wash				
0.2	liquid	normal	total hand	1951 µg		
Outdoor ML model, no new data for body			protected hand	12 µg		
		normal	total body	1151 µg		
			protected body	6 µg		
			head	15 µg		
			inhalation	2 µg		

ML Tank	Exposure (mg/kg bw/day) No PPE	With PPE
	0.00010	0.00003
A LCHH	No PPE	With PPE
	0.05020	0.00108
A HCHH	No PPE	With PPE
	0.23271	0.01071

Total MOE		
LCHH	No PPE	With PPE
	0.05031	0.00111
% of AOEL	83.8	1.8
HCHH	No PPE	With PPE
	0.23329	0.01078
% of AOEL	388.8	17.97

A GH-LCHH

relevant factors			Quantile Regression 75	Percentile 75	
TA (kg)	dense culture	protection			
0.2	normal culture	normal	total hand		1323 µg
			protected hand		0 µg
			total body		17207 µg
			protected body		107 µg
			head		3 µg
			inhalation		15 µg

Rain trousers only available in dense culture

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	normal culture	normal	total hand	6399 µg		
					protected hand	28 µg
			total body	80018 µg		
			protected body	3149 µg		
			head	357 µg		
			inhalation	23 µg		

Rain coat only available in dense culture

Table 7.2-19: Dense Crop: 0.2

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	%DA (conc.)	%DA (dil.)	BW (kg)	AOEL (mg/kg wb/day)
Trifloxystrobin	1	0.2	0.2	0.140%	16.0%	60	0.08

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	formulation type	Hand wash			
0.2	liquid	normal	total hand	1951 µg	
Outdoor ML model, no new data for body			protected hand	12 µg	
		normal	total body	1151 µg	
			protected body	6 µg	
			head	15 µg	
			inhalation	2 µg	

A GH-LCHH

relevant factors			Quantile Regression 75	Percentile 75	
TA (kg)	dense culture	protection			
0.2	dense culture	rain trousers		total hand	1323 µg
				protected hand	4 µg
				total body	148056 µg
				protected body	186 µg
				head	57 µg
				inhalation	125 µg

Rain trousers only available in dense culture

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	dense culture	rain coat	total hand	6570 µg	protected hand	481 µg
			total body	343055 µg		
			protected body	449 µg		
			head	599 µg		
			inhalation	107 µg		

Rain coat only available in dense culture

Exposure (mg/kg bw/day)

	No PPE	With PPE
ML Tank	0.00010	0.00003
A LCHH	0.40057	0.00273
A HCHH	0.02078	0.00583

Total MOE

	No PPE	With PPE
LCHH	0.40057	0.00276
% of AOEL	667.8	4.6
HCHH	0.02088	0.00583
% of AOEL	1559.8	97.8

Operator exposure, Trifloxystrobin, New Greenhouse AOEM (draft) – 95th Centile

Table 7.2-20: Normal Crop: 0.2

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (l/ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	a.i. (conc.)	%DA (rel.)	BW (kg)	ARfD (mg/kg wb/day)
Trifloxystrobin	1	0.2	0.2	0.14%	16.0%	60	0.6

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	formulation type	Hand wash			
0.2	liquid	normal	total hand	4759 µg	
			protected hand	40 µg	
Outdoor ML model, no new data for body			total body	45118 µg	
		normal	protected body	29 µg	
			head	155 µg	
			inhalation	3 µg	

A GH-LCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	normal culture	normal			total hand	4159 µg
					protected hand	6 µg
					total body	28078 µg
					protected body	150 µg
					head	9 µg
					inhalation	80 µg

Rain trousers only available in dense culture

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	normal culture	normal	total hand	13840 µg	protected hand	0 µg
			total body	308282 µg		
			protected body	28082 µg		
			head	357 µg		
			inhalation	105 µg		

Rain coat only available in dense culture

Exposure (mg/kg bw/day)

ML Tank	No PPE	With PPE
	0.00121	0.00006
A LCHH	No PPE	With PPE
	0.08853	0.00177
A HCHH	No PPE	With PPE
	1.02383	0.06158

Total MLA		
	No PPE	With PPE
LCHH	0.08853	0.00182
% of ARfD	29.5	0.6
HCHH	No PPE	With PPE
	1.02383	0.06158
% of ARfD	341.0	20.5

Table 7.2-21: Dense crop: 0.2

Version of 2015-05-13
This spreadsheet presents the new greenhouse model which is currently under development in order to complement the AOEM.
In this main worksheet the results of the computations are collected.

relevant factors	results	results
This section is for data entry. To avoid unintended changes, the table is write protected (without password), so only data entry fields can be changed.	This section shows the quantile regression estimate of the 75th percentile.	Estimate of the 75th percentile of a log-normal distribution (as recommended by EFSA), possibly linearly extrapolated.

Product: [formulation]
Data entry:

A.S.	Work rate (ha/day)	Dose rate (kg a.s./ha)	Total Amount (TA, kg)	%DA (conc.)	%DA (dil.)	BW (kg)	ARfD (mg/kg wb/day)
Trifloxystrobin	1	0.2	0.2	0.4%	16.0%	60	0.2

ML Tank (updated)

relevant factors			Quantile Regression 75		Percentile 75
TA (kg)	formulation type	Hand wash			
0.2	liquid	normal	total hand	4759 µg	
Outdoor ML model, no new data for body			protected hand	40 µg	
		normal	total body	45118 µg	
			protected body	29 µg	
			head	155 µg	
			inhalation	3 µg	

A GH-LCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	dense culture	rain trousers			total hand	4759.2 µg
					protected hand	35 µg
					total body	22785 µg
					protected body	358 µg
					head	93 µg
					inhalation	213 µg

Rain trousers only available in dense culture

A GH-HCHH

relevant factors			Quantile Regression 75		Percentile 75	
TA (kg)	dense culture	protection				
0.2	dense culture	rain coat	total hand	47590 µg		
					protected hand	0 µg
			total body	1140335 µg		
			protected body	21629 µg		
			head	1898 µg		
			inhalation	439 µg		

Rain coat only available in dense culture

Exposure (mg/kg bw/day)

	No PPE	With PPE
ML Tank	0.00121	0.00005
A LCHH	0.62206	0.00484
A HCHH	3.80682	0.07068

Total MLA

	No PPE	With PPE
LCHH	0.62327	0.00490
% of ARfD	207.8	1.6
HCHH	3.80803	0.07011
% of ARfD	1269.3	23.4

Table 7.2-22: Operator exposure, Fluopyram, Trolley Sprayer Study and EUROPOEM 2 (Spanish Requirements)

AOEL	0.05 mg/kg bw/day
Application Rate	0.2 kg a.i/ha
Area treated per day	1 ha
Dermal Absorption concentrate	0.083%
Dermal Absorption dilution	5.9%
kg a.i. applied (1 ha)	0.2

EUROPOEM II	High Crops	Low Crops	Trolley	
Body	852	196	176	mg/kg ai applied
Hands	72	57.8	72	mg/kg ai applied
Inhalation	0.77	0.443	0.4246	mg/kg ai applied

Mixing/Loading (AOEM, calculated with EFSA Model)	Work Clothing	Work Clothing + Gloves	
Knapsack (1 ha/day)	0.000559192	0.000417331	mg/kg bw/day

Manual Spraying	Work Clothing	Work Clothing + Gloves	
High Crops (EUROPOEM II) - 1 ha per day	0.033482667	0.020738667	mg/kg bw/day
Low Crops (EUROPOEM II) - 1 ha per day	0.016698667	0.006468067	mg/kg bw/day
Trolley Sprayer - 1 ha per day	0.019036667	0.006292667	mg/kg bw/day

Total Exposure: ML + A	Work Clothing	Work Clothing + Gloves	
High Crops (EUROPOEM II) - 1 ha with knapsack	0.034042	0.021156	mg/kg bw/day
Low Crops (EUROPOEM II) - 1 ha with knapsack	0.017258	0.006886	mg/kg bw/day
AEPLA Trolley Study - 1 ha (M/L knapsack)	0.019596	0.006710	mg/kg bw/day

% of systemic AOEL (RVNAS)		
	Work Clothing	Work Clothing + Gloves
	68.1	42.3
	34.5	13.8
	39.2	13.4

Table 7.2-23: Operator exposure, Trifloxystrobin, Trolley Sprayer Study and EUROPOEM 2 (Spanish Requirements)

AOEL	0.06 mg/kg bw/day
Application Rate	0.2 kg a.i/ha
Area treated per day	1 ha
Dermal Absorption concentrate	0.140%
Dermal Absorption dilution	0.95%
kg a.i. applied (1 ha)	0.2

EUROPOEM II	High Crops	Low Crops	Trolley	
Body	852	196	176	mg/kg ai applied
Hands	72	57.8	72	mg/kg ai applied
Inhalation	0.77	0.443	0.4246	mg/kg ai applied

Mixing/Loading (AOEM, calculated with EFSA Model)	Work Clothing	Work Clothing + Gloves	
Knapsack (1 ha/day)	0.000559192	0.000417331	mg/kg bw/day

Manual Spraying	Work Clothing	Work Clothing + Gloves	
High Crops (EUROPOEM II) - 1 ha per day	0.007544667	0.005492667	mg/kg bw/day
Low Crops (EUROPOEM II) - 1 ha per day	0.003927667	0.002280367	mg/kg bw/day
Trolley Sprayer - 1 ha per day	0.004252667	0.002200667	mg/kg bw/day

Total Exposure: ML + A	Work Clothing	Work Clothing + Gloves	
High Crops (EUROPOEM II) - 1 ha with knapsack	0.008104	0.005910	mg/kg bw/day
Low Crops (EUROPOEM II) - 1 ha with knapsack	0.004487	0.002698	mg/kg bw/day
AEPLA Trolley Study - 1 ha (M/L knapsack)	0.004812	0.002618	mg/kg bw/day

% of systemic AOEL (RVNAS)		
	Work Clothing	Work Clothing + Gloves
	13.5	9.8
	7.5	4.5
	8.	4.4

CP 7.2.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) or Acute Acceptable Operator Exposure Level (AAOEL/RVAAS) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

CP 7.2.3 Bystander and resident exposure

Outdoor

According to EFSA longer term exposure of bystanders is covered by the resident scenario.

