Document Title

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

Data Requirement(s)

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

Date

2021-03-22

Author(s)

[redacted]

Bayer AG

Crop Science Division

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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 SC 500 (500 g/L), abbreviation Fluopyram SC 500B G, is a SC formulation containing 500 g/L of Fluopyram. This formulation is registered throughout Europe under trade names such as Luna Privilege. FLU SC 500 was already a representative formulation of Bayer AG for the Annex I inclusion of Fluopyram under Council Directive 91/414/EEC. However, the specification registered for the original submission is now obsolete and has been replaced with specification 102000018148, the acute toxicity studies conducted with this specification were not submitted in the original submission and are summarized hereafter.

CP 7.1 Acute toxicity

An acute toxicity data package for Fluopyram SC 500 (abbreviation: FLU SC 500) (specification 102000016460) was submitted with the original dossier (study reports: M-283611-01-1, M-287416-01-1, M-296398-01-1, M-283578-01-2, M-283581-01-1 and M-281758-01-1). These studies are obsolete as the specification has been superseded with specification 102000018148.

The newly submitted Acute toxicity studies were performed with specification 102000018148, batch 2007-011657, details of which are presented in Table 7.1-1.

FLU SC 500 is non-toxic by the oral and dermal routes of exposure in Wistar rats. Acute inhalation exposure to FLU SC 500 in Wistar rats up to the maximal technically attainable concentration of 1911 mg/m^3 resulted in no deaths or signs of toxicity. FLU 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): none

Table 7.1-1: Acute toxicity studies with FLU SC 500 (Specification No.102000018148)

Study Type	Species	Results	Reference
Acute oral toxicity	Rat	LD_{50} > 2000 mg/kg bw	M-298203-01-1
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg bw	M-298209-01-1
Acute inhalation toxicity	Rat	LC_{50} > 1911 mg/m^3 (maximal technically attainable concentration)	M-301086-01-1
Skin irritation	Rabbit	Not irritating	M-298001-01-1
Eye irritation	Rabbit	Not irritating	M-298004-01-1
Skin sensitisation LLNA	Mouse	Not sensitizing	M-298792-01-1

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CP 7.1.1 Oral toxicity

Data Point:	KCP 7.1.1/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 SC 500 - Acute toxicity in the rat after oral administration
Report No:	AT03603
Document No:	M-283611-01-1
Guideline(s) followed in study:	OECD 423 (2001) EEC 67/548 Annex V - Method B.1. tris EPA OPPTS 870.1100 MAFF 12 Nousan No 862 (December 06, 2000)
Deviations from current test guideline:	none
Previous evaluation:	Yes, evaluated and accepted (Rev. 2.1, Vol 3 of DAR B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Due to change in specification study M-283611-01-1 now superseded by study M-298203-01-1 below.

Data Point:	KCP 7.1.1/02
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 (spec no. 102000018148) - Acute toxicity in the rat after oral administration
Report No:	AT04420
Document No:	M-298203-01-1
Guideline(s) followed in study:	OECD 423 (2001), EEC Directive 67/548 Annex V - Method B.1.tris (in its current version), US EPA 712-C-98-190 (1998), Health Effects Test Guidelines (OPPTS 870.1100)
Deviations from current test guideline:	--
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

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I. Materials and methods

A. Materials

1. Test material: Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.: 102000018148
Description: White suspension
Lot/Batch no.: 2007-011657
Content: Fluopyram (AE C656948): 501 g/L certified

Stability of test compound:	Guaranteed for study duration; expiry date: 3 December 2008
2. Vehicle:	Tap water
3. Test animals	
Species:	Wistar rat
Strain:	HsdCpb:Wu (SPF)
Age:	8 - 12 weeks
Weight at dosing:	175 - 187 g
Source:	[redacted]
Acclimatisation period:	At least 5 days
Diet:	Standard diet "Provimi Kliba 3883 PM S15 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 rats of the same sex according to the procedure described in OECD Test Guideline No 423. As there was no mortality at 2000 mg/kg no further step was necessary.
Application route/ exposure:	Single oral gavage dose
Application volume:	10 mL/kg bw
Fasting time:	Food was withheld from the animals for approximately 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	1 h – 6 h	No deaths	0
(2nd) 2000	0 / 3 / 3	30 min - 4 h	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				

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B. Clinical observations

Only decreased motility was observed.

C. Body weight

There were no toxicologically significant effects on body weight or body weight gain.

D. Necropsy

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

III. Conclusion

According to OECD guideline 423 the LD_{50} cut-off of FLUSC 500 is > 5000 mg/kg bw.

