Document Title

Summary of the toxicological studies for
Fosetyl-aluminium + Fluopicolide WG 71.11 (666.7 + 44.4 g/kg)

Data Requirements

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

**According to the Guidance Document SANCO/10181/2013 for
preparing dossiers for the approval of a chemical active substance**

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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
2015-09-14	Original Document MCP – Section 7 of Supplementary Dossier	M-533250-01-1
2016-05-03	Dossier update according to "Request for additional information on the supplementary dossier submitted by Bayer CropScience for the approval renewal of the active substance Fosetyl (2015-5865)" by RMS France on 2016-04-04: - The evaluation of the exposure of bystanders and residents using the new EFSA calculator has been added to Chapters CP 7.2.2 and CP 7.2.2.1 and as Table 7.2.2- 2 and Table 7.2.2.1- 4.	M-533250-02-1
2016-11-14	Dossier update according to "Request for additional information on the supplementary dossier submitted by Bayer CropScience for the approval renewal of the active substance Fosetyl (2015-5865)" by RMS France on 2016-04-04: - Study KCP 7.3/01, ███, M.; 2015; M-512858-01-1, has been amended, new study report, ███, 2016, M-512858-02-1	M-533250-03-1

[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

Fosetyl was included in Annex I to Directive 91/414/EEC in 2006 (Directive 2006/64/CE of 18 July 2006, Entry into Force on 1 May 2007). This Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of fosetyl under Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer CropScience (BCS) for the Annex I inclusion under Directive 91/414/EEC are contained in the DAR, its Addenda and are included in the Baseline Dossier provided by BCS. These data are only mentioned in the Supplementary Dossier for the sake of completeness and only general information (e.g. author, reference etc.) is available for these data. In order to facilitate discrimination between new data and data submitted during the Annex I inclusion process under Directive 91/414/EEC, the old data are written in grey typeface. For all new studies, detailed summaries are provided within this Supplementary Dossier. Additional information requested by the RMS France on 2016-04-04 during the evaluation of the Supplementary Dossier is highlighted in yellow. Additional information requested by the RMS France on 2016-11-14 during the evaluation of the Supplementary Dossier is highlighted in grey.

Fosetyl is the ISO common name for ethyl hydrogen phosphonate (IUPAC) but the aluminium salt fosetyl-aluminium (fosetyl-Al), a variant of fosetyl, is used in the formulated product.

The formulation Fosetyl-Al + Fluopicolide WG 71.11 (FEA + FLC WG 71.11) is a water dispersible granule (WG) formulation containing 666.7 g/kg of fosetyl-Al and 44.4 g/kg of fluopicolide. This formulation is registered throughout Europe under trade names such as Profiler. FEA + FLC WG 71.11 was not a representative formulation for the Annex I inclusion of fosetyl under Directive 91/414/EEC but has been evaluated as the representative formulation for the Annex I inclusion of fluopicolide under Directive 91/414/EEC.

CP 7.1   Acute toxicity

Fosetyl-Al + Fluopicolide WG 71.11 (FEA + FLC WG 71.11) has a very low acute oral and percutaneous toxicity in male and female rats.

An acute inhalation study has previously not been required for products containing only non-volatile active substances if they are not dusty with a significant proportion of inhalable particles or applied by spraying generating inhalable particles. Thus, no acute inhalation study has been conducted with FEA + FLC WG 71.11. The current data requirements for plant protection products, however, stipulate that acute inhalation studies should be performed with all products that are applied by spraying, such as FEA + FLC WG 71.11.

Since neither the active substances nor any of the co-formulants in FEA + FLC WG 71.11 are classified for acute inhalation toxicity, the calculation method laid down in Annex I, Section 3.1.3.6.2.3 of Regulation 1272/2008 is applied. The Acute Toxicity Estimate for the inhalation toxicity of FEA + FLC WG 71.11 is 9.8 mg/L. FEA + FLC WG 71.11 therefore does not require a classification for acute inhalation toxicity.

FEA + FLC WG 71.11 is irritating to eyes but not to skin. It has no skin-sensitizing potential (see Table 7.1- 1).

Table 7.1- 1:   **Acute toxicity studies with FEA + FLC WG 71.11**

Study Type	Species	Results	Reference
Acute oral toxicity	Rat	LD_{50} = 5000 mg/kg bw ($\male$+$\female$)	; 2003; M-220866-01-1
Acute dermal toxicity		LD_{50} > 2000 mg/kg bw ($\male$+$\female$)	; 2003; M-220872-02-1
Acute inhalation toxicity	–	No study ATE = 9.8 mg/L calculation method	–
Skin irritation	Rabbit	Non-irritating	; 2002; M-223952-01-1
Eye irritation		Eye irritant (reversible effects), Eye Irrit. 2, H319	; 2003; M-223965-01-1
Skin sensitisation (Modified Buehler Test, nine induction applications)	Guinea pig	Not sensitizing	; 2003; M-223976-01-1

CP 7.1.1   Oral toxicity

Report: KCP 7.1.1/01   ; 2003; M-220866-01-1
Title: Study for acute oral toxicity in rats Code: AE F053616 06 WG71 A1 (EXP11074B)
Report No.:   C036522
Document No.:   M-220866-01-1
Guideline(s):   EU (=EEC): 96/54/EEC Annex IV B, Part B.1; OECD: 423; USEPA (=EPA): OPPTS 870.1100
Guideline deviation(s): none
GLP/GEP: **yes**

Executive Summary
A study for acute oral toxicity in male and female Wistar rats was conducted with the test substance AE F053616 06 WG71 A1-EXP11074B (FEA + FLC WG 71.11). The study was conducted according to the Acute Toxic Class Method (OECD Guideline 423). Water was used as vehicle.
A dose of 2000 mg/kg body weight was tolerated by male and female rats without mortalities, clinical signs, effects on body weight development, and gross pathological findings. Thus, an LD_{50} cut-off value of 5000 mg/kg bw is assigned according to Annex 2d of OECD Guideline 423. Based on this result, FEA + FLC WG 71.11 is not classified for acute oral toxicity according to the criteria of Regulation 1272/2008.

1.   MATERIALS AND METHODS

A. MATERIALS
1. Test material:
  Name: AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11)
  Description: Lightly beige powder
  Batch / Lot No.:   OP220266
  Purity: 4.35% (w/w) fluopicolide
                       68.7% (w/w) fosetyl-Al.
  Stability of test compound: Expiry date: 2004-03-20. Stability and homogeneity in vehicle were not determined.
2. Vehicle: Demineralised water

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3. Test animals

Species:	Rat
Strain:	Wistar rats - HsdCpb: WU
Sex:	Males and females
Age:	Males: 8 weeks
	Females: 8-9 weeks
Weight at dosing:	Males: 193 – 195 g
	Females: 161 – 169 g
Source:	██████████████ Germany
Acclimatisation period:	At least 5 days
Diet:	████████® 3883.0.15, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	In groups in standard polycarbonate cages with low-dust wood granules bedding
Environmental conditions:	
Temperature:	22±2 °C
Humidity:	55±5%
Air changes:	ca. 10 h⁻¹
Photoperiod:	12-hour artificial lighting

B. STUDY DESIGN AND METHODS

1. In life dates: 2002-11-13 to 2002-11-27

2. Animal assignment and treatment

Dose:	2000 mg/kg bw
Application route:	Oral, gavage
Application volume:	10 mL/kg bw
Fasting time:	Before administration 17±1 h
Group size:	3 rats per sex
Post-treatment observation period:	14 days
Observations:	Clinical signs, mortality, body weight, gross necropsy

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no mortalities (see Table 7.1.1- 1).

Table 7.1.1- 1: Results of the acute-toxic class test in rats with FEA + FLC WG 71.11

Dose (mg/kg bw)	Toxicological findings*			Onset and duration of signs	Onset of death	Mortality (%)
				Males		
2000	0	0	3	-	–	0
				Females		
2000	0	0	3	-	–	0
			LD$_{50}$ = 5000 mg/kg bw (males and females)**			

* Number of dead animals/number of animals with clinical signs/number of animals tested.
** According to Annex 2d of OECD Guideline 423

B. CLINICAL OBSERVATIONS

There were no clinical signs of toxicity (see Table 7.1.1- 1).

C. BODY WEIGHT

There were no effects on body weight.

D. NECROPSY

There were no abnormalities observed at necropsy.

III. CONCLUSION

FEA + FLC WG 71.11 is non-toxic after oral administration. The acute oral LD_{50} for both sexes was greater than 2000 mg/kg bw. Thus, FEA + FLC WG 71.11 is not classified for acute oral toxicity according to the criteria of Regulation 1272/2008.