Indoor

The intended use of FLU+TFS SC 500 supported by this document refers to the professional indoor or protected treatment for which it is reasonable to conclude that no person unrelated to the treatment is allowed to be present when the treatment is conducted. Accordingly, bystander and resident exposure is not relevant.

CP 7.2.3.1 Estimation of bystander and resident exposure

A summary of the exposure models used for the estimation of bystander and Resident exposure to the active substance Fluopyram during application of FLU SC 500 according to the representative use is presented in the following table. Detailed calculations are presented on page 47 ff.

Table 7.2-24: Exposure models for intended uses

Critical use(s)	0.2 L / kg product/ha for Grapes
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

Regarding the resident exposure to direct drift, exposure calculations are performed for ground boom sprayer (for low crops) and broadcast air assisted applications (for high crops) separately, when relevant. The outcome of the estimation is presented in the following table(s).

Table 7.2-25: Estimated resident exposure, Fluopyram, Grapes

	Adult[2]			Child[2]		
Outdoor, Upward spraying, Vehicle-mounted Application rate: 2 x 0.05 kg a.s./ha, 7 days interval, Minimum water volume: 500 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00139	2.78	0.000908	0.00251	5.02	0.00165
Vapour	0.00023	0.46	0.00023	0.00107	2.14	0.00107
Surface deposits	6.22E-05	0.124	4.7E-05	0.000174	0.348	0.000132
Entry into treated crops[4]	0.00156	3.12	0.00125	0.00281	5.62	0.00224
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00243 (4.86%)			0.00509 (10.2%)
Entry into treated crops[5]	0.00063	1.26	0.000503	0.00113	2.27	0.000904
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00167 (3.33%)			0.0037 (7.39%)

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 5 m distance
[4] Default DFR = 3
[5] Measured DFR = 2.24

Table 7.2-26: Estimated bystander exposure, Trifloxystrobin, Grapes

	Adult[2]			Child[2]	
Outdoor, Upward spraying, Vehicle-mounted Application rate: 2 x 0.05 kg a.s./ha, 7 days interval, Minimum water volume: 500 L/ha					
Routes of exposure	**95th centile** (mg/kg bw/day)	**in % of AAOEL[1] (RVAAS)**	**95th centile** (mg/kg bw/day)	**in % of AAOEL[1] (RVAAS)**	
Spray drift[3]	0.00283	0.943	0.00511	1.7	
Vapour	0.00023	0.0767	0.00107	0.357	
Surface deposits	0.00013	0.0432	0.000329	0.11	
Entry into treated crops[4]	0.00139	0.463	0.0025	0.833	
Entry into treated crops	0.000483	0.161	0.000869	0.29	

[1] AAOEL (RVAAS) of TFS: 0.3 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 5 m distance
[4] Default DFR = 3
[5] Measured DFR = 1.93

Table 7.2-27: Estimated resident exposure, Trifloxystrobin, Grapes

	Adult[2]			Child[2]		
Outdoor, Upward spraying, Vehicle-mounted Application rate: 2 x 0.05 kg a.s./ha, 7 days interval, Minimum water volume: 500 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00123	2.06	0.000808	0.00223	3.72	0.00147
Vapour	0.00023	0.383	0.00023	0.00107	1.78	0.00107
Surface deposits	5.53E-05	0.0922	4.18E-05	0.000143	0.238	0.000108
Entry into treated crops[4]	0.00139	2.31	0.00111	0.0025	4.16	0.00199
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00219 (3.64%)			0.00464 (7.73%)
Entry into treated crops[5]	0.000483	0.804	0.000385	0.000869	1.45	0.000692
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00144 (2.41%)			0.00329 (5.48%)

[1] AOEL (RVNAS) of TFS: 0.06 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 5 m distance
[4] Default DFR = 3
[5] Measured DFR = 1.93

Conclusion

The Bystander/Resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) of FLU and TFS as well as the AAOEL of TFS will not be exceeded in Tier 1 under conditions of intended uses.

For the refinement of 'Entry into treated crops' with measured DFR data please refer to Detailed evaluation of DFR study.

Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of FLU+TFS SC 500.

Bystander and Resident exposure calculations (KCP 7.2.3.1)

Table 7.2-28: Bystander and resident exposure, Fluopyram, Grapes

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Grapes, **Outdoor**, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval** = 7 days
Percentage Absorption	Dermal for product = 0.083%	**Dermal for in use dilution** = 18%	**Oral** = 100%	**Inhalation** = 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[1]	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00251	% of RVNAS[1]	5.02%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	2.14%
	Surface deposits (75th percentile) mg/kg bw/day	0.000174	% of RVNAS[1]	0.348%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00281	% of RVNAS[1]	5.62%
	All pathways (mean) mg/kg bw/day	0.00509	% of RVNAS[1]	10.2%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00139	% of RVNAS[1]	2.78%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.46%
	Surface deposits (75th percentile) mg/kg bw/day	6.22E-05	% of RVNAS[1]	0.124%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00156	% of RVNAS[1]	3.12%
	All pathways (mean) mg/kg bw/day	0.00243	% of RVNAS[1]	4.86%

Measured DFR	2.24 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00113	% of RVNAS[1]	2.27%
	All pathways (mean) mg/kg bw/day	0.0037	% of RVNAS[1]	7.39%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00063	% of RVNAS[1]	1.26%
	All pathways (mean) mg/kg bw/day	0.00167	% of RVNAS[1]	3.33%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 7.2-29: Bystander and resident exposure, Trifloxystrobin, Grapes

Substance	Trifloxystrobin	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of 7.5*10-3Pa
Scenario	Grapes, **Outdoor,** Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval =** 7 days
Percentage Absorption	Dermal for product = 0.14%	**Dermal for in use dilution** = 16%	**Oral =** 60%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.06 mg/kg bw/day		RVAAS[2]	0.3 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	0.00511	% of RVNAS[1]	1.7%
	Vapour (95th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	0.357%
	Surface deposits (95th percentile) mg/kg bw/day	0.000329	% of RVNAS[1]	0.11%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.0025	% of RVNAS[1]	0.833%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	0.00283	% of RVNAS[1]	0.943%
	Vapour (95th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.0767%
	Surface deposits (95th percentile) mg/kg bw/day	0.00013	% of RVNAS[1]	0.0432%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.00139	% of RVNAS[1]	0.463%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00223	% of RVNAS[1]	3.72%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	1.78%
	Surface deposits (75th percentile) mg/kg bw/day	0.000143	% of RVNAS[1]	0.238%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0025	% of RVNAS[1]	4.17%
	All pathways (mean) mg/kg bw/day	0.00464	% of RVNAS[1]	7.73%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00123	% of RVNAS[1]	2.06%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.383%
	Surface deposits (75th percentile) mg/kg bw/day	5.53E-05	% of RVNAS[1]	0.0922%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00139	% of RVNAS[1]	2.31%
	All pathways (mean) mg/kg bw/day	0.00219	% of RVNAS[1]	3.64%

Measured DFR	1.93 µg a.s./cm² per kg a.s./kg			
Resident child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.000869	% of RVNAS[1]	1.45%
	All pathways (mean) mg/kg bw/day	0.00329	% of RVNAS[1]	5.48%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.000483	% of RVNAS[1]	0.804%
	All pathways (mean) mg/kg bw/day	0.00144	% of RVNAS[1]	2.41%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

CP 7.2.3.2 Measurement of bystander and/or resident exposure

Since the bystander/resident exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) as well as the Acute Acceptable Operator Exposure Level (AAOEL/RVAAS) will not be exceeded under conditions of intended uses a study to provide measurements of bystander/resident exposure to spray drift, vapour, surface deposits or entry into treated crops was not necessary and was therefore not performed.

CP 7.2.4 Worker exposure

A summary of the exposure model used for the estimation of worker exposure to the active substance fluopyram during application of FLU SC 500 according to the representative use is presented in Table 30. Detailed calculations are presented on page 55 ff.

CP 7.2.4.1 Estimation of worker exposure

A summary of the exposure models used for the estimation of worker exposure with default DFR (= 3 µg/cm²) to the active substance(s) after entry into a previously treated area or handling a crop treated with FLU SC 500 is presented in the following table.