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 oral route is low in the rat. The LD_{50} value which is > 2000 mg/kg bw does not trigger classification.

CP 7.1.2 Dermal toxicity

Data Point:	KCP 7.1.2/01
Report Author:	[redacted]
Report Year:	2009
Report Title:	AE B656948 SC500 - Acute toxicity in the rat after dermal application
Report No:	A71036/01
Document No:	M-287416-01-1
Guideline(s) followed in study:	OECD 402 (1987), EEC Directive 87/548 Annex V - Method B.3.; EPA 712-C-98192, OPPTS 870.1200
Deviations from current test guideline:	
Previous evaluation:	Yes, evaluated and accepted (rev. 2 to Vol.3 of DAR B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Due to change in specification study M-287416-01-1 now superseded by study M-298209-01-1 elow.

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Data Point:	KCP 7.1.2/02
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 (spec no. 102000018148) - Acute toxicity in the rat after dermal application
Report No:	AT04422
Document No:	M-298209-01-1
Guideline(s) followed in study:	OECD 402 (1987); EEC Directive 67/548 Annex V, Method B.3. (in its current version); US EPA 712-C-98-192 (1998), Health Effects Test Guidelines (OPPTS 870.1200)
Deviations from current test guideline:	--
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: Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.: 102000018148
Description: White suspension
Lot/Batch no.: 2007-011657
Content: Fluopyram (AE C656948): 501 g/L certified
Stability of test compound: Guaranteed for study duration; expiry date: 3 December 2008

2. Vehicle: none

3. Test animals

Species: Wistar rat
Strain: HsdCpb:Wu (SPF)
Age: 9 - 13 weeks
Weight at dosing: Males: 244 - 264 g; Females: 204 - 224 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.

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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	30.0	16.3 - 17.6
	Females	2000	30.0	13.6 - 14.9
Application route:	Dermal, semi-occlusive dressing			
Exposure:	24 hours			
Group size:	5 rats/sex/group			
Post-treatment observation period:	14 days			
Observations:	Mortality, clinical signs, 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.

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III. Conclusion

The median lethal dose of FLU 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} value which is > 2000 mg/kg bw does not trigger classification

CP 7.1.3 Inhalation toxicity

Data Point:	KCP 7.[redacted]/01
Report Author:	[redacted]
Report Year:	200[redacted]
Report Title:	AE C656948 SC500 - Acute inhalation toxicity in rats
Report No:	[redacted]T0360
Document No:	M-296398-01-1
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-6147 (2000)
Deviations from current test guideline:	--
Previous evaluation:	Yes, evaluated and accepted (Rev. 2 to Vol.3, DAR B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Due to change in specification study M-296398-01-1 now superseded by study M-301086-01-1 below.

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Data Point:	KCP 7.1.3/02
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 - Spec no 102000018148 - Activity ID TXGMP118 - Acute inhalation toxicity in rats
Report No:	AT04504
Document No:	M-301086-01-1
Guideline(s) followed in study:	OECD 403 (1981); Directive 92/69/EEC, Annex V, Method B.2. (1992); US-EPA, OPPTS 870.1300, Health Effects Guidelines (1998); Japan MAFF, Notification No. 12 Nousan-8147 (2000)
Deviations from current test guideline:	--
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:

Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.:	102000018148
Description:	White suspension
Lot/Batch no.:	2007-011657
Content:	Fluopyram (AE C656948): 501 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 3 December 2008

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

3. Test animals

Species:	Wistar rat
Strain:	HsdCpb:Wu (SPF)
Age:	Approx. 2 - 3 months old
Weight at dosing:	193 - 210 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

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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, rectal 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/m^3)	0	5000
Nominal concentration (mg/m^3)	Control water	15427.2
Gravimetric concentration (mg/m^3)	--	932.5
Actual concentration [1)] (mg/m^3)	--	1911
Dilution (test substance in %)	--	70
Inlet air flow (l/m)	15	15
Exhaust air flow (l/min)	13	13
Temperature (mean, °C)	22.2	23.2
Relative humidity (mean, %)	> 92.9	> 93.8
MMAD (µm)	--	3.46
GSD	--	1.94
Aerosol mass < 3 µm (%)	--	43.6
Mass recovered (mg/m^3)	--	860.1

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/(100-51.2)

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II. Results and discussion

A. Mortality

Table 7.1.1-2 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) 1911	0 / 0 / 5	No signs	No deaths	0
Female				
(Group 1) 0	0 / 0 / 5	No signs	No deaths	0
(Group 2) 1911	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				
LC_{50} > 1911 mg/m³ (maximal technically attainable concentration)				

B. Clinical observations

All rats tolerated the test without specific signs.