CP 7.1.2   Dermal toxicity

Report:	KCP 7.1.2/01 ████████████, 2003, M-220872-02-1
Title:	Study for acute dermal toxicity in rats Code: AE F053616 06 WG71 A1 (EXP11074B)
Report No.:	C036525
Document No.:	M-220872-02-1
Guideline(s):	EU (=EEC): 67/548/EEC Annex V, Part B.3; OECD: 402; USEPA (=EPA): OPPTS 870.1200
Guideline deviation(s):	none
GLP/GEP:	**yes**

Executive Summary

An acute dermal toxicity study with AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11) in Wistar rats was conducted as a limit test according to OECD 402. The test item was moistened in water and was administered occlusively to groups of each five male and female rats at the dose of 2000 mg/kg bw. The exposure duration was 24 h after which the application site was cleaned with water and soap. There were no clinical signs of toxicity, local skin reactions or mortality observed. The rats were subjected to necropsy at termination and there were no abnormalities detected. Based on this result, FEA + FLC WG 71.11 is not classified for acute percutaneous toxicity according to the criteria of Regulation 1272/2008.

I.   MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Name:	AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11)
Description:	Lightly beige powder
Batch / Lot No.:	OP220266
Purity:	4.35% (w/w) fluopicolide
	68.7% (w/w) fosetyl-Al.
Stability of test compound:	Expiry date: 2004-03-20.

2. Vehicle: Moistened with water

3. Test animals

Species:	Rat	
Strain:	Wistar rats - HsdCpb: WU	
Sex:	Males and females	
Age:	Males:	9 weeks
	Females:	12 weeks
Weight at dosing:	Males:	228 – 250 g
	Females:	203 – 213 g

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Fosetyl-aluminium + Fluopicolide WG 71.11

Source:	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ Germany
Acclimatisation period:	At least 5 days
Diet:	▮▮▮▮▮▮▮▮▮ ® 3883.0.15, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	In groups in standard polycarbonate cages with low-dust wood granules bedding
Environmental conditions:	
Temperature:	22±2 °C
Humidity:	55±5%
Air changes:	ca. 10 h^{-1}
Photoperiod:	12-hour artificial lighting

B. STUDY DESIGN AND METHODS

1. In life dates: 2002-11-13 to 2002-11-27

2. Animal assignment and treatment

Group size:	5 rats/sex
Dose:	2000 mg/kg bw
Application route:	Dermal, occlusive
Application area:	Up to 22.5 cm^2
Exposure duration:	24 h
Test substance removal:	The treated area was cleaned with soap and water
Post-treatment observation period:	14 days
Observations:	Clinical signs, local skin reactions, mortality, body weight, gross necropsy

II. RESULTS AND DISCUSSION

A. MORTALITY

There were no mortalities (see Table 7.1.2- 1).

Table 7.1.2- 1: Results of the acute percutaneous toxicity test with FEA + FLC WG 71.11

Dose (mg/kg bw)	Toxicological result*			Onset and duration of signs	Onset of death	Mortality (%)
Males						
2000	0	0	5	–	–	0
Females						
2000	0	0	5	–	–	0
LD$_{50}$: >2000 mg/kg bw (males and females)						

* 1st number = number of dead animals, 2nd number = number of animals with toxic signs,
3rd number = number of animals used

B. CLINICAL OBSERVATIONS

There were no clinical signs of toxicity (see Table 7.1.2- 1).

C. LOCAL SKIN REACTIONS

No skin reactions were observed at the site of application.

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D. BODY WEIGHT

There were no effects on body weight.

E. NECROPSY

There were no abnormalities observed at necropsy.

<div align="center">

III. CONCLUSION

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FEA + FLC WG 71.11 is non-toxic after dermal administration. The acute percutaneous LD_{50} for both sexes was greater than 2000 mg/kg bw. Thus, FEA + FLC WG 71.11 is not classified for acute percutaneous toxicity according to the criteria of Regulation 1272/2008.

CP 7.1.3   Inhalation

No inhalation test has been conducted with FEA + FLC WG 71.11. The potential for inhalation exposure to the product as is going to be negligible since both active substances are not volatile and the product is practically dust free (;   ; 2003; M-215267-01-1).

However, information on this endpoint is required for all products applied by spraying. For animal welfare reasons, a new inhalation study is not deemed reasonable. Instead, the inhalation toxicity is predicted using the provisions of Regulation 1272/2008, Annex I, Section 3.1.3.6.2.3. To this end, the available inhalation toxicity information is compiled for all components of FEA + FLC WG 71.11, in the respective CONFIDENTIAL part (Document JCP).

In conclusion, FEA + FLC WG 71.11 is predicted to be non-toxic if inhaled. The acute toxicity estimate for FEA + FLC WG 71.11 is 9.8 mg/L. Thus, FEA + FLC WG 71.11 is not classified for acute inhalation toxicity according to the criteria of Regulation 1272/2008.

CP 7.1.4   Skin irritation

Report: KCP 7.1.4/01   ; 2002; M-223952-01-1
Title: Acute dermal irritation in rabbits Code: AE F053616 06 WG71 A1 (EXP11074B)
Report No.:   C037987
Document No.:   M-223952-01-1
Guideline(s):   EU (=EEC): 92/69/EEC, B.4; OECD: 404
Guideline deviation(s):   none
GLP/GEP: **yes**

Executive Summary
A primary dermal irritation / corrosion study in New Zealand White Rabbits was conducted with AE F053616 06 WG71 A1 (FEA + FLC WG 71.11) according to OECD guideline 404.

A quantity of 0.5 g the test item was applied to a moistened cotton patch of size approximately 6 cm² and applied on to the prepared area of the skin. After 4 hours, the treated area was wiped off with a moistened cotton pad.

The degree of irritation was scored at 1, 24, 48 and 72 hours after removal of the test patch. Except for a very slight erythema (grade 1) noted in one animal one hour after removal of the dressing, no cutaneous reactions were recorded during the study. Mean scores over 24, 48 and 72 hours for each animal were 0.0, 0.0 and 0.0 for erythema and oedema. Based on this result, FEA + FLC WG 71.11 is not classified for primary skin irritation according to the criteria of Regulation 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Name:	AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11)
Description:	Granulous beige powder
Batch / Lot No.:	OP220266
Purity:	4.35% (w/w) fluopicolide
	68.7% (w/w) fosetyl-Al.
Stability of test compound:	Expiry date: 2004-03-20.

2. Vehicle: Moistened with water

3. Test animals

Species:	Rabbit
Strain:	New Zealand White
Sex:	Males
Age:	2-4 months
Weight at dosing:	2.5±0.1 kg
Source:	███████████, France.
Acclimatisation period:	At least 5 days
Diet:	110 pelleted diet (███████████████████████████), *ad libitum*
Water:	Drinking water filtered by a 0.22-µm membrane, *ad libitum*
Housing:	Individually in polystyrene cages (48.2 cm x 50 cm x 36.5 cm).
Environmental conditions:	
Temperature:	18±3 °C
Humidity:	30-70%
Air changes:	ca. 12 h^{-1}
Photoperiod:	12 h light / 12 h dark

B. STUDY DESIGN AND METHODS

1. In life dates: 2002-10-08 to 2002-10-11

2. Animal assignment and treatment

Group size:	3
Applied amount:	0.5 g, moistened with 0.5 mL deionised water
Application route:	Dermal, semi-occlusive
Application area:	6 cm^2
Exposure duration:	4 h
Test substance removal:	Residual test item was wiped off by means of a moistened cotton pad.
Post-treatment observation period:	4 days
Scoring times:	1, 24, 48, 72 h
Scoring system:	As laid down in OECD 404

II. RESULTS AND DISCUSSION

Except for a very slight erythema (grade 1) noted in one animal one hour after removal of the dressing, no cutaneous reactions were recorded during the study (see Table 7.1.4- 1). Mean scores over 24, 48 and 72 hours for each animal were 0.0, 0.0 and 0.0 for erythema and oedema.

Table 7.1.4- 1: Results of the skin irritation test with FEA + FLC WG 71.11

Rabbit No.	Scoring time (h)							
	1		24		48		72	
	E*	O*	E	O	E	O	E	O
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0

* E: erythema, O: oedema

III. CONCLUSION

FEA + FLC WG 71.11 is not irritating to rabbit skin. Thus, FEA + FLC WG 71.11 is not classified for primary skin irritation/ corrosivity according to the criteria of Regulation 1272/2008.