Table 7.2-30: Exposure models for intended uses

Critical use(s)	0.2 L / kg product/ha for Grapes 0.8 L / kg product/ha for Leaf vegetables and fresh herbs (greenhouse)
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874*

The following table shows the crop groups with their respective transfer coefficients (TC) and task duration relevant for the estimation of worker exposure after the intended use of FLU+TFS SC 500. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Table 7.2-31: Relevant parameters used for the worker exposure assessment

Crop / Crop Group	Nº of applications	Interval (Days)	TC[1] (cm²/hour)	Task Duration (hours)
Grapes	2	7	1000[2]	8
Leaf vegetables and fresh herbs	2	7	380[3]	8

[1] TC = transfer coefficients
[2] TC assuming arms, body and legs covered.
[3] TC assuming hands, arms, body and legs covered.

The outcome of the estimation is presented in the following table.

Table 7.2-32: Estimated worker exposure for re-entry in Grapes

Active substance	Application rate (kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.05	0.0673	135
TFS		0.0598	99.7

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
TFS: 0.06 mg/kg bw/day
[2] Assuming arms, body and legs covered (workwear)

Table 7.2-33: Estimated worker exposure for re-entry in Leaf vegetables and fresh herbs

Active substance	Application rate (kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.2	0.0155	30.9
TFS		0.0137	22.9

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
TFS: 0.06 mg/kg bw/day

[2] Assuming arms, body and legs covered (workwear with gloves)

Refinement of generic DFR value (KCP 7.2)

Table 7.2-33: Exposure models for intended uses

Critical use(s)	0.2 L / kg product/ha for Grapes
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

The following table shows the parameters of the used DFR studies. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Table 7.2-34: Relevant parameters used for the worker exposure assessment

Active substance	Crop / Crop Group	Application rate (kg a.s./ha)	N° of applications	Interval (Days)	TC[1] (cm²/hour)	Task Duration (hours)	Measured DFR (µg/cm²/kg a.s./ha)
FLU	Grapes	0.05	2	/	10100[2]	8	2.24
TFS							1.93

[1] TC = transfer coefficients

[2] TC assuming arms, body and legs covered.

The outcome of the estimation is presented in the following table.

Table 7.2-35: Estimated worker exposure for re-entry in Grapes

Active substance	Application rate (kg a.s./ha)	DFR (µg/cm²/kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.05	3[3]	0.673	135
		2.24[4]	0.271	54.3
TFS		3[3]	0.0598	99.7
		1.93[4]	0.0208	34.7

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
TFS: 0.06 mg/kg bw/day
[2] Assuming arms, body and legs covered (workwear)
[3] Calculation with default DFR according to model
[4] Calculation with measured DFR assuming highest DFR after maximum number of applications

Conclusion

The worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) of FLU and TFS will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).
For the greenhouse (**indoor**) use a refinement with DFR data was not applied as the tier 1 approach already provides a safe use.
Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of FLU+TFS SC 500.

Detailed evaluation of DFR study relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Data Point:	KCP 7.2.3.2/01
Report Author:	[redacted]
Report Year:	2016
Report Title:	Determination of the dislodgeable foliar residues (DFR) of trifloxystrobin and AE C656948 in/on grape after spraying of AE C656948 & CGA279202 SC 500 in the field in the North of France
Report No:	15-2924
Document No:	M-569303-01-1
Guideline(s) followed in study:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Summary

The magnitude of the dislodgeable foliar residues (DFR) of the substances AE C656948 (fluopyram, FLU) and CGA279202 (trifloxystrobin, TFS) in washings from grape leaf punches was determined after two spray applications of the formulation AE C656948 & CGA279202 SC 500 (containing 250 g/L AE C656948 and 250 g/L trifloxystrobin).

The study included one supervised residue trial conducted in Northern Europe (France) during the 2015 season.

The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 7.2-36: Application summary

Trial Number / Country	Crop	Appl. Number	Interval (days)	Growth Stage (BBCH)	Dose rate (L/ha)	Water rate (L/ha)	Appl. rate (kg a.s./ha)	
							FLU	TFS
15-2924-01 France	Grape	1	-	73	0.2	262	0.05	0.05
		2	14	77	0.2	292	0.05	0.05

Appl. = Application; a.s. = active substance.

Representative leaf punch samples were obtained, prepared, identified, transported and stored following the corresponding study plan and EPA OPPTS Guideline 875.2100 (1996).

Forty leaf disks representing a total area of 400 cm² (double-sided surface) were collected out of the potential worker contact zone including upper, middle, lower, interior and exterior portions of grape foliage after the spray application was dry, according to study schedule. The application equipment used in the study was representative for the crop, the region and the task.

Control samples were collected prior to the first application. Field fortification samples were also generated at the field test site.

Leaf discs were dislodged with a 0.01 % Aerosol OT surfactant solution yielding a total amount of 200 mL of dislodging solution. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after sample collection.

Absolut (µg/cm²) DFR of fluopyram and trifloxystrobin are summarised in Table 38. No residues above the LOQ were found in the control samples. Results were neither corrected for laboratory nor for field spike recoveries.

Table 7.2-37: Weather Information during the study time

Date/Period of Time	Activity	Mean Temp. [°C]	Rainfall [mm]	Sunshine [h]
2015-06-25	Sampling	20	0	13
2015-06-26	Treatment, Sampling	22	0	12
2015-06-29	Sampling	22	0	13
2015-07-03	Sampling	27	0	10
2015-07-10	Treatment, Sampling	21	0	15
2015-07-13	Sampling	20	0	7
2015-07-17	Sampling	24	0	7
2015-07-24	Sampling	20	0	5
2015-07-31	Sampling	17	0	7
2015-08-07	Sampling	22	1	4
2015-08-14	Sampling	20	6	1
June 2015	-	19	27	311
July 2015	-	21	18	256
August 2015	-	21	125	210

Climatic data recording was not conducted according to GLP.

Table 7.2-38: Dislodgeable Foliar Residue summary in/on grape

Trial No. Country	DALT	Residues [µg/cm²]*	
		a.s. fluopyram	a.s. trifloxystrobin
15-2924-01 France	-1	< 0.01	< 0.01
	0	**0.112**	**0.0965**
	3	0.0442	0.0417
	7	0.00962	0.0128
	14	< 0.01	< 0.01
	-0	< 0.01	< 0.01
	0	0.0925	0.0775
	3	0.0432	0.0325
	7	0.0111	< 0.01
	14	< 0.01	< 0.01
	21	< 0.01	< 0.01
	28	< 0.01	< 0.01
	35	< 0.01	< 0.01

DALT = Days After Last Treatment; a.s. = active substance; "-" = before the application;
* = average values of sub-plots T1, T2 and T3

Conclusion

The highest mean value observed in the residue trial was 0.112 µg AE C656948/cm² and 0.0965 µg trifloxystrobin/cm² sampled at the day of the first application. Taking into account an application rate

of 0.05 kg per ha this leads to a normalized DFR value of **2.24 µg/cm²/kg/ha AE C656948** and **1.93 µg/cm²/kg/ha trifloxystrobin**.

Worker exposure calculations (KCP 7.2.4.1)

Table 7.2-39: Worker exposure, Fluopyram, Grapes

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Grapes, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval** = 7 days
Percentage Absorption	Dermal for product = 0.083%	**Dermal for in-use dilution** = 18%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker – Hand harvesting	Potential exposure mg/kg bw/day	0.2		% of RVNAS[1]	400%
	Working clothing mg/kg bw/day	0.0673		% of RVNAS[1]	135%
	Working clothing and gloves mg/kg bw/day	-		% of RVNAS[1]	-%
Measured DFR	2.24 µg a.s./cm² per kg a.s./ha				
Worker – Hand harvesting (Measured)	Potential exposure mg/kg bw/day	0.0806		% of RVNAS[1]	161%
	Working clothing mg/kg bw/day	0.0271		% of RVNAS[1]	54.3%
	Working clothing and gloves mg/kg bw/day	-		% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 7.2-40: Worker exposure, Trifloxystrobin, Grapes

Substance	Trifloxystrobin	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.05 kg a.s. /ha	**Spray dilution =** 0.1 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Grapes, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 2 **Application interval =** 7 days
Percentage Absorption	Dermal for product = 0.14%	**Dermal for in use dilution** = 16%	**Oral =** 60%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.06 mg/kg bw/day		RVAAS[2]	0.3 mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker Hand harvesting –	Potential exposure mg/kg bw/day		0.178	% of RVNAS[1]	296%
	Working clothing mg/kg bw/day		0.0598	% of RVNAS[1]	99.7%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%
Measured DFR	1.93 µg a.s./cm² per kg a.s./ha				
Worker Hand harvesting (Measured) –	Potential exposure mg/kg bw/day		0.0618	% of RVNAS[1]	103%
	Working clothing mg/kg bw/day		0.0208	% of RVNAS[1]	34.7%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table7.2-41: Worker exposure, Indoor, Fluopyram, Leaf vegetables and fresh herbs

Substance	Fluopyram	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.2 kg a.s. /ha	**Spray dilution** = 0.4 g a.s./l		**Vapour pressure** = low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario	Leaf vegetables and fresh herbs, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m		**Number of applications** = 2 **Application interval** = 7 days	
Percentage Absorption	Dermal for product = 0.083%	**Dermal for in use dilution** = 18%	**Oral** = 100%	**Inhalation** = 100%			
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	= mg/kg bw/day			
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days			
Worker – Reaching, picking	Potential exposure mg/kg bw/day		0.155	% of RVNAS[1]	309%		
	Working clothing mg/kg bw/day		0.0666	% of RVNAS[1]	133%		
	Working clothing and gloves mg/kg bw/day		0.0153	% of RVNAS[1]	30.9%		