A battery of reflex measurements was made on the first post exposure day. All rats revealed normal reflexes

C. Body weight

After exposure body weight development of the rats showed no significant differences. Isolated significant data changes are toxicologically irrelevant.

D. Rectal temperatures

Rectal temperature measured shortly after cessation of exposure was lower (P<0.01) in the treated female group. This decrease was small and not considered to be of toxicological relevance.

E. Necropsy

Individual gross-pathological examinations of the rats revealed no observable necropsy finding.

III. Conclusion

The test substance (liquid aerosol) proved to be essentially acutely non-toxic in rats. For both genders combined, the LC_{50} is greater than 1911 mg/m³ (maximal technically attainable concentration).

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 inhalation route is low in the rat. The LC_{50} value was > 1911 mg/m³. As this was the maximal technically attainable concentration, and as there were no deaths or clinical signs, no classification is warranted for acute inhalation toxicity.

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CP 7.1.4 Skin irritation

Data Point:	KCP 7.1.4/01
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 - Acute skin irritation/corrosion on rabbits
Report No:	AT03614
Document No:	M-283578-01-2
Guideline(s) followed in study:	OECD 404 (2002) EEC Directive 67/548 Annex V, Method B.4 (1967) (or its current version) EPA OPPTS 870.2500 MAFF 12 Nousan No 8626 (December 06, 2000)
Deviations from current test guideline:	--
Previous evaluation:	Yes, evaluated and accepted (rev. 2 to Vol.3 of DAR B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Data Point:	KCP 7.1.4/02
Report Author:	[redacted]
Report Year:	1944
Report Title:	Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes
Report No:	M-681853-01-1
Document No:	M-681853-01-1
Guideline(s) followed in study:	--
Deviations from current test guideline:	--
Previous evaluation:	Yes, evaluated and accepted (rev. 2 to Vol.3 of DAR B6 August 2012)
GLP/Officially recognised testing facilities:	not applicable
Acceptability/Reliability:	Yes

Due to change in specification study M-283578-01-2 now superseded by study M-298001-01-1 below.

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Data Point:	KCP 7.1.4/03
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 (spec no. 102000018148) - Acute skin irritation/corrosion on rabbits
Report No:	AT04416
Document No:	M-298001-01-1
Guideline(s) followed in study:	OECD 404; Directive 67/548/EEC, Annex V, Method B.4.; US-EPA 712-C-98-196, OPPTS 870.2500
Deviations from current test guideline:	--
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: Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.: 102000018148
Description: White suspension
Lot/Batch no.: 2007-011657
Content: Fluopyram (AE C656948): 501 g/L certified
Stability of test compound: Guaranteed for study duration; expiry date: 3 December 2008

2. Vehicle: none

3. Test animals

Species: Albino rabbit
Strain: Crl:KBL(NZW)BR
Age: Young adult
Weight at dosing: 2.9 - 3.0 kg
Source: [redacted]
Acclimatisation period: At least 5 days
Diet: Standard diet "Ssniff K-Z" 4mm (Ssniff Spezialdiaeten GmbH, Soest, Germany), 100g per day per animal; 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

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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 (Score)

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 SC 500 is not irritating to the skin of rabbits.

The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008: 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.

CP 7.1.5 Eye irritation

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Data Point:	KCP 7.1.5/01
Report Author:	[redacted]
Report Year:	2007
Report Title:	AE C656948 SC 500 - Acute eye irritation on rabbits
Report No:	AT03615
Document No:	M-283581-01-1
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:	--
Previous evaluation:	Yes, evaluated and accepted (rev. 2 to Vol.3 of DAR B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Due to change in specification study M-283581-01-1 now superseded by study M-298004-01-1 below.

Data Point:	KCP 7.1.5/02
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500 (spec no. 102000018148) - Acute eye irritation on rabbits
Report No:	AT04415
Document No:	M-298004-01-1
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:	--
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: Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.:	102000018148
Description:	White suspension
Lot/Batch no.:	2007-011657
Content:	Fluopyram (AE C656948): 501 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 3 December 2008

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2. Vehicle:	None
3. Test animals	
Species:	Rabbit
Strain:	Crl:KBL(NZW)BR
Age:	Young adult
Weight at dosing:	2.8 - 3.0 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:	0.1 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 (at beginning and end of study)

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

III. Conclusion

FLU 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.