CP 7.1.5 Eye irritation

Report: KCP 7.1.5/01 ; 2003; M-223965-01-1
Title: Acute eye irritation in rabbits, Code: AE F053616 06 WG71 A1 (EXP11074B)
Report No.: C037993
Document No.: M-223965-01-1
Guideline(s): EU (=EEC): 92/69/EEC, B.5; OECD: 405
Guideline deviation(s): none
GLP/GEP: yes

Executive Summary
An acute eye irritation / corrosion study in New Zealand White rabbits was conducted with AE F053616 06 WG71 A1 (EXP11074B, FEA + FLC WG 71.11) according to the 2002 version of OECD 405. On test day one, a quantity of 100 mg of the test item was instilled into the left conjunctival sac. The right eye remained untreated. All the rabbits were treated in a similar manner. The treated eyes were not rinsed.
There was conjunctival redness (maximum score: 3), chemosis (maximum score: 3), and corneal opacity (maximum score: 2) in all rabbits. Two rabbits also displayed iritis (maximum score: 1). All eye reactions had completely reversed by Day 10 after exposure at the latest.
In two animals, the mean scores for conjunctival and cornea effects observed between 24 and 72 h exceeded the threshold values for classification as eye irritant in Category 2 (H319 – Causes serious eye irritation) but did not reach or exceed the threshold for classification as severe eye irritant.
Based on these results, FEA + FLC WG 71.11 is classified as Eye Irrit. 2 (H319 – Causes serious eye irritation) according to the criteria of Regulation 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS
1. Test material:
Name: AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11)
Description: Granulous beige powder
Batch / Lot No.: OP220266
Purity: 4.35% (w/w) fluopicolide
68.7% (w/w) fosetyl-Al.
Stability of test compound: Expiry date: 2004-03-20.

2. Vehicle: Test substance was applied as delivered.

3. Test animals

Species:	Rabbit
Strain:	New Zealand White
Sex:	Males
Age:	2 to 4 months
Weight at dosing:	2.8 ± 0.1 kg
Source:	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ France
Acclimatisation period:	At least 5 days
Diet:	110 pelleted diet (▮▮▮▮▮▮▮▮▮▮▮▮▮▮ France), *ad libitum*
Water:	Drinking water filtered by a 0.22-µm membrane, *ad libitum*
Housing:	Individually in polystyrene cages (48.2 cm x 58 cm x 36.5 cm).
Environmental conditions:	
Temperature:	18 ± 3 °C
Humidity:	30-70%
Air changes:	approx. $12\,h^{-1}$
Photoperiod:	12 h light / 12 h dark

B. STUDY DESIGN AND METHODS

1. In life dates: 2002-10-15 to 2012-10-24

2. Animal assignment and treatment

Group size:	3
Applied amount:	100 mg
Application route:	Instillation into conjunctival sac
Test substance removal:	Eyes were not rinsed
Post-treatment observation period:	10 days
Scoring times:	1, 24, 48, 72 h and Day 5-10 post-instillation
Scoring system:	As laid down in OECD 405

II. RESULTS AND DISCUSSION

There was conjunctival redness (maximum score: 3), chemosis (maximum score: 3), and corneal opacity (maximum score: 2) in all rabbits. Two rabbits also displayed iritis (maximum score: 1). All eye reactions had completely reversed by Day 10 after exposure at the latest (see Table 7.1.5- 1).

In two animals, the mean scores for conjunctival and cornea effects observed between 24 and 72 h exceeded the threshold values for classification as eye irritant in Category 2 (H319 – Causes serious eye irritation) but did not reach or exceed the threshold for classification as eye damaging (Category 1, H318 – Causes serious eye damage).

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Table 7.1.5- 1:   Results of the eye irritation test with FEA + FLC WG 71.11

Rabbit No.	Scoring time	Conjunctiva		Iris (0-2)	Corneal opacity (0-4)
		Redness (0-3)	Chemosis (0-4)		
1	1 h	2	1	0	0
	24 h	**2**	**2**	**1**	**1**
	48 h	**1**	**1**	**0**	**1**
	72 h	**1**	**1**	**0**	**0**
	Day 5	0	0	0	0
	Mean score 24, 48, 72 h	**1.3**	**1.3**	**0.3**	**0.7**
2	1 h	2	3	0	0
	24 h	**3**	**3**	**1**	**2**
	48 h	**3**	**3**	**1**	**2**
	72 h	**3**	**3**	**1**	**2**
	Day 5	2	2	0	0
	Day 6	2	2	0	0
	Day 7	2	2	0	0
	Day 8	1	1	0	0
	Day 9	1	0	0	0
	Day 10	0	0	0	0
	Mean score 24, 48, 72 h	**3.0**	**3.0**	**1.0**	**2.0**
3	1 h	2	2	0	0
	24 h	**2**	**2**	**0**	**1**
	48 h	**2**	**2**	**0**	**2**
	72 h	**2**	**2**	**0**	**1**
	Day 5	1	1	0	0
	Day 6	1	1	0	0
	Day 7	1	1	0	0
	Day 8	1	1	0	0
	Day 9	1	1	0	0
	Day 10	0	0	0	0
	Mean score 24, 48, 72 h	**2.0**	**2.0**	**0.0**	**1.3**

III. CONCLUSION

FEA + FLC WG 71.11 is irritating to rabbit eyes. Thus, FEA + FLC WG 71.11 is classified as Eye Irrit. 2 (H319 – Causes serious eye irritation) according to the criteria of Regulation 1272/2008.

CP 7.1.6   Skin sensitization

Report:	KCP 7.1.6/01 ▮▮▮▮▮▮ ; 2003; M-223976-01-1
Title:	Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications) Code: AE F053616 06 WG71 A1 (EXP11074B)
Report No.:	C037998
Document No.:	M-223976-01-1
Guideline(s):	EU (=EEC): 96/54/EEC, B.6; OECD: 406
Guideline deviation(s):	The Buehler test was conducted in a modified version using 9 instead of 3 inductions
GLP/GEP:	**yes**

Executive Summary

The potential of the test item AE F053616 06 WG71 A1 (EXP 11074B; FEA + FLC WG 71.11) to induce delayed contact hypersensitivity following cutaneous application was evaluated in guinea pigs according to the modified Buehler method.

Thirty guinea pigs (15 males and 15 females) were allocated to two groups: a control group (five males and five females) and a treated group (ten males and ten females).

During a 3-week induction period, the animals of the treated group received nine topical applications of the test item. The application sites were covered by an occlusive dressing for 6 hours on each occasion. The animals of the control group received applications of purified water under the same experimental conditions.

On day 29, after a rest period of 9 days, animals of both groups were challenged by a topical application of the test item to the right flank. Purified water was applied to the left flank under the same experimental conditions. Test item and purified water were maintained under an occlusive dressing for 6 hours.

Skin reactions were evaluated approximately 24 and 48 hours after removal of the pads.

Test item concentrations were as follows: Induction 50% (w/w) on days 1, 3, 5, 8, 10, 12, 15, 17 and 19.

Challenge: 25% (w/w) on day 29. The vehicle used was purified water.

No clinical signs and no deaths related to treatment were noted during the study.

During the induction period, no well-defined skin reactions were observed.

After the challenge application, at the 24-hour reading, a discrete erythema was noted in 4/10 animals of the control group and in 4/20 animals of the treated group. At the 48-hour reading, a discrete erythema persisted on the right treated flank of 1/10 animals of the control group and appeared on the left control flank of 1/20 animals of the treated group; no other erythema was noted.

No cutaneous reactions attributed 1:0, delayed contact hypersensitivity were recorded during the study. A contemporary reliability check using 2-mercaptobenzothiazole showed a high rate of sensitization demonstrating the reliability of the test system.

Based on this result, FEA + FLC WG 71.11 is not classified as skin sensitizer according to the criteria of Regulation 1272/2008.

I.   MATERIALS AND METHODS

A. MATERIALS

1. Test material:

Name:	AE F053616 06 WG71 A1 - EXP11074B (FEA + FLC WG 71.11)
Description:	Granulous beige powder
Batch / Lot No.:	OP220266
Purity:	4.35% (w/w) fluopicolide
	68.7% (w/w) fosetyl-Al.
Stability of test compound:	Expiry date: 2004-03-20.