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

[2] RVAAS = Reference Value Acutely toxic active Substance

Table 7.2-42: Worker exposure, Indoor, Trifloxystrobin, Leaf vegetables and fresh herbs

Substance	Trifloxystrobin	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.2 kg a.s. /ha	**Spray dilution** = 0.4 g a.s./l		**Vapour pressure** = low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario	Leaf vegetables and fresh herbs, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m		**Number of applications** = 2 **Application interval** = 7 days	
Percentage Absorption	Dermal for product = 0.14%	**Dermal for in use dilution** = 16%	**Oral** = 60%	**Inhalation** = 100%			
RVNAS[1] (AOEL)	0.06 mg/kg bw/day		RVAAS[2]	0.3 mg/kg bw/day			
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days			
Worker – Reaching, picking	Potential exposure mg/kg bw/day		0.137	% of RVNAS[1]	229%		
	Working clothing mg/kg bw/day		0.0592	% of RVNAS[1]	98.7%		
	Working clothing and gloves mg/kg bw/day		0.0137	% of RVNAS[1]	22.9%		

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL

[2] RVAAS = Reference Value Acutely toxic active Substance

CP 7.2.4.2 Measurement of worker exposure

Since the bystander/resident exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) will not be exceeded under conditions of intended uses a study to provide measurements of bystander/resident exposure to spray drift, vapour, surface deposits or entry into treated crops was not necessary and was therefore not performed.

Combined exposure

The product is a mixture of 2 active substances. Therefore a combined exposure assessment is provided.

Exposure Assessment of the active substances (Fluopyram, Trifloxystrobin) in FLU+TFS SC 500

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

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/RVNAS and AAOEL/RVAAS. This is equivalent to the predicted exposure as % of systemic AOEL/RVNAS and AAOEL/RVAAS to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Outdoor

Table 7.2-43: Risk assessment from combined exposure for Operators with PPE

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Estimated exposure / AAOEL (RVAAS) (HQ)[3]
Grapes	Fluopyram	0.0546	-
	Trifloxystrobin	0.0419	0.0406
	Cumulative risk Operators (HI)[1]	**0.0965**	**0.0406**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient, 75th percentile
[3] HQ = Hazard Quotient, 95th percentile

Table 7.2-44: Risk assessment from combined exposure for Workers

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Measured DFR[3]
Grapes	Fluopyram	1.35	0.543
	Trifloxystrobin	0.997	0.347
	Cumulative risk Workers (HI)[1]	**2.35**	**0.89**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient
[3] Hazard Quotient, for addition the value of the default DFR is used, when measured DFR not available

Table 7.2-45: Risk assessment from combined exposure for Bystander

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]	Measured DFR[4]
Adult[1] *Grapes*	Fluopyram	-	-
	Trifloxystrobin	0.00943	0.00161
	Cumulative risk Bystander – Adult (HI)[2]	**0.00943**	**0.00161**
Child[1] *Grapes*	Fluopyram	-	-
	Trifloxystrobin	0.017	0.0029
	Cumulative risk Bystander – Child (HI)[2]	**0.017**	**0.0029**

[1] The highest exposure value from the 95th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) is taken into consideration
[2] HI = Hazard Index
[3] HQ = Hazard Quotient
[4] Measured DFR is only for entry into treated crops value taken into consideration

Table 7.2-46: Risk assessment from combined exposure for Residents

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]	Measured DFR[4]
Adult[1] *Grapes*	Fluopyram	0.0486	0.0333
	Trifloxystrobin	0.0364	0.0241
	Cumulative risk Resident – Adult (HI)[2]	**0.085**	**0.0574**
Child[1] *Grapes*	Fluopyram	0.102	0.0739
	Trifloxystrobin	0.0773	0.0548
	Cumulative risk Resident – Child (HI)[2]	**0.179**	**0.129**

[1] The highest exposure value either from the 95th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI = Hazard Index
[3] HQ = Hazard Quotient
[4] Measured DFR is only for entry into treated crops value taken into consideration

Indoor

Table 7.2-47: Risk assessment from combined exposure for Operators with PPE

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Estimated exposure / AAOEL (RVAAS) (HQ)[3]
ECPA Greenhouse Model,	Fluopyram	0.034	-
	Trifloxystrobin	0.028	-

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Estimated exposure / AAOEL (RVAAS) (HQ)[3]
Low Crop standard, 0.2 kg a.s./ha	**Cumulative risk Operators (HI)[1]**	**0.062**	-
ECPA Greenhouse Model, Low Crop, intensive contact with treated crop, 0.2 kg a.s./ha	Fluopyram	0.122	-
	Trifloxystrobin	0.099	-
	Cumulative risk Operators (HI)[1]	**0.221**	-
Dutch Greenhouse model, Handheld	Fluopyram	0.31	-
	Trifloxystrobin	0.23	-
	Cumulative risk Operators (HI)[1]	**0.54**	-
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, normal crop, 0.2 kg a.s./ha	Fluopyram	0.023	-
	Trifloxystrobin	0.018	-
	Cumulative risk Operators (HI)[1]	**0.044**	-
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, normal crop, 0.2 kg a.s./ha	Fluopyram	0.238	-
	Trifloxystrobin	0.179	-
	Cumulative risk Operators (HI)[1]	**0.417**	-
New Greenhouse AOEM – 75th centile (draft), Handheld, LCHH, dense crop, 0.2 kg a.s./ha	Fluopyram	0.057	-
	Trifloxystrobin	0.046	-
	Cumulative risk Operators (HI)[1]	**0.103**	-
New Greenhouse AOEM – 75th centile (draft), Handheld, HCHH, dense crop, 0.2 kg a.s./ha	Fluopyram	0.127	-
	Trifloxystrobin	0.098	-
	Cumulative risk Operators (HI)[1]	**0.225**	-
New Greenhouse AOEM – 95th centile (draft), Handheld, LCHH, normal crop, 0.2 kg a.s./ha	Fluopyram	-	-
	Trifloxystrobin	-	0.006
	Cumulative risk Operators (HI)[1]	**-**	**0.006**
New Greenhouse AOEM – 95th centile (draft), Handheld, HCHH, normal crop, 0.2 kg a.s./ha	Fluopyram	-	-
	Trifloxystrobin	-	0.205
	Cumulative risk Operators (HI)[1]	**-**	**0.205**
New Greenhouse AOEM – 95th centile (draft), Handheld, LCHH, dense crop, 0.2 kg a.s./ha	Fluopyram	-	-
	Trifloxystrobin	-	0.016
	Cumulative risk Operators (HI)[1]	**-**	**0.016**

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Estimated exposure / AAOEL (RVAAS) (HQ)[3]
New Greenhouse AOEM – 95th centile (draft), Handheld, HCHH, dense crop, 0.2 kg a.s./ha	Fluopyram	-	-
	Trifloxystrobin	-	0.234
	Cumulative risk Operators (HI)[1]	**-**	**0.234**
AEPLA Trolley Study	Fluopyram	0.134	-
	Trifloxystrobin	0.044	-
	Cumulative risk Operators (HI)[1]	**0.178**	**-**
EUROPOEM 2 Model, high crop	Fluopyram	0.423	-
	Trifloxystrobin	0.098	-
	Cumulative risk Operators (HI)[1]	**0.521**	**-**
EUROPOEM 2 Model, low crop	Fluopyram	0.138	-
	Trifloxystrobin	0.045	-
	Cumulative risk Operators (HI)[1]	**0.183**	**-**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient, 75th percentile
[3] HQ = Hazard Quotient, 95th percentile

Table 7.2-48: Risk assessment from combined exposure for Workers

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]
Leaf vegetables and fresh herbs	Fluopyram	0.309
	Trifloxystrobin	0.229
	Cumulative risk Workers (HI)[1]	**0.538**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient
[3] Hazard Quotient, for addition the value of the default DFR is used

Conclusion

The Hazard Index is < 1. Thus combined exposure to Fluopyram and Trifloxystrobin is not expected to present a risk for operators, workers, bystanders and residents in both representative uses. No further refinement of the assessment is required.

Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of FLU+TFS SC 500.

CP 7.3 Dermal absorption

Fluopyram

Comparative dermal absorption, *in vitro* using rat and human skin

Data Point:	KCP 7.3/01
Report Author:	[redacted]
Report Year:	2014
Report Title:	In vitro human skin penetration of 14C-fluopyram in the fluopyram and trifloxystrobin SC 500 formulation
Report No:	S13-04169
Document No:	M-475331-01-1
Guideline(s) followed in study:	OECD Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004). OECD Environmental Health and Safety Publication Series on testing and Assessment N° 28; Guidance Document for the Conduct of Skin Absorption Studies (March 2004). EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption. EFSA Journal 2012: 10(4): 2665.
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Material and methods

Human skin: Source: Banque de Tissu de Lyon and Biopredic, France.
Number and sex: 3 donors, female.
Anatomical region: Abdomen.
Thickness: 312 to 400 µm.

Test Material:

Non-radiolabelled: Batch: NEL7687-2.
Purity = 99.4%.