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CP 7.1.6 Skin sensitization

Data Point:	KCP 7.1.6/01
Report Author:	[redacted]
Report Year:	2006
Report Title:	AE C656948 SC 500 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No:	SA 06267
Document No:	M-281758-01-1
Guideline(s) followed in study:	OECD guideline 429 (2002); Equivalent to US EPA OPPTS Guideline No 870.2600
Deviations from current test guideline:	--
Previous evaluation:	Yes, evaluated and accepted (rev. 2 to 6.1.3 of DAR, B6 August 2012)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Due to change in specification study M-281758-01-1 now superseded by study M-298792-01-1 below.

Data Point:	KCP 7.1.6/02
Report Author:	[redacted]
Report Year:	2008
Report Title:	AE C656948 SC 500-Spec No 102000018148: Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No:	SA 07365
Document No:	M-298792-01-1
Guideline(s) followed in study:	O.E.C.D. guideline 429 (2002)
Deviations from current test guideline:	--
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

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I. Materials and methods

A. Materials

1. Test material: Fluopyram SC 500
Equivalent to: AE C656948 SC 500
Abbreviation: FLU SC 500

Specification no.:	102000018148
Description:	White suspension
Lot/Batch no.:	2007-011657
Content:	Fluopyram (AE C656948): 501 g/L certified
Stability of test compound:	Guaranteed for study duration; expiry date: 3 December 2008

2. Vehicle: 1% Pluronic Acid L92® in water

3. Test animals

Species:	Mouse
Strain:	CBA/J
Age:	At least 8 weeks
Weight at dosing:	19 - 22 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, 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

Following an accidental trauma, one animal treated at a concentration of 25% was found dead on Study Day 2.

No clinical signs were observed during the study.

No cutaneous reactions were observed in the vehicle or treated groups.

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

The proliferation index values of the test substance were 1.0, 1.1, and 1.5 at treatment concentrations of 25, 50, and 100%, respectively.

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

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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	3556	10	355.6	
FLU SC 500 25% in 1% aqueous Pluronic Acid	2145	6	357.5	1.0
FLU SC 500 50% in 1% aqueous Pluronic Acid	3790	10	379.0	1.1
FLU SC 500 100% (undiluted)	5457	10	545.7	1.5

Negative lymphoproliferative responses (SI<3) were noted for FLU 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 SC 500 was found to be a non-sensitizing formulation in the Local Lymph Node Assay.

III. Conclusion

FLU 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 SC 500 (500 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 SC 500 (500 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 SC 500 formulation are provided in the following sections.

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

Product	FLU SC 500					
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.					
Active substance(s) (incl. content)	**Substance Concentration** [g/L or g/kg]	**$AOEL_{systemic}$ (RVNAS)** [mg/kg bw/d]	**Inhalation absorption [%]**	**Oral absorption [%]**	**Dermal absorption**	
					Concentrate [%]	Dilution [%]
Fluopyram (FLU)	500	0.05	100	100	0.43	30

**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 uses within the zone/ EU is given in Document D1 and Document D2 submitted with this dossier.

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**	**Residents**
1	Apple (MABSD) (BBCH 71-89)	F	spraying (broadcast, overall) HCTM	a) 1 b) 1	a) 0.075 b) --	500 – 1000	as per growth stage	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				

* 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 Gap covers the representative use in the scope of operator, resident/bystander and worker exposure.

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CP 7.2.1 Operator exposure

CP 7.2.1.1 Estimation of operator exposure

A summary of the exposure models used for the estimation of operator 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 in Table 7.7-8.

Table 7.3-4: Exposure models for intended uses

Critical use(s)	0.15 L / kg product/ha for Pome fruit
Model(s)	*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 outcome of the estimation is presented in the following table(s).

Table 7.5-6: Estimated operator exposure, Fluopyram, Pome fruit

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Upward spraying, Vehicle-mounted Application rate: 0.075 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.0158	31.6
	with PPE[3]	0.00587	11.7

[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

Conclusion

The operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) 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 SC 500.

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Operator exposure calculations (KCP 7.2.1.1)

Table 7.7-8: Operator exposure, Fluopyram, Pome fruit, no PPE / with PPE

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.075 kg a.s. /ha	**Spray dilution =** 0.15 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Pome fruit, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications** = 2 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 0.43%	**Dermal for in use dilution** = 30%	**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		0.0486	% of RVNAS[1]	97.2%
	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		**0.0158**	% of RVNAS[1]	**31.6%**
	Acute systemic exposure mg/kg bw/day		-	% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day		**0.00587**	% of RVNAS[1]	**11.7%**
	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

CP 7.2.1.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) 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 7.2.2 Bystander and resident exposure

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

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CP 7.2.2.1 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 in Table 7.13-14.