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2. Vehicle: Purified water

3. Test animals

Species:	Guinea pigs
Strain:	Hartley Crl: (HA) BR
Sex:	Males + females
Age at first induction:	1-2 months
Weight at first induction:	Males: 346 ± 18 g
	Females: 346 ± 11 g
Source:	████████████████, France.
Acclimatisation period:	At least 5 days
Diet:	106 pelleted diet (███████████████████, France)., *ad libitum*
Water:	Drinking water filtered by a 0.22-µm membrane, *ad libitum*
Housing:	Individually in polycarbonate cages with stainless steel lid (48 cm x 27 cm x 20 cm)

Environmental conditions:

Temperature:	22 ± 2 °C
Humidity:	30-70%
Air changes:	approx. 12 h⁻¹
Photoperiod:	12 h light / 12 h dark

B. STUDY DESIGN AND METHODS

1. In life dates: 2002-10-21 to 2002-11-21

2. Animal assignment and treatment

Group size:	Pre-study: 2 (1/sex) for induction; 4 (2/sex) for challenge
	Control: 10 (5/sex)
	Test item: 20 (10/sex)

Induction:

Exposure route:	Epicutaneous, occlusive
Schedule:	Days 1, 3, 5, 8, 10, 12, 15, 17 and 19
Concentrations:	50% (w/w)
Application site:	Anterior left flank
Exposure duration:	6 h

Challenge:

Exposure route:	Epicutaneous, occlusive
Schedule:	Day 29
Concentrations:	25% (w/w)
Application site:	Posterior right flank
Exposure duration:	6 h
Scoring times:	24 and 48 h after end of challenge exposure
Scoring system:	Magnusson-Kligman scale as laid down in OECD 406
Negative controls:	Negative controls received sham inductions with vehicle (water) but were challenged with the test substance as described above.
Reliability check	Positive control: 2-mercaptobenzothiazole (20% w/w for induction and challenge), conducted in October 2002

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II. RESULTS AND DISCUSSION

A. MORTALITY
There were no mortalities.

B. CLINICAL OBSERVATIONS
Hypoactivity and dyspnoea were observed in 1/10 animals of the control group between day 19 and day 22. No other clinical signs were observed during the study.

C. BODY WEIGHT
There were no effects on body weight.

C. SKIN REACTIONS
During the induction period, no well-defined skin reactions were observed.
After the challenge application, at the 24-hour reading, a discrete erythema was noted in 4/10 animals of the control group and in 4/20 animals of the treated group (see Table 7.1.6- 1). At the 48-hour reading, a discrete erythema persisted on the right treated flank of 1/10 animals of the control group and appeared on the left control flank of 1/20 animals of the treated group; no other erythema was noted.
No cutaneous reactions attributed to delayed contact hypersensitivity were recorded during the study.

Table 7.1.6- 1: Results of the Buehler test with FEA + FLC WG 71.11

Sex	Animal number	Day 30 (after 24 hours)		Day 31 (after 48 hours)	
		Left flank (vehicle)	Right flank (test item)	Left flank (vehicle)	Right flank (test item)
Control group					
Male	51	0	1	0/S	0/S
	52	0	1	0	0/S
	53	0	1	0	0
	54	0	1	0	0
	55	0	1	0	1
Female	66	0	0	0	0
	67	0	0	0	0
	68	0	0	0	0
	69	0	0	0/S	0
	70	0	0	0/S	0/S
Treated group					
Male	56	0	0	0	0
	57	0	1	0/S	0/S
	58	0	0	0/S	0/S
	59	0	0	0	0
	60	0	0	0	0
	61	0	0	0/S	0
	62	0	1	0	0/S
	63	0	0	0	0
	64	0	0	1	0
	65	0	0	0	0

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Sex	Animal number	Day 30 (after 24 hours)		Day 31 (after 48 hours)	
		Left flank (vehicle)	Right flank (test item)	Left flank (vehicle)	Right flank (test item)
Female	71	0	0	0	0
	72	0	0	0	0
	73	0	1	0	0
	74	0	0	0	0
	75	0	0	0	0
	76	0	0	0	0
	77	0	0	0	0
	78	0	0	0	0
	79	0	1	0/S	0/S
	80	0	0	0	0

S : dryness of the skin

III. CONCLUSION

FEA + FLC WG 71.11 is not skin sensitizing in the Buehler test. Thus, FEA + FLC WG 71.11 is not classified as skin sensitizer according to the criteria of Regulation 1272/2008.

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 substances or other components in the plant protection product that would require further investigations.

CP 7.1.8   Supplementary studies for combinations of plant protection products

No such studies are necessary since FEA + FLC WG 71.11 is not intended for use in combination with other plant protection products.

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CP 7.2 Data on exposure

Evaluations of the exposure of operators, bystanders, residents and re-entry workers to fosetyl-aluminium (fosetyl-Al) when used in Fosetyl-Al + Fluopicolide WG 71.11 (FEA + FLC WG 71.11) formulation are provided in the following sections.

CP 7.2.1 Operator exposure

FEA + FLC WG 71.11 is a water dispersible granule containing 666.7 g/kg fosetyl-Al and 44.4 g/kg fluopicolide. The proposed representative use is as a fungicide on grapes. Applications of FEA + FLC WG 71.11 will be achieved via broadcast air assisted sprayers. Water will be the diluent carrier in all situations. The full representative GAP information is given in document D1 and is summarised in Table 7.2.1- 1.

Table 7.2.1- 1: Application parameters for FEA + FLC WG 71.11.

Application technique	Crop(s)	Growth stage	F or G	Maximum dose rate		Spray volume (L/ha)	Max N° of treat-ments	Spray Interval (day)	PHI (day)
				kg/ha product	kg/ha fosetyl-Al				
BAA	Grapes	15-81	F	3	2	100-1000	3	10-14	21

BAA = Broadcast air assisted sprayer, F = Field use, G = Greenhouse use

Dermal absorption:

The following dermal absorption values for fosetyl-Al are used in the present risk assessment (for details see Section CP 7.3):

- 1% for the concentrate (measured at 666.7 g/L) and 4% (measured at 2 g/L with a predicted lowest in-use concentration of 2 g/L) for the spray dilution.

Acceptable Operator Exposure Level AOEL:

An AOEL of **5 mg/kg bw/day** is established for fosetyl-Al[1] based on the NOAEL of 500 mg/kg bw/day obtained in a 90-day mechanistic rat study using a safety factor of 100 with no adjustment for oral absorption being necessary (see also Document MCA, Section 5).

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[1] Fosetyl, EFSA Scientific Report (2005) 54, 1-79, Conclusion of the peer review.

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Operator exposure estimates
Operator exposures to FEA + FLC WG 71.11 are estimated using the German model[2], the UK-POEM[3] and the new EFSA calculator[4] (although not implemented at the time of writing) with the relevant scenario "Tractor-mounted/trailed broadcast air assisted sprayer". Details are given in Section CP 7.2.1.1 and in Table 7.2.1.1- 1 to Table 7.2.1.1- 3.

The results of the exposure calculations are summarized in Table 7.2.1- 2.

Table 7.2.1- 2: **Predicted systemic exposure as a proportion of the AOEL**

Substance	PPE	Total systemic exposure (mg/kg bw/day)*	% of AOEL#
German model Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles. **8 ha**			
Fosetyl-Al	No PPE [1]	0.11566	2
	With PPE [2]	0.02775	0.6
UK-POEM Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles. **15 ha**			
Fosetyl-Al	No PPE [3]	1.762588	35
	With PPE [4]	1.734273	35
EFSA Calculator Tractor-mounted/trailed broadcast air assisted sprayer: hydraulic nozzles, **10 ha**			
Fosetyl-Al	No PPE [5]	0.1680997	3
	With PPE [6]	0.0483231	1

\# Fosetyl-Al: AOEL = 5 mg/kg bw/day
1) Lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes.
2) Gloves during mixing/loading and a standard coverall during application.
3) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear
4) In addition to typical work wear (see 3) protective gloves are worn during mixing and loading and when handling contaminated surfaces.
5) Potential exposure without RPE/PPE.
6) In addition to typical work wear (see 3) protective gloves are worn during mixing and loading and when handling contaminated surfaces.

Overall assessment
Exposure estimates predict no unacceptable risk. Operators using FEA+FLC WG 71.11 for the representative use on grapes should wear adequate work clothing (e.g. a long sleeved shirt, trousers and sturdy foot wear). All three models predict that the product is safe to use without additional PPE. However, the notifier recommends that they also wear protective gloves as a good farming practice during mixing/loading and when handling contaminated surfaces.

2
(1992) Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Berlin-Dahlem, no 277, 1 - 112 (1992).
3   Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) – A User's Guide (UK MAFF); 1992, revised model 2007.
4   EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874.: Version 30/03/2015.

CP 7.2.1.1   Estimation of operator exposure

Operator exposure to fosetyl-Al in the FEA + FLC WG 71.11 formulation is estimated using the German Model, as well as the UK-POEM and the soon to be implemented EFSA calculator for tractor-mounted/trailed broadcast air assisted sprayer.

In the following paragraphs the assumptions used for the calculations are summarised.