Radiolabelled: [phenyl-UL-^{14}C]-fluopyram
Batch: KML 9643.
Specific activity: 139.06 µCi/mg.
Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the Fluopyram + Trifloxystrobin SC 500 formulation containing fluopyram at a concentration of 250 g/L and trifloxystrobin at a concentration of 250 g/L. It was used at three nominal concentrations of fluopyram: neat; 250 g/L, 0.2 g/L and 0.033 g/L.

Test system: A flow-through diffusion cell system was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was

positioned. The receptor fluid used in this study was PBS 0.01M pH 7.4 + 6% polyoxyethylene 20 oleyl ether. The skin surface temperature was maintained at 32°C ± 1°C, with a fixed water bath integrated in the dynamic system (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1 mL/h.

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. The skin integrity was evaluated before use by measuring the TEWL. The absence of water on the skin was controlled using a Tewameter which allows measurement of water evaporation from skin surfaces based on the diffusion principle and expresses the results digitally in $g/m^2/h$. The measurement was carried out away from any heating source and air stream after at least 1 hour stabilisation. The human skin was included in the study if the TEWL was ≤ 4 $g/m^2/h$.

Treatment: The dose preparation was applied to the split-thickness skin sample with a positive displacement pipette at the rate of approximately 10 µL/cm² exposed skin. The specific activity of 6 aliquots of fluopyram and the homogeneity of the test items were checked on the day of preparation, before and during application. The homogeneity of the test items before the application was acceptable if the obtained CV was < 5%. The specific activity of the test items obtained during the application was used to calculate the recovery. The coefficient of variation between this series of samples was stated as a measure of variability of the application system.

Sampling: The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The receptor fluid was collected in one vial per time point and per cell at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 10h, 12h, 15h, 18h, 21h and 24h post the start of application. At 8 hours post-application, the skin was swabbed with 10% v/v Tween 80 in water using cotton buds and then with 9 x 1 mL of UHQ water. The washing solution was added to the skin surface then removed using a pipette and was collected for analysis. Then, skin surface was carefully dried with three cotton-buds in order to remove and retain the non-absorbed dose. 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. The strips were performed using adhesive scotch tape Magic 3M®. In order to standardise stripping, a weight of 150 g/cm² was placed top of the Scotch tape for 10 s before taking off. A maximum of 15 strips were performed until the slightly shiny layer below the *stratum corneum* was visible, corresponding to the viable epidermis (presumed to be the region around the *stratum spinosum*). All strips were analysed separately. The first two strips are considered in the calculation as material likely to be lost to the external environment due to desquamation of the superficial external layers of the skin surface.

Radioassay: Samples were analysed for radiolabel content by scintillation counter (LS6500, Beckman). The related software is WinConnection P/W 513860 V2.11. Calculations were performed using Excel 2010 directly from the raw

data obtained with the scintillation counter. The software runs calculations using 7 decimal points, but in general less numbers are printed on the raw data sheets. Conversion of the counts per minute (cpm) to disintegrations per minute (dpm) was performed directly by the microprocessor in the instrument using a quench curve of the appropriate scintillation cocktail stored in the instrument database.

Findings:

Fluopyram 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 tables.

Table 7.3-49: **Distribution of radioactivity at 24 hours after dose application of [14C]-fluopyram in the FLU+TFS SC 500 formulation at the rate of 250 g/L to human skin samples (All cells).**

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	250	250	234	234	TRA0010 00AJ340	TRA0010 00AJ340		
Cell N°	A	B	C	D	E	F	MEAN	SD
Skin Excess	99.12	96.94	99.98	99.04	97.27	97.49	98.31	1.23
SC1	0.05	0.01	0.04	0.04	0.08	n.d.	0.04	0.03
SC2	0.03	0.01	0.01	0.02	0.03	n.d.	0.02	0.01
Total SC1 + SC2	**0.08**	**0.02**	**0.05**	**0.06**	**0.11**	**n.d.**	**0.05**	**0.04**
TOTAL NON-ABSORBED	**99.20**	**96.96**	**100.03**	**99.10**	**97.38**	**97.49**	**98.36**	**1.24**
Skin	n.d.	n.d.	n.d.	0.01	0.09	n.d.	0.02	0.04
Stratum Corneum (SC3+)	0.40	0.21	0.22	0.07	0.08	n.d.	0.16	0.14
TOTAL DOSE SITE	**0.40**	**0.21**	**0.22**	**0.08**	**0.17**	**n.d.**	**0.18**	**0.14**
Receptor fluid (0 - 12h)	n.d.	n.d.	n.d.	n.d.	0.03	0.02	0.01	0.02
Receptor fluid (0 - 24h)	n.d.	n.d.	n.d.	n.d.	0.05	0.02	0.01	0.02
%Ratio receptor 12h/24h	100	100	100	100	100	100	**100**	**0**
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.00
TOTAL DIRECT	**0.00**	**0.00**	**0.00**	**0.00**	**0.05**	**0.02**	**0.01**	**0.02**
POTENTIAL (dose site+ receptor)	0.40	0.21	0.22	0.08	0.22	0.02	0.19	0.13
POTENTIAL (skin+ receptor)	**0.00**	**0.00**	**0.00**	**0.01**	**0.14**	**0.02**	**0.03**	**0.06**
TOTAL RECOVERY	**99.6**	**97.2**	**100.3**	**99.2**	**97.6**	**97.5**	**98.6**	**1.3**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?					Yes. (exclude SC values)			
Mean Recovery <95%?					No correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%skin +%receptor) + (SD*1) = **0.083%**			

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a.: not applicable
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.

Table 7.3-50: Distribution of radioactivity at 24 hours after dose application of [14C]-fluopyram in the FLU+TFS SC 500 formulation at the rate of 0.20 g/L to human skin samples (All cells).

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)						Group Human HD N=6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	250	250	234	234	TRA0010 00AJ340	TRA0010 00AJ340		
Cell N°	G	H	I	J	K	L	MEAN	SD
Skin Excess	127.60	134.62	110.67	98.30	97.82	101.73	111.79	15.82
SC1	4.32	4.02	2.38	4.14	3.12	2.90	3.48	0.79
SC2	2.52	0.63	0.78	1.60	1.53	1.35	1.40	0.68
Total SC1 + SC2	**6.84**	**4.65**	**3.16**	**5.74**	**4.65**	**4.25**	**4.88**	**1.27**
TOTAL NON ABSORBED	**134.44**	**139.27**	**113.83**	**104.04**	**102.47**	**105.98**	**116.67**	**16.19**
Skin	2.59	0.41	0.37	0.77	0.27	0.09	0.75	0.93
Stratum Corneum (SC3+)	8.83	3.20	2.61	3.62	2.80	1.48	3.76	2.59
TOTAL DOSE SITE	**11.42**	**3.61**	**2.98**	**4.39**	**3.07**	**1.57**	**4.51**	**3.51**
Receptor fluid (0 - 12h)	3.91	2.04	1.32	1.09	3.25	2.97	2.43	1.13
Receptor fluid (0 - 24h)	5.05	2.51	1.70	1.58	3.47	3.18	2.92	1.29
%Ratio receptor 12h/24h	77	81	78	69	94	93	82	10
Receptor chamber	0.19	0.05	0.08	0.10	0.19	0.12	0.12	0.06
TOTAL DIRECT	**5.24**	**2.56**	**1.78**	**1.68**	**3.66**	**3.30**	**3.04**	**1.34**
POTENTIAL (dose site+ receptor)	16.66	6.17	4.76	6.07	6.73	4.87	7.54	4.53
POTENTIAL (skin+ receptor)	**7.83**	**2.97**	**2.15**	**2.45**	**3.93**	**3.39**	**3.79**	**2.08**
TOTAL RECOVERY	151.1	145.4	118.6	110.1	109.2	110.9	124.2	19.0
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?					Yes, (exclude SC values)			
Mean Recovery <95%?					No correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%dose site +%receptor) + (SD*1) = **5.9%**			

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a. : not applicable
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.

Table 7.3-51: **Distribution of radioactivity at 24 hours after dose application of [14C]-fluopyram in the FLU+TFS SC 500 formulation at the rate of 0.033 g/L to human skin samples (All cells).**

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	250	250	234	234	TRA0010 00AJ340	TRA0010 00AJ340		
Cell N°	M	N	O	P	Q	R	MEAN	SD
Skin Excess	92.50	105.18	81.88	81.20	61.91	85.84	84.74	14.32
SC1	2.01	5.14	6.62	5.68	3.64	2.12	4.20	1.92
SC2	0.72	3.40	3.08	2.34	2.08	1.02	2.11	1.08
Total SC1 + SC2	**2.73**	**8.54**	**9.70**	**8.02**	**5.72**	**3.14**	**6.31**	**2.92**
TOTAL NON ABSORBED	**95.23**	**113.72**	**91.58**	**89.22**	**67.53**	**88.98**	**91.04**	**14.78**
Skin	0.19	0.80	0.54	1.32	0.38	0.10	0.64	0.63
Stratum Corneum (SC3+)	2.15	6.45	2.83	3.02	5.12	2.60	3.70	1.70
TOTAL DOSE SITE	**2.34**	**7.25**	**3.37**	**4.34**	**5.48**	**2.70**	**4.33**	**1.88**
Receptor fluid (0 - 12h)	7.58	11.99	9.84	7.18	23.33	11.68	11.94	5.95
Receptor fluid (0 - 24h)	8.39	13.72	12.86	8.47	30.14	12.76	15.48	6.56
%Ratio receptor 12h/24h	90	87	83	85	89	95	88	4
Receptor chamber	0.00	5.62	0.49	0.26	0.86	0.37	1.27	2.15
TOTAL DIRECT	**8.39**	**19.35**	**12.35**	**8.73**	**27.00**	**12.63**	**14.74**	**7.19**
POTENTIAL (dose site+ receptor)	10.73	26.60	15.72	13.07	32.48	15.33	19.07	8.50
POTENTIAL (skin+ receptor)	**8.58**	**20.15**	**12.89**	**10.55**	**27.36**	**12.73**	**15.38**	**7.06**
TOTAL RECOVERY	**106.0**	**140.3**	**107.3**	**102.8**	**100.0**	**104.3**	**110.1**	**15.0**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?					Yes (exclude SC values)			
Mean Recovery <95%?					No correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%skin +%receptor) + (SD*1) = **22%**			

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a.: not applicable
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.