Table 7.9-10: Exposure models for intended uses

Critical use(s)	0.15 L / kg product/ha for Pome fruit
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 broadcast air assisted applications (for high crops) separately, when relevant. The outcome of the estimation is presented in the following table(s).

Table 7.11-12: Estimated resident exposure, Fluopyram, Pome fruit

	Adult[2]			Child[2]		
Outdoor, Upward spraying, Vehicle-mounted Application rate: 1 x 0.075 kg a.s./ha, 365 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]	0.00347	6.94	0.00227	0.00626	12.5	0.00412
Vapour	0.00023	0.46	0.00023	0.00107	2.14	0.00107
Surface deposits	0.000432	0.865	0.00032	0.0011	2.19	0.000811
Entry into treated crops[4]	0.00211	4.22	0.00168	0.0038	7.59	0.00303
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.0045 (9%)			0.00902 (18%)

[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

Conclusion
The Bystander/Resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) 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 SC 500.

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Bystander and Resident exposure calculations (KCP 7.2.3.1)

Table 7.13-14: Bystander and resident exposure, Fluopyram, Pome fruit

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.075 kg a.s. /ha	**Spray dilution =** 0.15 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Pome fruit, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 0.43%	**Dermal for in use dilution** = 30%	**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	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00626	% of RVNAS[1]	12.5%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	2.14%
	Surface deposits (75th percentile) mg/kg bw/day	0.0011	% of RVNAS[1]	2.19%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0038	% of RVNAS[1]	7.59%
	All pathways (mean) mg/kg bw/day	0.00902	% of RVNAS[1]	18%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00347	% of RVNAS[1]	6.94%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.46%
	Surface deposits (75th percentile) mg/kg bw/day	0.000432	% of RVNAS[1]	0.865%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00211	% of RVNAS[1]	4.22%
	All pathways (mean) mg/kg bw/day	0.0045	% of RVNAS[1]	9%

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

CP 7.2.2.2 Measurement of bystander and/or resident exposure

Since the bystander/resident exposure estimations carried out indicated that the Acceptable Operator Exposure Level (AOEL/RVNAS) 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.

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CP 7.2.3 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 7.15-16.

CP 7.2.3.1 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. Detailed calculations are presented in Table 21.

Table 7.15-16: Exposure models for intended uses

Critical use(s)	0.15 L / kg product/ha for Pome fruit
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 SC 500. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Table 7.17-18: Relevant parameters used for the worker exposure assessment

Crop / Crop Group	Nº of applications	Interval (Days)	TC[1] (cm²/hour)	Task Duration (hours)
Pome fruit	1	365	4500[2]	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 tables.

Table 7.19-20: Estimated worker exposure for re-entry in Pome fruit

Active substance	Application rate (kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.075	0.0405	81

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

Conclusion
The worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) 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 SC 500.

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Worker exposure calculations (KCP 7.2.4.1)

Table 21: Worker exposure, Fluopyram, Pome fruit

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.075 kg a.s. /ha	**Spray dilution =** 0.15 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Pome fruit, Outdoor, Upward spraying, Vehicle-mounted			**Buffer =** 5 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 0.43%	**Dermal for in use dilution** = 30%	**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 – Searching, reaching, picking	Potential exposure mg/kg bw/day		0.203	% of RVNAS[1]	405%
	Working clothing mg/kg bw/day		0.405	% of RVNAS	81%
	Working clothing and gloves mg/kg bw/day		0.203	% of RVNAS[1]	40.5%

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

Refinement of generic DFR value (KCP 7.2)

Since the worker 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 worker exposure was not necessary and was therefore not performed.

CP 7.2.3.2 Measurement of worker exposure

Since the worker 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 worker exposure was not necessary and was therefore not performed.

Combined exposure

Not relevant if the product contains only one active substance.

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CP 7.3 Dermal absorption

Data Point:	KCP 7.3/03
Report Author:	[redacted]
Report Year:	2014
Report Title:	In-vitro human skin penetration of 14C-fluopyram in the fluopyram SC 500 formulation
Report No:	S13-04167
Document No:	M-475328-01-1
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:	--
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: Cui de Chauliac or Polyclinique Grand Sud, France.
Number and sex: 3 donors, female.
Anatomical region: Abdomen.
Thickness: 302 to 398 µm.