German Model
Treated area: 8 ha/day.
Max. dose rate: 3 kg product/ha, i.e.,
     - FEA: 2 kg a.s./ha.
Body weight: 70 kg.

UK-POEM
Treated area: 15 ha/day.
Max. dose rate: 3 kg product/ha, i.e.,
     - FEA: 2 kg a.s./ha.
Min. spray volume: 100 L/ha.
Work duration: 6 hours/day.
Body weight: 60 kg.

EFSA Calculator
Treated area: 10 ha/day.
Max. dose rate: 3 kg product/ha, i.e.,
     - FEA: 2 kg a.s./ha.
Min. spray volume: 100 L/ha.
Work duration: 6 hours/day.
Body weight: 60 kg.

Dermal absorption:
     - FEA: 1% for the concentrate and 4% for the in-use dilution.

Personal protective equipment (PPE):
     No PPE: No additional PPE is worn during mixing/loading and application.
     With PPE: Gloves are worn during mixing/loading and when handling contaminated surfaces.

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Table 7.2.1.1- 1:   Predicted systemic exposure to fosetyl-Al according to the German model/no PPE and with PPE

Operator exposure estimate: German model. Tractor-mounted/trailed broadcast air-assisted sprayer

Product:	FEA+FLC WG 71.11			
Active substance:	FEA	a.s. concentration:	667	[g/l or kg]
Formulation:	WG	PPE during mix/loading: Respiration:	None	
Dose [l or kg/ha]:	3.0	Hands:	Gloves	
Work rate [ha/day]:	8	PPE during application: Respiration:	None	
Body weight [kg]:	70	Hands:	None	
Inhalation absorption [%]	100	Head:	None	
Dermal absorption [%]	1.0	(concentrate)	Body:	Standard protective coverall
	4.0	(dilution)		

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
						I = Inhalation
I_M =	0.008	16.0008	0.001829	1.0	0.001829	D = Dermal
$D_{M(H)}$ =	2.0	16.0008	0.4572	0.01	0.004572	M = Mix/Loading
I_A =	0.018	16.0008	0.004114	1.0	0.004114	A = Application
$D_{A(C)}$ =	1.2	16.0008	0.2743	1.0	0.274299	H = Hands
$D_{A(H)}$ =	0.7	16.0008	0.16	1.0	0.160008	C = Head
$D_{A(B)}$ =	9.6	16.0008	2.1944	0.05	0.109752	B = Body

Absorbed dose:

Route		Absorption [%]	No PPE Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]	With PPE Estimated route exposure [mg/kg bw/day]	Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	1.0	0.457166	0.004572	0.004572	0.000046
	Application	4.0	2.628703	0.105148	0.544027	0.021761
Inhalation:	Mix/Loading	100	0.001829	0.001829	0.001829	0.001829
	Application	100	0.004114	0.004114	0.004114	0.004114
	Total =			**0.115663**		**0.02775**

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Table 7.2.1.1- 2: **Predicted systemic exposure to fosetyl-Al according to the UK POEM/no PPE and with PPE**

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM) WITH GERMAN MODEL MIX/LOAD DATA (75th PERCENTILE)

Application method	Tractor-mounted/trailed broadcast air-assisted sprayer: 500 l/ha		
Product	**FEA+FLC WG 71.11**	Active substance	**FEA**
Formulation type	WG or SG	a.s. concentration	**666.7** mg/g
Dermal absorption from product	**1** %	Dermal absorption from spray	4 %
PPE during mix/loading	Gloves	PPE during application	None
Dose	**3** kg product/ha	Work rate/day	**15** ha
Application volume	**100** L/ha	Duration of spraying	**6** h

DERMAL EXPOSURE DURING MIXING AND LOADING

Hand contamination/kg a.s.	5.72	mg/kg a.s.	
Hand contamination/day	171.60858	mg/day	
Protective clothing	None		Gloves
Transmission to skin	100	%	1 %
Dermal exposure to a.s.	171.60858	mg/day	1.7160858 mg/day

INHALATION EXPOSURE DURING MIXING AND LOADING

Inhalation exposure/kg a.s.	0.0358	mg/kg a.s.	
Inhalation exposure/day	1.0740537	mg/day	
RPE	None		None
Transmission through RPE	100	%	100 %
Inhalation exposure to a.s.	1.0740537	mg/day	1.07405 mg/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed broadcast air-assisted sprayer 500 l/ha						
Application volume	100	spray/ha					
Volume of surface contamination	400	ml/h					
Distribution	Hands	Trunk	Legs				
	10%	65%	25%				
Clothing	None	Permeable	Permeable	None	Permeable	Permeable	
Penetration	100%	2%	5%	100%	2%	5%	
Dermal exposure	10	5.2	5	ml/h	10	5.2	5 ml/h
Duration of exposure	6	h					
Total dermal exposure to spray	121.2	ml/day			121.2	ml/day	
Concentration of a.s. in spray solution	20.001	mg/ml			20.001	mg/ml	
Dermal exposure to a.s.	2424.1212	mg/day			2424.1212	mg/day	

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure to spray	0.05	ml/h	
Duration of exposure	6	h	
Concentration of a.s. in spray	20.001	mg/ml	
Inhalation exposure to a.s.	6.0003	mg/day	
Percent absorbed	100	%	
Absorbed dose	6.0003	mg/day	

ABSORBED DOSE

	No PPE				PPE (if used)			
	Mix/load		Application		Mix/load		Application	
Dermal exposure to a.s.	171.60858	mg/day	2424.1212	mg/day	1.716086	mg/day	2424.1212	mg/day
Percent absorbed	1	%	4	%	1	%	4	%
Absorbed dose (dermal route)	1.7160858	mg/day	96.964848	mg/day	0.017161	mg/day	96.964848	mg/day
Inhalation exposure to a.s.	1.0740537	mg/day	6.0003	mg/day	1.074054	mg/day	6.0003	mg/day
Absorbed dose	2.7901395	mg/day	102.965148	mg/day	1.09121	mg/day	102.965148	mg/day

PREDICTED EXPOSURE

Total absorbed dose	105.7552875	mg/day	104.05636	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	1.762588125	mg/kg bw/day	1.7342727	mg/kg bw/day

AOEL	5	mg/kg bw/day	
%AOEL	35.3 %		34.7 %

Table 7.2.1.1- 3: Predicted systemic exposure to fosetyl-Al according to the EFSA Calculator/no PPE and with PPE

Exposure assessment

Substance	Fosetyl-Al	Formulation = Wettable granules, soluble granules	Application rate-2 kg a.s. /ha	Spray dilution = 20 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Grapes / Outdoor / Upward spraying / Vehicle-mounted			Buffer = 5	Number applications =3. Application interval = 10 days
Percentage Absoprtion	Dermal for product = 1	Dermal for in use dilution = 4	Oral = 100	Inhalation = 100	
RVNAS	5 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day		0.1694	% of RVNAS	3.66%
	Acute systemic exposure mg/kg bw/day		0.9131	% of RVAAS	
Mixing and Loading	Gloves = No		Clothing = Work wear - arms, body and legs covered	RPE = None	Soluble bags = No
Application	Gloves = No		Clothing = Work wear - arms, body and legs covered	RPE = None	Closed cabin = No
Exposure (including PPE options above)	Longer term systemic exposure mg/kg bw/day		0.0505	% of RVNAS	1.01%
	Acute systemic exposure mg/kg bw/day		0,2244	% of RVAAS	

CP 7.2.1.2   Measurement of operator exposure

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

CP 7.2.2   Bystander and resident exposure

No EU-wide validated and accepted/implemented official model is currently available for estimation of bystander and residential exposure.

An approach is presented in this document that considers both dermal exposure – derived from available drift data – and inhalation exposure – derived from an operator exposure model simulating a bystander who is exposed in a similar way as an unprotected operator spraying in the field. Additionally, exposure to residents is assessed as well.

This approach is following a guidance of the German Federal Institute for Risk Assessment (BfR)[5] and is in line with what has been published by US EPA and UK CRD recently. All technical details with regard to figures and assumptions are provided in this guidance.

<mark>At the request of the RMS resident exposure using the new EFSA calculator is also presented in this chapter.</mark>

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[5] ████████ ; Guidance for Exposure and Risk Evaluation for Bystanders and Residents exposed to Plant Protection Products during and after Application, Journal für Verbraucherschutz und Lebensmittelsicherheit *Journal of Consumer Protection and Food Safety* (2008, in preparation).

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No acute non-dietary risk assessment is included in this submission. Lack of scientific guidance or methodology is an acceptable reason for waiving according to Guidance of the European Commission[6]. The absence of such guidance on derivation of an appropriate reference dose ("AAOEL") was recognized by
- the European Food Safety Authority[7], and
- the European Commission Standing Committee[8].