The data from Cell Q differ from the data for Cell R which used the same donor. The swabbing procedure appears to have been less efficient and the levels found in the receptor fluid are approximately double those of cell R suggesting that the skin sample may have been damaged. The following chart visually demonstrates the difference in profile obtained for cell Q compared to the duplicate cell R and the other skin samples that were tested.

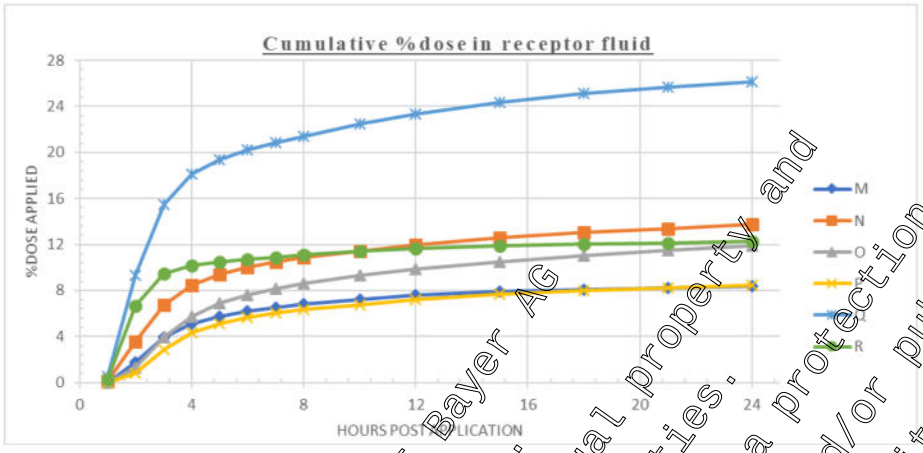

Table 7.3-52: Distribution of radioactivity at 24 hours after dose application of [14C] fluopyram in the FLU+TFS SC 500 formulation at the rate of 0.033 g/L to human skin samples (Reported cells).

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose applied)						
Sex	Female	Female	Female	Female	Female	Group Human HD N= 5 K N° = 1.2	
Donor N°	250	250	234	204	TRA0010008A J340		
Cell N°	M	N	O	P	R	MEAN	SD
Skin Excess	92.50	105.18	81.88	81.20	85.84	89.32	9.94
SC1	2.01	5.14	6.62	5.68	3.12	4.31	2.12
SC2	0.72	3.40	3.08	2.34	1.02	2.11	1.20
Total SC1 + SC2	**2.73**	**8.54**	**9.70**	**8.02**	**3.14**	**6.43**	**3.25**
TOTAL NON ABSORBED	**95.23**	**113.72**	**91.58**	**89.22**	**88.98**	**95.75**	**10.36**
Skin	0.19	0.80	0.54	1.82	0.10	0.69	0.69
Stratum Corneum (SC3+)	2.15	6.45	2.83	3.02	2.60	3.41	1.73
TOTAL DOSE SITE	**2.34**	**7.25**	**3.37**	**4.84**	**2.70**	**4.10**	**2.00**
Receptor fluid (0 - 12h)	9.58	11.99	9.84	7.18	11.68	9.65	2.24
Receptor fluid (0 - 24h)	8.39	13.73	10.86	8.47	12.26	10.94	2.40
%Ratio receptor 12h/24h	90	87	83	85	95	**88**	**5**
Receptor chamber	0.00	0.62	0.49	0.26	0.37	1.35	2.39
TOTAL DIRECT	**8.39**	**19.35**	**12.35**	**8.73**	**12.63**	**12.29**	**4.41**
POTENTIAL (dose site+ receptor)	10.73	26.60	15.72	13.57	15.33	16.39	6.04
POTENTIAL (skin+ receptor)	**8.58**	**20.15**	**12.89**	**10.55**	**12.73**	**12.98**	**4.38**
TOTAL RECOVERY	**106.1**	**140.3**	**107.3**	**102.8**	**104.3**	**112.14**	**15.83**
Evaluation according to EFSA Guidance (2017)							
Absorption >75% within half of study duration?					Yes (exclude SC values)		
Mean Recovery ≥ 95%?					No correction needed		
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%skin +%receptor) + (SD*1.2) = **18%**		

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

Conclusion:

The dermal penetration through human dermatomed skin of [^{14}C]-fluopyram in the fluopyram + trifloxystrobin SC 500 formulation was investigated at three nominal concentrations corresponding to the neat product (250 g /L) and to two representative spray dilutions of 0.20 and 0.033 g/L.

Concentrate

The mean percentage of fluopyram in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 0.083%.

Intermediate Dose level

The mean percentage of fluopyram in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 5.9%.

Low Dose level (Spray dilution)

The mean percentage of fluopyram in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 18%.

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for fluopyram in the FLU+TFS SC 500 formulation:

- 0.083% for the neat formulation (250 g/L)
- 5.9% for the intermediate dose (0.20 g/L)
- 18% for the low dose (0.033 g/L)

Trifloxystrobin

Comparative dermal absorption, *in vitro* using rat and human skin

Data Point:	KCP 7.3/02
Report Author:	[redacted]
Report Year:	2014
Report Title:	[14C]-trifloxystrobin (FLU + TFS SC 500) - In vitro dermal absorption study using human skin
Report No:	SA 13189
Document No:	M-486321-01-1
Guideline(s) followed in study:	OECD Guideline for the testing of Chemicals Skin Absorption In Vitro Method Guideline 428 (April 2004). OECD Environmental Health and Safety Publication Series on testing and Assessment N° 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004). EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption. EFSA Journal 2012; 10(4): 2665.
Deviations from current test guideline:	none
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Material and methods

Human skin: Source: Xenometrix, Hegenheim, France.
Number and sex: 6 donors, female.
Anatomical region: Abdomen.
Thickness: 389.4 to 483 µm.

Test Material:

Non-radiolabelled: Batch: NLL5391-14.
Purity = 99.6%.

Radiolabelled: [trifluoromethylphenyl-^{14}C]-trifloxystrobin
Batch: KML 9678.
Specific activity: 3.72 MBq/mg.
Radiopurity of the formulation: >98%.

Formulation: The formulation used in this experiment was the FLU+TFS SC 500 formulation (specification N° 102000012886) containing trifloxystrobin (250 g/L) and fluopyram (250 g/L). It was used at three nominal concentrations of trifloxystrobin: neat, 250 g/L, 0.2 g/L and 0.033 g/L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C

(close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

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

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

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

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

Findings:

Trifloxystrobin 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 tables.

Table 7.3-53: Distribution of radioactivity at 24 hours after dose application of [14C]-trifloxystrobin in the FLU+TFS SC 500 formulation at the rate of 250 g/L to human skin samples (All cells).