Test Material:

Non-radiolabelled: Batch: NLL7687-2
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 SC 500 formulation (specification number 102000018148-01). It was used at three nominal concentrations of fluopyram: neat; 500 g/L and representative spray dilutions of 2.5 g/L and 0.023 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

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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/cm^2 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/cm^2 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.

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Table 7.3-1: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopyram in an SC 500 formulation at the rate of 500 g/L to human skin samples (All cells).

Results expressed in terms of percentage of applied radioactivity.							Group Human HD N= 6 K N= 51	
Sex	Female							
Donor N°	203	203	180	180	207	207		
Sample/Cell N°	A	B	C	D	E	F	Mean	SD
Swabs/Dislogeable dose/donor	103.48	102.75	103.01	103.42	102.85	104.95	103.34	0.66
SC 1	0.01	0.03	0.07	0.07	0.05	0.02	0.04	0.03
SC2	0.006	0.01	0.04	0.80	0.10	0.01	0.16	0.32
SURFACE	0.016	0.04	0.11	0.87	0.15	0.03	0.20	0.33
TOTAL NON ABSORBED	**103.50**	**102.79**	**103.12**	**104.29**	**103**	**104.58**	**103.55**	**0.73**
Skin	0.01	0.004	0.17	0.06	0.16	0.05	0.08	0.07
TOTAL SC 3+	0.01	0.09	0.07	n.d.	0.38	0.04	0.10	0.14
TOTAL DOSE SITE	**0.02**	**0.094**	**0.24**	**0.06**	**0.54**	**0.09**	**0.17**	**0.19**
Receptor fluid (0-12h)	0.005	n.d.	0.09	0.08	0.01	0.007	0.03	0.04
Receptor fluid (0-24h)	0.01	n.d.	0.13	0.09	0.02	0.01	0.04	0.05
%Ratio receptor 12h/24h	50	100	69	89	50	70	71	20
Receptor chamber	n.d.	n.d.	0.01	n.d.	0.005	n.d.	0.003	0.004
TOTAL DIRECT	**0.01**	**n.d.**	**0.14**	**0.09**	**0.03**	**0.01**	**0.05**	**0.06**
TOTAL POTENTIAL (dose site+ direct)	**0.03**	**0.09**	**0.38**	**0.15**	**0.57**	**0.10**	**0.22**	**0.21**
TOTAL POTENTIAL (skin exeluding SC + direct)	0.02	0.004	0.31	0.15	0.19	0.06	0.12	0.12
TOTAL RECOVERY	**103.5**	**102.9**	**103.5**	**104.4**	**103.6**	**104.7**	**103.77**	**0.67**

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) = **0.43%**

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.

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Table 7.3-2: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopyram in an SC 500 formulation at the rate of 2.5 g/L to human skin samples (All Cells).

Results expressed in terms of percentage of applied radioactivity.							Group Human ID N= 6 K N= 51	
Sex	Female							
Donor N°	203	203	180	180	207	207		
Sample/Cell N°	G	H	I	J	K	L	Mean	SD
Swabs/Dislogeable dose/donor	99.22	86.48	66.54	96.44	84.46	91.03	87.36	11.66
SC 1	0.88	1.55	4.62	4.42	2.81	2.72	2.83	1.50
SC2	0.13	3.08	1.66	0.88	2.73	0.04	1.42	1.30
SURFACE	1.01	4.63	6.28	5.30	5.54	2.76	4.25	1.99
TOTAL NON ABSORBED	**100.23**	**91.11**	**72.82**	**101.74**	**90.00**	**93.79**	**91.62**	**10.37**
Skin	0.86	3.14	16.08	0.34	1.35	0.43	3.70	6.15
TOTAL SC 3+	0.67	5.63	5.26	2.97	5.33	1.84	3.62	2.10
TOTAL DOSE SITE	**1.53**	**8.77**	**21.34**	**3.31**	**6.68**	**2.27**	**7.32**	**7.41**
Receptor fluid (0-12h)	0.09	0.19	0.70	0.24	0.20	0.22	0.27	0.22
Receptor fluid (0-24h)	0.23	0.29	1.42	0.30	0.29	0.27	0.47	0.47
%Ratio receptor 12h/24h	39	66	49	80	69	81	64	17
Receptor chamber	0.20	0.05	0.45	0.02	0.07	0.02	0.14	0.17
TOTAL DIRECT	**0.43**	**0.34**	**1.87**	**0.32**	**0.36**	**0.29**	**0.60**	**0.62**
TOTAL POTENTIAL (dose site+ direct)	**1.96**	**9.11**	**23.21**	**3.63**	**7.04**	**2.56**	**7.92**	**7.98**
TOTAL POTENTIAL (skin exeluding SC + direct)	1.29	3.48	17.95	0.66	1.71	0.72	4.30	6.77
TOTAL RECOVERY	**102.2**	**100.2**	**96.1**	**105.4**	**97.0**	**96.4**	**99.6**	**3.7**

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) = 1**6%**

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.