Therefore, this waiver is presented in line with the Guidance of the European Commission.

However as the residential estimates cover an average exposure over a longer duration it is likely that the residential calculations adequately cover bystander safety.

Exposure estimates and proportions of the systemic AOELs accounted for by the estimates are summarised in the following Table 7.2.2- 1 and Table 7.2.2- 2. Detailed information and calculations are presented in Section CP 7.2.2.1.

Table 7.2.2- 1:   Predicted systemic exposures as a proportion of the AOEL

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
	Bystander of high crop application (tractor-mounted)			
	Bystander: adult	0.016547		0.331
	Bystander: child	0.013993	5	0.280
	Resident exposure after high crop application (tractor-mounted)			
	Resident: adult	0.0018707		0.0374
	Resident: child	0.0084259	5	0.1685

* Assumes a 60 kg bystander for an adult and 16.15 kg for a child.
Dermal absorption value of 4% was used. Inhalation absorption was taken as 100% for both compounds.

Table 7.2.2- 2:   Predicted systemic exposures as a proportion of the AOEL using the EFSA calculator

Substance	Scenario	Total systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
	Resident exposure after high crop application (tractor-mounted)			
	Resident: adult	0.0561		1.12
Fosetyl-Al	Resident: child	0.1054	5	2.11

* Assumes a 60 kg bystander for an adult and 10 kg for a child.
Dermal absorption value of 4% was used. Inhalation absorption was taken as 100% for both compounds.

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[6] Guidance Document for applicants on preparing dossiers for the approval of a chemical new active substance and for the renewal of approval of a chemical active substance according to Regulation (EU) No 283/2013 and Regulation (EU) No 284/2013. SANCO/10181/2013, May 2013.

[7] 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.

[8] Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. SANTE-10832-2015.

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Assessment

The results of the calculations reveal that the situation with respect to bystander and resident exposure is favourable for the intended use of FEA + FLC WG 71.11.

CP 7.2.2.1   Estimation of bystander and resident exposure

The following definitions and assumptions for <u>bystanders and residents</u> may be applied.

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

<u>Bystanders</u> may inadvertently be present within or directly adjacent to an area for a short period of time, typically a matter of minutes, where application of a plant protection product is in progress or has recently taken place. They may be exposed to plant protection products mainly *via* the dermal route from spray drift and by inhalation of drifting spray droplets. Hand held application is considered to be worse case compared to field crop sprayer.

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

Table 7.2.2.1- 1:   **Percent Drift Values for Different Crops (Rautmann *et al.*, 2001, current version 27.03.2006) – 2 applications.**

Crop, Distance 10 m	Percent Drift (2 applications) (82nd percentile values)
Field crops	0.24
Fruit crops, early	9.61
Fruit crops, late	3.11
Grapes	1.07
Hops	4.18
Vegetables, ornamentals & small fruit:	
< 50 cm	0.24
> 50 cm	1.07

Exposure calculations are performed according to the following equations:

a) Bystander exposure to fosetyl-Al in the FEA + FLC WG 71.11 formulation

Dermal exposure due to spray drift following 2 high crop applications using a tractor mounted field sprayer:

$$SDE_B = (AR \times D \times BSA \times DA) / BW$$

Where:
SDE_B	= Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day).	
AR	= Application Rate (mg/m^2)	4 kg a.s./ha = 400 mg/m^2.
D	= Drift (%)	11.81% (10 m distance) for 2 applications.
BSA	= Exposed Body Surface Area (m^2)	1 m^2 (adult), 0.21 m^2 (child).
DA	= Dermal Absorption (%)	4%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

Inhalation exposure due to spray drift:

$$SIE_B = (I_A^* \times AR \times A \times T \times IA) / BW$$

Where:
SIE_B	= Systemic Exposure of Bystanders via the Inhalation Route (mg/kg bw/day).	
I_A^*	= Specific Inhalation Exposure (mg/kg a.s. handled per day)	0.018 mg/kg a.s. (high crop tractor sprayer).
AR	= Application Rate (kg a.s./ha)	4 kg a.s./ha.
A	= Area Treated (ha/day)	8 ha (field crop sprayer).
T	= Time [Duration] (min)	5 min.
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

Total Systemic Exposure of Bystanders:

Adults and Children: $SE_B = SDE_B + SIE_B$ (mg/kg bw/day).

Where:
SE_B	= Systemic Exposure of Bystanders (mg/kg bw/day).
SDE_B	= Systemic Dermal Exposure of Bystanders (mg/kg bw/day).
SIE_B	= Systemic Inhalation Exposure of Bystanders (mg/kg bw/day).

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Table 7.2.2.1- 2: **Calculations for bystander exposure to fosetyl-al in FEA + FLC WG 71.11**

Adults	Children
Bystander of high crop application (tractor-mounted)	
Dermal Exposure	Dermal Exposure
SDE_B = (AR x D x BSA x DA)/BW	SDE_B = (AR x D x BSA x DA)/BW
SDE_B = (200 x 0.1181 x 1 x 0.04) / 60	SDE_B = (200 x 0.1181 x 0.21 x 0.04) / 16.15
SDE_B = 0.015747 mg/kg/day	SDE_B = 0.012285 mg/kg/day
Inhalation Expsoure	Inhalation Expsoure
SIE_B = (I_A* x AR x A x T x IA)/BW	SIE_B = (I_A* x AR x A x T x IA)/BW
SIE_B = (0.018 x 2 x 8 x 0.1667 x 1.00) / 60	SIE_B = (0.010345 x 2 x 8 x 0.1667 x 1.00) / 16.15
SIE_B = 0.00080000 mg/kg/day	SIE_B = 0.00170812 mg/kg/day
Total Sytemic Exposure	Total Sytemic Exposure
$SE_B = SDE_B + SIE_B$	$SE_B = SDE_B + SIE_B$
= 0.016547 mg/kg/day	= 0.013993 mg/kg/day
%AOEL = 0.3309	%AOEL = 0.2799

b) Residential exposure to fosetyl-Al in the FEA+FLC WG 71.11 formulation

Dermal exposure *via* deposits caused by spray drift:

$$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$$

Where:
SDE$_R$ = Systemic Exposure of Residents via the Dermal Route (mg/kg bw/day).
AR   = Application Rate (mg/cm^2)   4 kg a.s./ha = 0.04 mg/cm^2.
D   = Drift (%)   9.61% (10 m distance) for 2 applications.
TTR   = Turf Transferable Residues (%)   5%.
TC   = Transfer Coefficient (cm^2/hour)   7300 cm^2/h (adult), 2600 cm^2/h (child).
H   = Exposure Duration (hours)   2 h.
DA   = Dermal Absorption (%)   4%.
BW   = Body Weight (kg/person)   60 kg (adult), 16.15 kg (child).

Inhalation exposure due to vapour drift:

$$SIE_R = (AC_V \times IR \times IA) / BW$$

Where:
SIE$_R$ = Systemic Exposure of Residents via the Inhalation Route (mg/kg bw/day).
AC$_V$ = Airborne Concentration of Vapour (mg/m^3): 0 mg/m^3 (vapour pressure of a.s. < 10^{-5} Pa).
IR   = Inhalation Rate (m^3/day)   16.57 m^3/day (adult), 8.31 m^3/day (child).
IA   = Inhalation Absorption (%)   100%.
BW   = Body Weight (kg/person)   60 kg (adult), 16.15 kg (child).

As the vapour pressure of fosetyl-Al is <10^{-7} Pa at 25 °C the product is considered as non-volatile and therefore $AC_V = 0$ and $SIE_R = 0$.

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In addition, oral exposure of children is estimated by the following equations:
Children's hand-to-mouth transfer:

$SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$

Where:
SOE_H	= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day).	
AR	= Application Rate (mg/cm^2)	4 kg a.s./ha = 0.04 mg/cm^2.
D	= Drift (%)	9.61% (10 m distance) for 2 applns.
TTR	= Turf Transferable Residues (%)	5%.
SE	= Saliva Extraction Factor (%)	50% (EPA default value).
SA	= Surface Area of Hands (cm^2)	20 cm^2.
Freq	= Frequency of Hand to Mouth (events/hour)	20 events/h.
H	= Exposure Duration (hours)	2 h.
OA	= Oral Absorption (%)	100%.
BW	= Body Weight (kg/person)	16.15 kg (child).

Children's object-to-mouth transfer

$SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$

Where:
SOE_O	= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day).	
AR	= Application Rate (mg/cm^2)	4 kg a.s./ha = 0.04 mg/cm^2.
D	= Drift (%)	9.61% (10 m distance) for 2 applns.
DFR	= Dislodgeable Foliar Residues (%)	20%.
IgR	= Ingestion Rate for Mouthing of Grass/Day (cm^2)	25 cm^2/day.
OA	= Oral Absorption (%)	100%.
BW	= Body Weight (kg/person)	16.15 kg (child).