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	522-01-0812 II	528-01-0913 II	524-01-0813 V	527-01-0913 III	520-01-0813 II	524-01-0813 VI		
Cell N°	H01	H02	H03	H04	H05	H06	MEAN	SD
Skin wash 8h	101.15	97.86	95.37	101.07	101.83	95.43	98.79	2.96
Skin wash 24h	n.d.	0.01	0.09	0.01	0.01	n.d.	0.02	0.03
Surrounding swabs 24 h	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Total swabs	**101.15**	**97.87**	**95.46**	**101.08**	**101.84**	**95.43**	**98.81**	**2.94**
SC1	0.006	0.024	0.106	0.042	0.010	0.001	0.03	0.04
SC2	0.002	0.007	0.037	0.010	0.007	0.001	0.01	0.01
Total SC1 + SC2	**0.01**	**0.03**	**0.15**	**0.05**	**0.02**	**0.003**	**0.04**	**0.05**
Donor chamber	0.09	0.03	0.26	0.04	n.d.	n.d.	0.07	0.10
TOTAL NON ABSORBED	**101.25**	**97.94**	**95.87**	**101.17**	**101.86**	**95.44**	**98.92**	**2.88**
Skin	0.0020	0.0048	0.0414	0.0247	0.0023	0.0035	0.01	0.02
Surrounding skin	n.d.	0.0014	0.0009	0.0011	0.0021	0.0013	n.d.	0.00
Total skin	**0.002**	**0.006**	**0.042**	**0.026**	**0.004**	**0.005**	**0.01**	**0.02**
SC3	0.0022	0.0028	0.0186	0.0135	0.0023	0.0015	0.007	0.007
SC4	0.0014	0.0033	0.0146	0.0037	0.0023	0.0013	0.004	0.005
SC5	0.0017	0.0022	0.0322	0.0031	0.0025	0.0011	0.007	0.012
SC6	0.0015	0.0016	0.0076	n.s.	0.0017	0.0010	0.003	0.003
SC7	0.0012	0.0018	0.0132	n.s.	0.0014	0.0011	0.004	0.005
SC8	0.0016	0.0012	n.s.	n.s.	0.0018	0.0010	0.001	0.000
SC9	0.0013	0.0013	n.s.	n.s.	ND	n.s.	0.001	0.000
SC10	0.0012	0.0012	n.s.	n.s.	0.0013	n.s.	0.001	0.000
SC11	0.0013	n.s.	n.s.	n.s.	n.s.	n.s.	0.001	0.000
SC12	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.a.	n.a.
SC13	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.a.	n.a.
SC14	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.a.	n.a.
SC15	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.a.	n.a.
Total SC3+	**0.01**	**0.02**	**0.09**	**0.02**	**0.01**	**0.01**	**0.03**	**0.03**
TOTAL DOSE SITE	**0.02**	**0.02**	**0.13**	**0.05**	**0.02**	**0.01**	**0.04**	**0.04**
Receptor fluid (0 - 12h)	0.032	0.033	0.031	0.040	0.030	0.028	**0.032**	**0.004**
Receptor fluid (0 - 24h)	0.051	0.052	0.050	0.062	0.049	0.046	**0.052**	**0.005**
%Ratio receptor 12h/24h	62	63	62	65	62	61	**63**	**1**
Residual Rec Fluid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	**0.05**	**0.05**	**0.05**	**0.06**	**0.05**	**0.05**	**0.05**	**0.01**
POTENTIAL (dose site+ receptor)	**0.07**	**0.07**	**0.18**	**0.11**	**0.07**	**0.06**	**0.09**	**0.05**
POTENTIAL (skin+ receptor)	0.05	0.06	0.09	0.09	0.05	0.05	0.07	0.02
TOTAL RECOVERY	**101.3**	**98.0**	**96.1**	**101.3**	**101.9**	**95.5**	**99.01**	**2.87**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?					No. (include SC values except SC1 & SC2))			
Mean Recovery<95%?					No correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%dose site +%receptor) + (SD*1) = **0.14%**			

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a. : not applicable
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.

Table 7.3-54: **Distribution of radioactivity at 24 hours after dose application of [14C]-trifloxystrobin in the FLU+TFS SC 500 formulation at the rate of 0.20 g/L to human skin samples (All cells).**

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	522-01-0813 I	520-01-0813 II	524-01-0813 IV	527-01-0913 III	524-01-0813 VI	476-01-0912 III-1		
Cell N°	H07	H08	H09	H10	H11	H12	MEAN	SD
Skin wash 8h	86.61	78.69	101.43	97.02	94.91	100.61	93.21	8.86
Skin wash 24h	3.29	6.09	1.35	0.45	1.20	0.71	2.09	2.15
Surrounding swabs 24 h	0.005	n.d.	0.029	n.d.	n.d.	0.039	0.01	0.02
Total swabs	**89.91**	**84.78**	**102.81**	**97.47**	**95.52**	**101.43**	**95.32**	**6.90**
SC1	0.20	2.61	0.15	0.04	1.71	0.30	0.83	1.07
SC2	0.09	1.07	0.08	0.02	0.00	0.14	0.23	0.42
Total SC1 + SC2	**0.28**	**3.68**	**0.23**	**0.06**	**1.71**	**0.43**	**1.07**	**1.41**
Donor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL NON ABSORBED	**90.19**	**88.46**	**103.04**	**97.53**	**97.22**	**101.86**	**96.38**	**5.95**
Skin	0.03	1.30	0.02	0.09	0.04	0.12	0.28	0.55
Surrounding skin	n.d.	n.d.	0.02	n.d.	0.01	0.03	0.01	0.01
Total skin	**0.03**	**1.40**	**0.04**	**0.09**	**0.05**	**0.15**	**0.29**	**0.55**
SC3	0.055	0.615	0.207	0.018	0.000	0.088	0.165	0.235
SC4	0.036	0.324	0.257	0.028	0.000	0.071	0.119	0.136
SC5	0.029	0.700	n.s.	0.017	n.s.	0.068	0.204	0.332
SC6	0.024	0.399	n.s.	0.014	n.s.	0.046	0.121	0.186
SC7	0.016	n.s.	n.s.	0.008	n.s.	0.030	0.020	0.015
SC8	0.012	n.s.	n.s.	0.010	n.s.	0.031	0.018	0.012
SC9	0.006	n.s.	n.s.	0.006	n.s.	0.024	0.012	0.010
SC10	0.013	n.s.	n.s.	n.s.	n.s.	0.021	0.017	0.006
SC11	0.000	n.s.	n.s.	n.s.	n.s.	0.019	0.010	0.014
SC12	0.000	n.s.	n.s.	n.s.	n.s.	0.014	0.007	0.010
SC13	n.s.	n.s.	n.s.	n.s.	n.s.	0.017	0.017	0.000
SC14	n.s.	n.s.	n.s.	n.s.	n.s.	0.051	0.051	0.000
SC15	n.s.	n.s.	n.s.	n.s.	n.s.	0.008	0.008	0.000
Total SC3+	**0.19**	**2.04**	**0.46**	**0.10**	**n.d.**	**0.49**	**0.55**	**0.76**
TOTAL DOSE SITE	**0.22**	**3.44**	**0.50**	**0.19**	**0.05**	**0.64**	**0.84**	**1.29**
Receptor fluid (0 - 12h)	0.062	0.044	0.154	0.171	0.217	0.143	0.13	0.07
Receptor fluid (0 - 24h)	0.052	0.061	0.245	0.238	0.391	0.332	0.22	0.13
%Ratio receptor 12h/24h	86	73	63	72	55	43	65	15
Residual Rec. fluid	n.d.	n.d.	0.03	n.d.	0.04	0.05	0.02	0.02
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	**0.07**	**0.06**	**0.27**	**0.24**	**0.43**	**0.38**	**0.24**	**0.15**
POTENTIAL (dose site+ receptor)	0.29	3.50	0.77	0.42	0.48	1.02	1.08	1.22
POTENTIAL (skin+ receptor)	0.10	1.46	0.31	0.32	0.48	0.52	0.53	0.48
TOTAL RECOVERY	**90.5**	**92.0**	**103.8**	**98.0**	**97.7**	**102.9**	**97.5**	**5.5**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?					No. (include SC values except SC1 & SC2)			
Mean Recovery ≥95%?					No correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%dose site +%receptor) + (SD*1) = **2.3%**			

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a. : not applicable
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.

In the study report both Cells H07 and H08 were excluded from the reported cells due to “technical problems with the swabbing”. However, using the modified Z-score as a statistical test for outliers it would appear that only cell H08 should be considered to be an outlier due principally to the higher levels of radioactivity found in the stratum corneum and skin compared to the other cells. This is most probably linked to the relatively low swabbing efficiency observed by the study director in the report for this cell.

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 threshold. 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:

$$Mi = 0.6745 * (Xi - Median(Xi)) / MAD$$

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 an "Outlier".

Table 7.3-55: Modifed Z-score result for the stratum corneum (SC3+), skin and potential absorption results for TFS following application of [14C]- trifloxystrobin in the FLU+TFS SC 500 formulation at the rate of 8.20 g/L to human skin samples (All cells).

Cell N°	SC3+		mean-value	mod Z score
H07	0.19	NORMAL	0.14	-0.4
H08	2.04	OUTLIER	1.71	**5.2**
H09	0.47	NORMAL	-0.14	0.4
H10	0.06	NORMAL	0.27	-0.8
H11	0	NORMAL	0.33	-1.0
H12	0.5	NORMAL	0.17	0.5
	SKIN		mean-value	mod Z score
H07	0.03	NORMAL	0.035	-0.6
H08	1.4	OUTLIER	-1.335	**22.5**
H09	0.02	NORMAL	0.045	-0.8
H10	0.09	NORMAL	-0.025	0.4
H11	0.04	NORMAL	0.025	-0.4
H12	0.12	NORMAL	-0.055	0.9
	POTENTIAL (%dose site+ direct)		mean-value	mod Z score
H07	0.32	NORMAL	0.315	-0.8
H08	3.53	OUTLIER	-2.895	**7.5**
H09	0.78	NORMAL	-0.145	0.4
H10	0.43	NORMAL	0.205	-0.5
H11	0.49	NORMAL	0.145	-0.4
H12	1.05	NORMAL	-0.415	1.1

Table 7.3-56: **Distribution of radioactivity at 24 hours after dose application of [14C]-trifloxystrobin in the FLU+TFS SC 500 formulation at the rate of 0.20 g/L to human skin samples (Reported cells).**