Cell I presented significantly higher radioactivity levels in the skin than the other cells in the group, including cell J that used a skin sample from the same donor as cell I. There was a corresponding lower level in the skin swabs suggesting that the difference was due to a poor swabbing technique for that particular cell. The study report presented a statistical analysis using the Dixon's test that demonstrated that the total potential absorbed value for cell I could be considered to be an outlier in this group.

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Table 7.3-3: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopyram in an SC 500 formulation at the rate of 2.5 g/L to human skin samples (Reported Cells).

Results expressed in terms of percentage of applied radioactivity.						Group Human ID N= 5 K N° = 12	
Sex	Female						
Donor N°	203	203	180	207	207		
Sample/Cell N°	G	H	J	K	L	Mean	SD
Swabs/Dislogeable dose/donor	99.22	86.48	96.44	84.46	91.03	91.53	6.30
SC 1	0.88	1.55	4.42	2.81	2.72	2.48	1.36
SC2	0.13	3.08	0.88	2.73	0.04	1.37	1.44
SURFACE	1.01	4.63	5.30	5.54	2.76	3.85	1.92
TOTAL NON ABSORBED	**100.23**	**91.11**	**101.74**	**90.00**	**93.79**	**95.37**	**5.33**
Skin	0.86	3.14	0.34	1.35	0.43	1.22	1.14
TOTAL SC 3+	0.67	5.63	2.97	5.33	1.84	3.29	2.16
TOTAL DOSE SITE	**1.53**	**8.77**	**3.31**	**6.68**	**2.27**	**4.51**	**3.09**
Receptor fluid (0-12h)	0.09	0.19	0.24	0.20	0.22	0.19	0.06
Receptor fluid (0-24h)	0.23	0.29	0.30	0.29	0.27	0.28	0.03
%Ratio receptor 12h/24h	39	66	80	69	81	67	17
Receptor chamber	0.20	0.05	0.02	0.07	0.02	0.07	0.08
TOTAL DIRECT	**0.43**	**0.34**	**0.32**	**0.36**	**0.29**	**0.35**	**0.05**
TOTAL POTENTIAL (dose site+ direct)	**1.96**	**9.11**	**3.63**	**7.04**	**2.56**	**4.86**	**3.08**
TOTAL POTENTIAL (skin excluding SC + direct)	1.29	3.48	0.66	1.71	0.72	1.57	1.15
TOTAL RECOVERY	**102.2**	**100.2**	**105.4**	**97.0**	**96.4**	**100.24**	**3.73**

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) = **8.6%**

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.

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Table 7.3-4: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopyram in an SC 500 formulation at the rate of 0.023 g/L to human skin samples (All Cells).

Results expressed in terms of percentage of applied radioactivity.							Group Human LD N= 6 K N° 51	
Sex	Female							
Donor N°	203	203	180	180	207	207		
Sample/Cell N°	M	N	O	P	Q	R	Mean	SD
Swabs/Dislogeable dose/donor	63.63	64.76	48.92	57.22	70.87	69.75	62.53	8.26
SC 1	3.55	1.41	5.86	4.80	2.00	1.08	3.03	2.16
SC2	5.14	0.83	3.27	1.92	0.50	0.53	2.03	1.86
SURFACE	8.69	2.24	9.13	6.72	2.50	1.61	5.15	3.43
TOTAL NON ABSORBED	**72.32**	**67.00**	**58.05**	**63.94**	**73.37**	**71.36**	**67.67**	**5.91**
Skin	4.34	5.01	7.46	6.23	0.30	2.33	4.27	2.61
TOTAL SC 3+	9.41	3.09	6.92	2.22	3.23	1.74	4.44	3.04
TOTAL DOSE SITE	**13.72**	**8.10**	**14.38**	**8.45**	**3.53**	**4.07**	**8.71**	**4.61**
Receptor fluid (0-12h)	7.24	4.97	16.26	11.91	17.83	15.75	12.33	5.25
Receptor fluid (0-24h)	10.82	9.01	22.17	17.84	19.20	18.69	16.29	5.18
%Ratio receptor 12h/24h	67	55	73	67	93	84	73	14
Receptor chamber	1.00	1.00	1.25	2.33	0.00	0.75	1.06	0.76
TOTAL DIRECT	**11.82**	**10.01**	**23.42**	**20.17**	**19.20**	**19.44**	**17.34**	**5.24**
TOTAL POTENTIAL (dose site+ direct)	**25.54**	**18.11**	**37.80**	**28.62**	**22.73**	**23.51**	**26.05**	**6.71**
TOTAL POTENTIAL (skin exeluding SC + direct)	16.13	15.02	30.88	26.40	19.50	21.77	21.62	6.11
TOTAL RECOVERY	**98.0**	**85.2**	**95.5**	**93.5**	**95.9**	**94.7**	**93.90**	**4.20**