Total systemic exposure of residents is then estimated for:

Adults: $SE_R = SDE_R + SIE_R$ (mg/kg bw/day).
Children: $SE_R = SDE_R + SIE_R + SOE_H + SOE_O$ (mg/kg bw/day)

Where:
SE_R	= Systemic Exposure of Residents (mg/kg bw/day).
SDE_R	= Systemic Dermal Exposure of Residents (mg/kg bw/day).
SIE_R	= Systemic Inhalation Exposure of Residents (mg/kg bw/day).
SOE_H	= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day).
SOE_O	= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day).

Table 7.2.2.1- 3:   **Calculations for resident exposure to fosetyl-Al in FEA+FLC WG 71.11.**

Adults			Children		
Resident: Exposure after 2 applications with Field Crop, tractor mounted/trailed broadcast air assisted sprayer					
Dermal exposure:			Dermal exposure:		
$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$			$SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$		
$(0.04 \times 0.0961 \times 0.05 \times 7300 \times 2 \times 0.04) / 60$			$(0.04 \times 0.0961 \times 0.05 \times 2600 \times 2 \times 0.04) / 16.15$		
Absorbed dose:	0.00187075	mg/kg bw/d	Absorbed dose:	0.00247539	mg/kg bw/d
Inhalation exposure:			Inhalation exposure:		
$SIE_R = (AC_V \times IR \times IA) / 1000 \times BW$			$SIE_R = (AC_V \times IR \times IA) / BW$		
$(0 \times 16.57 \times 100\%) / 60$			$(0 \times 8.31 \times 100\%) / 16.15$		
Absorbed dose:	0.0	mg/kg bw/d	Absorbed dose:	0.0	mg/kg bw/d
			Oral exposure (hand-to-mouth transfer):		
			$SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$		
			$(0.04 \times 0.0961 \times 0.05 \times 0.5 \times 20 \times 20 \times 2 \times 1) / 16.15$		
			Absorbed dose	0.00476037	mg/kg bw/d
			Oral exposure (object-to-mouth transfer):		
			$SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$		
			$(0.04 \times 0.0961 \times 0.2 \times 25 \times 1) / 16.15$		
			Absorbed dose	0.00119009	mg/kg bw/d
Total systemic exposure;			**Total systemic exposure:**		
$SE_R = SDE_R + SIE_R$			$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$		
Total absorbed dose:	**0.00187075**	mg/kg bw/d	**Total absorbed dose:**	**0.00842586**	mg/kg bw/d
% of AOEL:	**0.037**		**% of AOEL:**	**0.1685**	

Resident exposure using the EFSA calculator:

Bystander and resident exposure to fosetyl-Al during and following the use of the FEA WG 80 formulation is estimated using the EFSA calculator and the scenario "Upward spraying, Vehicle-mounted".

Four pathways of exposure are considered (EFSA PPR Panel, 2010):
- spray drift (at the time of application)
- vapour (may occur after the PPP has been applied)
- surface deposits
- entry into treated crops

75th percentiles are considered for the single pathways and the total exposure from all pathways is calculated as mean value. A summary of the exposure calculations using the EFSA calculator for the critical GAP (see Table 7.2.1-1) is presented below.

Table 7.2.2.1- 4: **Resident exposure calculation (using the EFSA calculator)**

Substance	Fosetyl-Al	Formulation = Wettable granules, soluble granules	Application rate 2 kg a.s. /ha	Spray dilution = 20 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	Number applications = 3, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 1	Dermal for in use dilution = 4	Oral = 100	Inhalation = 100	
RVNAS	5 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day		0.1141	% of RVNAS	2.28%
	Vapour (75th percentile) mg/kg bw/day		0.0011	% of RVNAS	0.02%
	Surface deposits (75th percentile) mg/kg bw/day		0.0037	% of RVNAS	0.07%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0327	% of RVNAS	0.65%
	All pathways (mean) mg/kg bw/day		0.1054	% of RVNAS	2.11%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day		0.0623	% of RVNAS	1.25%
	Vapour (75th percentile) mg/kg bw/day		0.0002	% of RVNAS	0.00%
	Surface deposits (75th percentile) mg/kg bw/day		0.0007	% of RVNAS	0.01%
	Entry into treated crops (75th percentile) mg/kg bw/day		0.0182	% of RVNAS	0.36%
	All pathways (mean) mg/kg bw/day		0.0561	% of RVNAS	1.12%

CP 7.2.2.2   Measurement of bystander and resident exposure

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

CP 7.2.3 Worker exposure

The worker re-entry exposure has been calculated for fosetyl-Al following application of the FRA +
FLC WG 71.11 formulation for the representative use on grapes. The estimation is provided in the
following section.

CP 7.2.3.1 Estimation of worker exposure

The greatest potential for worker exposure following re-entry will be contamination *via* the skin. Risk
of inhalation exposure during re-entry is generally confined to a brief period after application, while
the product is drying, which will be rapid under outdoor conditions and would generally be avoided
according to good agricultural practices. Exposure to workers entering treated areas are predicted
using an exposure model proposed by ████████ *et al.*[9] (1998) and ████ *et al.*[10] (2001). The
following assumptions are made:

- Re-entry exposure is predominantly *via* the dermal route (contact with the foliage)
- Residues on the foliage depend on:
    - i)   application rate
    - ii)   extent of remaining residues from previous applications
    - iii)   the Leaf Area Index (LAI) [total size of foliage compared to surface area]
- Transfer of residues from foliage to the clothes or skin of workers depends mainly on the
  intensity of contact with the foliage.
- Activities with a similar pattern can be grouped and a generic Transfer Coefficient (TC)
  applied
- Dislodgeable Foliar Residue (DFR) is calculated using a default value of 3 µg as/cm² per kg
  as/ha. This figure is based Brouwer *et al.*[11] (2001)
- Workers re-enter the treated culture shortly after the spray has dried on plant surfaces,
  nevertheless it is now recommended to use the higher dermal absorption values amongst neat
  and dilated values.

The dermal exposure calculation is performed according to the following equation:

$$D = DFR \times TC \times WR \times AR \times P$$

Where:

DFR   = Dislodgeable foliar residues (µg as/ cm²).
TC   = Transfer Coefficient (cm²/person/h).
WR   = Work rate (hours/day).
AR   = Application rate (kg as/ha).
P   = Protection factor for PPE (P = 1 no PPE, just a long sleeved shirt, or 0.1 when
          adequate clothing and gloves are worn).

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[9] ████████████████████████: Label instructions for the protection of workers re-entering crop
growing areas after application of plant protection products; Nachrichtenbl. Deut. Pflanzenschutzd. 50 (10),
(1998), 267 - 269).

[10] ██
████████ (2001) Uniform principles for safeguarding the health of workers re-entering crop growing
areas after application of plant-protection products, Worker exposure to agrochemicals, ████████████████
████████████, chapter 8, 107- 117, CRC Press (2001).

[11] ██: (2001); Modeling re-entry exposure estimates:
techniques and application rates; Worker exposure to agrochemicals, ████████████████████████████████,
chapter 9, 119- 138, CRC Press (2001).

DFR values:

A maximum of 3 applications is considered in this risk assessment resulting in an estimated worst case DFR of 9 µg as/cm² per kg as/ha for the EUROPOEM II assessment whilst a default half-life of 30 days was applied when using the EFSA calculator.

Transfer Coefficient values:

A TC value of 10100 cm²/person/h has been used in this risk assessment. This value was obtained from the Europoem II data for grapes and is also used in the new EFSA calculator.

Predicted exposures are compared with the AOEL fosetyl-Al. Systemic exposure values assume the highest measured dermal absorption value for fosetyl-Al in the FEA + FLC WG 71.11 formulation (4%). A body weight of 60 kg is assumed for the re-entry worker. Exposure estimates based proportions of the systemic AOELs accounted for by the estimates are summarised in the following Table. Detailed calculations are presented on the following pages.

Table 7.2.3.1- 1: Summary of predicted fosetyl-Al worker exposures (no PPE) arising from the use of FEA+FLC WG 71.11 and comparison with the respective AOEL

Active substance	Model	Systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
FEA	Europoem	0.9696000	5	19
	EFSA	0.7833273		16

*3% dermal absorption, 60 kg worker

Assessment

The exposure of workers to fosetyl-Al when entering treated areas is well within acceptable levels following application of FEA + FLC WG 71.11 to grapes.