Results expressed in terms of percentage of applied radioactivity

	Distribution of radioactivity (% dose applied)					Group Human HD N= 5	
Sex	Female	Female	Female	Female	Female		
Donor N°	522-01-0813 I	524-01-0813 IV	527-01-0913 III	524-01-0813 VI	476-01-0912 III-1	K N° 1.2	
Cell N°	H07	H09	H010	H11	H12	MEAN	SD
Skin wash 8h	86.61	101.43	97.02	94.92	100.61	96.00	5.97
Skin wash 24h	3.29	1.35	0.45	1.20	0.77	1.42	1.11
Surrounding swabs 24 h	0.005	0.029	n.d.	n.d.	0.039	0.01	0.02
Total swabs	**89.91**	**102.81**	**97.47**	**95.52**	**101.43**	97.43	5.13
SC1	0.20	0.15	0.04	1.71	0.30	0.48	0.69
SC2	0.09	0.08	0.02	n.d.	0.14	0.06	0.05
Total SC1 + SC2	**0.28**	**0.23**	**0.06**	**1.71**	**0.43**	0.54	0.66
Donor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	0.00	0.00
TOTAL NON-ABSORBED	**90.19**	**103.04**	**97.53**	**97.22**	**101.86**	97.96	5.05
Skin	0.03	0.02	0.09	0.04	0.13	0.06	0.04
Surrounding skin	n.d.	0.02	n.d.	0.01	0.02	0.01	0.01
Total skin	**0.03**	**0.04**	**0.09**	**0.05**	**0.15**	0.07	0.05
SC3	0.055	0.207	0.018	0.000	0.088	0.07	0.08
SC4	0.036	0.251	0.028	0.000	0.071	0.08	0.10
SC5	0.029	n.s.	0.017	n.s.	0.068	0.04	0.03
SC6	0.024	n.s.	0.014	n.s.	0.046	0.03	0.02
SC7	0.016	n.s.	0.008	n.s.	0.036	0.02	0.01
SC8	0.022	n.s.	0.010	n.s.	0.031	0.02	0.01
SC9	0.006	n.s.	0.006	n.s.	0.024	0.01	0.01
SC10	0.013	n.s.	n.s.	n.s.	0.021	0.02	0.01
SC11	0.000	n.s.	n.s.	n.s.	0.019	0.01	0.01
SC12	0.000	n.s.	n.s.	n.s.	0.014	0.01	0.01
SC13	n.s.	n.s.	n.s.	n.s.	0.017	0.02	0.00
SC14	n.s.	n.s.	n.s.	n.s.	0.051	0.05	0.00
SC15	n.s.	n.s.	n.s.	n.s.	0.008	0.01	0.00
Total SC3+	**0.19**	**0.46**	**0.10**	n.d.	**0.49**	**0.25**	**0.22**
TOTAL DOSE SITE	**0.22**	**0.50**	**0.19**	**0.05**	**0.64**	**0.32**	**0.24**
Receptor fluid (0 - 12h)	0.062	0.154	0.171	0.217	0.143	0.15	0.06
Receptor fluid (0 - 24h)	0.092	0.245	0.238	0.391	0.332	0.26	0.12
%Ratio receptor 12h/24h	86	63	72	55	43	58	12
Residual Rec Fluid	n.d.	0.03	n.d.	0.04	0.05	0.02	0.02
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	0.00	0.00
TOTAL DIRECT	**0.07**	**0.27**	**0.24**	**0.43**	**0.38**	**0.28**	**0.14**
POTENTIAL (dose site+ receptor)	**0.29**	**0.77**	**0.42**	**0.48**	**1.02**	**0.60**	**0.29**
POTENTIAL (skin+ receptor)	**0.10**	**0.31**	**0.32**	**0.48**	**0.52**	**0.35**	**0.17**
TOTAL RECOVERY	**90.5**	**103.8**	**98.0**	**97.7**	**102.9**	**98.57**	**5.30**

Evaluation according to EFSA Guidance (2017)	
Absorption ≥75% within half of study duration?	No. (include SC values except SC1 & SC2)
Mean Recovery <95%?	No correction needed
Total % Potentially Absorbable adjusted according to EFSA (2017)	Mean (%dose site +%receptor) + (SD*1.2) = **0.95%**

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a. : not applicable

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.

Table 7.3-57: Distribution of radioactivity at 24 hours after dose application of [14C]-trifloxystrobin in the FLU+TFS SC 500 formulation at the rate of 0.033 g/L to human skin samples (All cells).

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	520-01-0813 IV	522-01-0813 II	476-01-0912 III-1	528-01-0913 III	527-01-0913 III	524-01-0813 V		
Cell N°	H013	H014	H15	H16	H17	H18	MEAN	SD
Skin wash 8h	74.64	83.87	91.48	78.52	80.26	56.90	77.61	11.64
Skin wash 24h	4.44	9.76	6.13	11.85	1.77	2.67	6.10	3.99
Surrounding swabs 24 h	0.00	0.00	0.00	0.55	0.10	0.05	0.12	0.22
Total swabs	**79.08**	**93.63**	**97.60**	**90.92**	**82.13**	**59.62**	**83.83**	**13.77**
SC1	9.67	2.00	2.82	4.26	4.99	11.16	5.82	3.74
SC2	2.98	0.96	1.01	1.47	2.06	3.10	1.93	0.95
Total SC1 + SC2	**12.65**	**2.96**	**3.83**	**5.73**	**7.06**	**14.27**	**7.75**	**4.68**
Donor chamber	0.00	0.00	0.00	0.72	1.04	0.00	0.29	0.46
TOTAL NON ABSORBED	**91.73**	**96.59**	**101.43**	**97.37**	**90.22**	**73.89**	**91.87**	**9.70**
Skin	5.35	1.25	0.60	2.76	3.47	12.43	4.31	4.32
Surrounding skin	0.07	0.05	0.07	0.13	0.10	0.07	0.08	0.03
Total skin	**5.42**	**1.30**	**0.67**	**2.89**	**3.57**	**12.50**	**4.39**	**4.32**
SC3	2.33	1.18	0.66	1.45	1.48	2.91	1.67	0.81
SC4	2.85	0.52	0.62	0.85	1.79	1.48	1.35	0.89
SC5	1.43	0.49	0.55	0.84	1.35	n.s.	0.78	0.55
SC6	n.s.	0.21	0.25	n.s.	1.48	n.s.	0.32	0.58
SC7	n.s.	0.67	0.33	n.s.	1.80	n.s.	0.47	0.71
SC8	n.s.	0.16	0.28	n.s.	1.15	n.s.	0.27	0.45
SC9	n.s.	0.10	0.20	n.s.	0.60	n.s.	0.15	0.23
SC10	n.s.	0.18	0.22	n.s.	2.74	n.s.	0.52	1.09
SC11	n.s.	n.s.	0.13	n.s.	0.00	n.s.	0.02	0.05
SC12	n.s.	n.s.	0.14	n.s.	0.00	n.s.	0.02	0.06
SC13	n.s.	n.s.	0.11	n.s.	0.00	n.s.	0.02	0.04
Total SC3+	**6.62**	**3.52**	**3.49**	**3.14**	**12.38**	**4.40**	**5.59**	**3.56**
TOTAL DOSE SITE	**12.04**	**4.82**	**4.16**	**6.03**	**15.95**	**16.90**	**9.98**	**5.73**
Receptor fluid (0 - 12h)	0.035	0.302	0.456	0.309	0.093	0.711	0.32	0.25
Receptor fluid (0 - 24h)	0.085	0.443	0.909	1.182	0.093	1.326	0.67	0.54
%Ratio receptor 12h/24h	41	68	50	26	100	54	57	25
Residual Rec Fluid	0.00	0.00	0.00	0.26	0.29	0.00	0.09	0.14
Receptor chamber	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TOTAL DIRECT	**0.08**	**0.44**	**0.91**	**1.45**	**0.38**	**1.33**	**0.77**	**0.55**
POTENTIAL (dose site+ receptor)	**12.12**	**5.26**	**5.07**	**7.48**	**16.33**	**18.23**	**10.75**	**5.69**
POTENTIAL (skin+ receptor)	5.50	1.74	1.58	4.34	3.95	13.83	5.16	4.51
TOTAL RECOVERY	**103.9**	**101.9**	**106.5**	**104.8**	**106.6**	**92.1**	**102.62**	**5.44**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration?				No. (include SC values except SC1 & SC2)				
Recovery <95%?				No correction needed				
Total % Potentially Absorbable adjusted according to EFSA (2017)				Mean (%dose site +%receptor) + (SD*1) = **16%**				

SD: standard deviation; N: number of skin cells used for calculation
n.d.: not detected (below the limit of detection); n.a. : not applicable

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.

Whilst the study director eliminated cell H18 due to the relatively low swabbing efficiency there was no statistically significant difference in the final potentially absorbed values, so all of the cells have been retained in this summary.

Conclusion:

The dermal penetration through human dermatomed skin of [^{14}C]-trifloxystrobin in the trifloxystrobin SC 500 formulation was investigated at three nominal concentrations corresponding to the neat product (250 g /L) and to two representative spray dilutions of 0.20 and 0.033 g/L.

Concentrate

The mean percentage of trifloxystrobin in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 0.14%.

Intermediate Dose level

The mean percentage of trifloxystrobin in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 0.95%.

Low Dose level (Spray dilution)

The mean percentage of trifloxystrobin in the FLU+TFS SC 500 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 16%.

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for trifloxystrobin in the FLU+TFS SC 500 formulation:

- 0.14% for the neat formulation (250 g/L)
- 0.95% for the intermediate dose (0.20 g/L)
- 16% for the low dose (0.033 g/L)

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information / data provided separately (Document JCP).