Evaluation according to EFSA Guidance (2017)	
Absorption >75% within half of study duration?	No (include SC values except SC1 & SC2)
Mean Recovery <95%?	Correction needed
Total % Potentially Absorbable adjusted according to EFSA (2017)	Mean (%dose site +%receptor) + (SD*1) = **33%**

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.

Cell N was excluded from this group as the mass balance value was below 90% and therefore outside the OECD 428 acceptable range (100 ± 10%). The study report presented a statistical analysis using the Dixon's test that demonstrated that the total recovery value for cell N could be considered to be an outlier in this group.

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Table 7.3-5: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopyram in an SC 500 formulation at the rate of 0.023 g/L to human skin samples (Reported Cells).

Results expressed in terms of percentage of applied radioactivity.						Group Human ID N= 5 K N° = 12	
Sex	Female						
Donor N°	203	180	180	207	207		
Sample/Cell N°	M	O	P	Q	R	Mean	SD
Swabs/Dislogeable dose/donor	63.63	48.92	57.22	70.87	69.75	62.08	9.16
SC 1	3.55	5.86	4.80	2.00	1.08	3.46	1.96
SC2	5.14	3.27	1.92	0.50	0.53	2.27	1.97
SURFACE	8.69	9.13	6.72	2.50	1.61	5.73	3.49
TOTAL NON ABSORBED	**72.32**	**58.05**	**63.94**	**73.37**	**71.36**	**67.81**	**6.60**
Skin	4.31	7.46	6.23	0.30	2.33	4.13	2.89
TOTAL SC 3+	9.41	6.92	2.22	3.23	1.74	4.70	3.32
TOTAL DOSE SITE	**13.72**	**14.38**	**8.45**	**3.53**	**4.07**	**8.83**	**5.14**
Receptor fluid (0-12h)	7.24	16.26	11.91	17.83	15.75	13.80	4.26
Receptor fluid (0-24h)	10.82	22.17	17.84	19.20	18.69	17.74	4.20
%Ratio receptor 12h/24h	67	73	67	93	84	77	11
Receptor chamber	1.00	1.25	2.33	n.d.	0.75	1.07	0.85
TOTAL DIRECT	**11.82**	**23.42**	**20.17**	**19.2**	**19.44**	**18.81**	**4.26**
TOTAL POTENTIAL (dose site+ direct)	25.54	37.8	28.62	22.73	23.51	27.64	6.12
TOTAL POTENTIAL (skin excluding SC + direct)	**16.13**	**30.88**	**26.4**	**19.5**	**21.77**	**22.94**	**5.80**
TOTAL RECOVERY	**97.99**	**95.48**	**93.48**	**95.91**	**94.65**	**95.50**	**1.67**

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) = **30%**

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.

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Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-fluopyram in the FLU SC 500 formulation was investigated at three concentrations corresponding to the neat product (500 g /L) and to two representative dilutions of 2.5 g/L and 0.023 g/L, respectively.

Concentrate

The mean percentage of fluopyram in the SC 500 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.43% for the human skin.

Intermediate Dose level (Spray dilution)

The mean percentage of fluopyram in the SC 500 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 8.6% for human skin.

Low Dose level (Spray dilution)

The mean percentage of fluopyram in the SC 500 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining in the skin)* over a period of 24 hours for the low dose rate was 30% for human skin.

Therefore, the following dermal absorption value can be proposed for use in the non-dietary risk assessments for [^{14}C]- fluopyram in the FLU SC 500 formulation:

- 0.43% for the neat formulation (500 g/L)
- 8.6% for the intermediate dose (2.5 g/L)
- 30% for the low dose (0.023 g/L).

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information – data provided separately (Document JCP).

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