Detailed calculations of worker exposure during re-entry:

Europoem II:

Product Name: FEA+FLC WG 71.11
Active substance: FEA

$$D = DFR \times TC \times WR \times AR \times P$$

		µg/cm²		cm²/pers/h	hrs/day		kg/ha	
D	=	9	x	10100	x 8	x	2	x 1
D	=	1454400 µg a.s./pers/day						
	=	1454.4 mg a.s./pers/day						
	=	24.24 mg/kg bw/day						

using 4.00% dermal absorption (highest value)

S	=	24.24 x 0.0400
	=	0.969600 mg/kg bw/day

EFSA Calculator:

Worker exposure from residues on foliage for FEA+FLC WG 71.11			
Crop type	Grapes		
Indoor or outdoor	Outdoor		
Application method	Upward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Hand harvesting		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	2 kg a.s./ha		i_AppRate
Number of applications	3		i_AppNo
Interval between multiple applications	10 days		i_AppInt
Half-life of active substance	30 days		i_HalflifeAS
Multiple application factor	2.4		d_MAF
Dermal absorption of the product	1.00%		i_AbsorpProduct
Dermal absorption of the in-use dilution	4.00%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	6 µg a.s/cm²		d_DFR
Working hours	8 hr		d_WorkHr
Dermal transfer coefficient - Total potential exposure	30000 cm²/hr		d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	10100 cm²/hr		d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm²/hr		d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA ha/hr*10^(-3)		d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10^(-3)		d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10^(-3)		d_InhalTcSoc

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	139.6028765	46.9996351	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	2.3267186	0.7833273		
% of RVNAS	46.53%	15.67%		

2. Details

	Systemic exposure		Formula	Comments
	[mg a.s. /day]	[mg a.s./kg bw/day]		
Dermal - Potential	139.6028765	2.3267186	d_DermTcUCV*d_WorkHr*i_DFR*d_MAF/1000*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	46.9996351	0.7833273	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Inhalation				Na for outdoor activities

CP 7.2.3.2 Measurement of worker exposure

Not considered to be necessary as a safe use was predicted in the previous section.

CP 7.3 Dermal absorption

The dermal penetration through human dermatomed skin of $[^{14}C]$-fosetyl-Al in the FLC + FEA WG 71.11 formulation was investigated at three concentrations corresponding to the neat product (666.7 g fosetyl-Al/kg) and to two representative dilutions (20 and 2 g fosetyl-Al/L), respectively.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 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 0.05% for the human skin. Applying the new EFSA guidance this value adjusts to 0.1%.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 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 0.88% for human skin. Applying the new EFSA guidance this value adjusts to 1%.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 2.0% for human skin. Applying the new EFSA guidance this value adjusts to 4%.

According to the new EFSA guidance[12] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were met by the high group in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for $[^{14}C]$-fosetyl-Al in the FLC + FEA WG 71.11 formulation:

- 0.1% for the neat formulation (666.7 g fosetyl-Al/kg)

- 1% for the intermediate dose (20 g fosetyl-Al/L)

- 4% for the low dose (2 g fosetyl-Al/L).

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12 EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.

Report:	KCP 7.3/01▮▮▮▮▮; 2016; M-512858-02-1
Title:	Fosetyl-Al WG 71.11 (FEA+FLC WG 66.67+4.44): [14C]-Fosetyl-Al - In vitro dermal absorption study using human skin
Report No.:	SA 14048
Document No.:	M-512858-02-1
Guideline(s):	OECD Guideline for the testing of Chemicals
	Skin Absorption In Vitro Method Guideline 428 (April 2004).
	OECD Environmental Health and Safety Publications Series on testing and Assessment N° 28, Guidance Document for the Conduct of Skin Absorption Studies (March 2004).
	EFSA Panel on Plant Protection Products and their Residues (PPR) Guidance on Dermal Absorption, EFSA Journal 2012: 10(4): 2665
Guideline deviation(s):	none
GLP/GEP:	**yes**

Material and methods

Human skin: Source: ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮, France.
Number and sex: minimum of 6 donors per dose level, female.
Anatomical region: Abdomen.
Thickness: 382 to 495 µm.

Test Material:
Non-radiolabelled: Batch: 201405007.
Purity = 96.0% (w/w).

Radiolabelled: [ethyl-2-^{14}C]-fosetyl-Al.
Batch: 8316AKY001-8.
Specific activity: 4.02 MBq/mg.
Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the fluopicolide + fosetyl-Al WG 71.11 formulation (specification N° 102000024700) containing fluopicolide (44.4 g/kg) and fosetyl-Al (666.7 g/kg). It was used at three nominal concentrations of fosetyl-Al: neat, 666.7 g/L with 2 spray dilutions of 20 g/L and 2 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. Skin samples with a TEWL of greater than 15 g/m²h 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 5 mg/cm^2 for the neat formulation (as a powder) and 10 μL/cm^2 for the spray dilutions.. 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:

Fosetyl-Al was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

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

The study results are presented in Table 7.3- 1

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Table 7.3- 1: **Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]-fosetyl-Al in a FLC + FEA WG 71.11 formulation at the nominal rates of 666.7 g/kg, 20 g/L and 2 g/L to human skin samples.**

Results expressed in terms of percentage of applied radioactivity

Dose Levels Species	Distribution of radioactivity (% dose)					
	Neat formulation: High dose (666.7g/kg) Human (n=4)		Dilution: Intermediate dose (20 g/L) Human (n=6)		Dilution: Low dose (2 g/L) Human (n=6)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (8h)	102.54	6.04	105.32	1.33	96.56	2.71
Skin swabs (24h)[a]	0.07	0.12	0.01	0.01	0.13	0.18
Total skin swabs	102.61	5.96	105.33	1.33	96.69	2.66
Surface Dose (1st two tape-strips)	0.05	0.07	0.002	0.002	0.23	0.42
Donor chamber	0.11	0.16	0.10	0.04	0.06	0.07
Total % non-absorbed	**102.8**	**5.81**	**105.4**	**1.35**	**96.98**	**2.78**
SKIN COMPARTMENT						
Skin [b]	*0.02*	*0.01*	0.007	0.004	0.96	2.00
Stratum corneum [c]	0.03	0.04	0.01	0.01	0.15	0.23
Total % at dose site	**0.05**	**0.04**	**0.02**	**0.01**	**1.11**	**2.01**
RECEPTOR COMPARTMENT						
Receptor fluid (0-24h)	0.03	0.03	0.15	0.26	0.72	0.46
Receptor fluid terminal	n.d.		0.002	0.006	0.04	0.03
Receptor chamber	n.d.		0.71	0.04	0.15	0.17
Total % directly absorbed [d]	*0.03*	*0.03*	*0.86*	*0.26*	*0.90*	*0.51*
STUDY: Total % Potentially Absorbable [e]	0.05	0.02	0.88	0.26	2.02	2.41
TOTAL % RECOVERY	**102.9**	**5.80**	**106.3**	**1.36**	**98.99**	**4.32**
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	Yes		No		No	
standard deviation >25%	Yes		Yes		Yes	
recovery <95%	No		No		No	
adjusted: **Total % Potentially Absorbable [f]**	**0.1**		**1**		**4**	

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

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

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Fosetyl-aluminium + Fluopicolide WG 71.11

Conclusion:

The dermal penetration through human dermatomed skin of $[^{14}C]$-fosetyl-Al in the FLC + FEA WG 71.11 formulation was investigated at three concentrations corresponding to the neat product (666.7 g fosetyl-Al/kg) and to two representative dilutions (20 and 2 g fosetyl-Al/L), respectively.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 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 0.05% for the human skin. Applying the new EFSA guidance this value adjusts to 0.1%.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 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 0.88% for human skin. Applying the new EFSA guidance this value adjusts to 1%.

The mean percentage of fosetyl-Al in the FLC + FEA WG 71.11 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 2.0% for human skin. Applying the new EFSA guidance this value adjusts to 4%.

According to the new EFSA guidance[13] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were met by the high group in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for $[^{14}C]$-fosetyl-Al in the FLC + FEA WG 71.11 formulation:

- 0.1% for the neat formulation (666.7 g fosetyl-Al/kg)

- 1% for the intermediate dose (20 g fosetyl-Al/L)

- 4% for the low dose (2 g fosetyl-Al/L).

CP 7.4   Available toxicological data relating to co-formulants

CONFIDENTIAL information, please refer to the respective Document JCP.

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[13]   EFSA Panel on Plant Protection Products and their Residues (PPR); Guidance on Dermal Absorption. EFSA Journal 2012;10(4):2665. [30 pp.] doi:10.2903/j.efsa.2012.2665.