Document Title

Summary of the toxicological studies for Aclonifen SC 600 G

Data Requirement(s)

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

Document MCP

Section 7: Toxicological studies

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

Date

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Version history

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

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Aclonifen was included in Annex I to Council Directive 91/414/EEC in 2008 (Directive 2008/116/EC, Entry into Force on 01 August 2009).

The formulation Aclonifen SC 600 G (or Aclonifen 600 g/L), is a suspension concentrate formulation containing 600 g/L of aclonifen This formulation is registered throughout Europe under trade names such as Bandur (Aclonifen-SC600; AE-F068300-00-SC50-A2; EXP-04209). Aclonifen SC 600 G was already a representative formulation of Bayer for the Annex I inclusion of aclonifen under Council Directive 91/414/EEC.

This present dossier in support of approval renewal includes all the data submitted at the time of the Annex I inclusion, in summaries updated and re-evaluated as necessary to take account of current validity criteria and data requirements.

CP 7.1 Acute toxicity

Aclonifen SC 600 G is a Suspension Concentrate (SC) formulation containing aclonifen (600 g/L). This formulation is identical to Bandur which was evaluated during the Annex I inclusion of aclonifen and the *in vivo* studies were found to be acceptable. A summary of the acute toxicity studies including irritancy and skin sensitisation can be found in the table below and the individual study summaries are provided in the subsections CP 7.1.1 to 7.1.6.

All studies for the acute toxicity endpoints were presented and evaluated during the EU process for the Annex I inclusion of aclonifen under Council Directive 91/414/EEC. A short overall summary of these studies is provided in Section CP 7.1 to 7.6

Summary of acute toxicity studies with Aclonifen SC 600 G:

Endpoint	Species (Sex)	Results	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
Acute oral toxicity	Rat (M & F)	LD_{50} > 5596 mg/kg bw	None	KCP 7.1.1/01 M-208817-01-1 [redacted] 1989
Acute dermal toxicity	Rat (M & F)	LD_{50} > 2000 mg/kg bw	None	KCP 7.1.2/01 M-208819-01-1 [redacted] 1989
Acute inhalation toxicity	Not submitted (aclonifen: LC_{50} > 5.06 mg/L air)			----
Acute skin irritation	Rabbit (M)	Not irritant	None	KCP 7.1.4/01 M-208821-01-1 [redacted] 1989
Acute eye irritation	Rabbit (M)	Not irritant	None	KCP 7.1.5/01 M-208824-01-1 [redacted] 1989
Skin sensitization	Guinea pig (M & K) Modified Buehler test	Not sensitising	None	KCP 7.1.6/01 M-175869-01-1 [redacted] 1995
	Mice (F)	Not sensitising	None	KCP 7.1.6/02

	Local Lymph Node Assay			M-232345-01-1 [redacted], 2004
	Mice (F) Local Lymph Node Assay	Not sensitising	None	KCP 7.1.6/03 M-259889-01-1 [redacted], 2005

Overall, Aclonifen SC 600 G was found to be of low acute toxicity following exposure via oral, dermal and inhalation routes of administration. It was found to be not irritating to rabbit skin or to rabbit eye and not to be a skin sensitizer using the M&K and LLNA tests.

CP 7.1.1 Oral toxicity

Data Point:	KCP 7.1.1/01
Report Author:	[redacted]
Report Year:	1989
Report Title:	Acute oral toxicity study (and limit test) of EXP4209 in rats
Report No:	C025169
Document No:	M-208817-01-1
Guideline(s) followed in study:	OECD: 401, 1982
Deviations from current test guideline:	Current Guideline: OECD 401, 1987 No deviation
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

An acute oral toxicity study was conducted on rats. The product Bandur (EXP 4209) was administered by gavage as the pure suspension to Sprague Dawley rats. A limit test (2000 mg/kg bw) was first performed (5 animals/sex), since there were mortalities in the limit test (1 male and 1 female) it was followed by a range-finding study using dosage of 1590, 2520, 3990, 6320 and 10020 mg/kg bw (1 animal/sex/dose). Then, a main study was performed using dosage of 3200, 5000 and 8000 mg/kg bw (5 animals/sex/dose). The observation period was 14-days.

In the range-finding study the female given the top dose (10020 mg/kg bw) died. Mortality occurred in the main study at all doses tested. Clinical signs were piloerection and lethargy accompanied by a slight dyspnea and sometimes abnormal body carriage (hunched posture). Signs were more marked in high dose group than in low dose groups. In surviving animals, the signs disappeared during the first 2 to 5 days depending on the dosage.

There was no treatment-related effect on body weight. The macroscopic examination of the animals at the end of the study revealed greenish pale kidneys in all animals.

Based on the above results, the median lethal dose (LD_{50}) and the oral LD50 of Bandur and its 95 % confidence limits was calculated to be 5596 (3303 -9479) mg/kg bw for rats. Bandur or Aclonifen is therefore not classified for oral toxicity according to Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: EXP 4209 (Bandur)

Description:	Suspension Concentrate (SC), colour: yellow
Lot/Batch:	OP 880633
Purity:	The theoretical content of active substance aclonifen was 600 +/- 30 g/L and the measured content was 599 g/L (Certificate of analysis N° BA 10013 of 22/06/88).
Stability of test compound:	Shown to be stable (see MCP2)

2. Vehicle: None

3. Test animals:

Species:	Rat
Strain:	Sprague Dawley rats
Age:	Data not given
Weight at dosing:	Main study/ representative: 282 ± 10.3 (males), 230 ± 20.0 (females)
Source:	[redacted]
Acclimatisation period:	One week
Diet:	Altromin R+ M, typ 1324, Charge 62, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	2-3 rats/cage. In macrolon cages type III

4. Environmental conditions:

Temperature:	20°C ± 2°C
Humidity:	50% relative humidity
Air changes:	12-15 times/hour
Photoperiod:	Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 14 October 1988 to 07 November 1988 (main study).

2. Animal assignment and treatment

The test substance was administered by gavage as the pure suspension to Sprague Dawley rats. A limit test (2000 mg/kg bw) was first performed (5 animals/sex) followed by a range-finding, using dosage of 1590, 2520, 3990, 6320 and 10020 mg/kg bw (1 animal/sex/dose). Then, a main study was

performed using dosage of 3200, 5000 and 8000 mg/kg bw (5 animals/sex/dose). The study did not include a control group.

The substance was given orally by gavage as the pure suspension.

All animals were observed for clinical signs of toxicity immediately after treatment and once daily in the early morning up to the end of the 2 weeks observation period.

All surviving animals were sacrificed on Day 14 and subjected to gross/macroscopic necropsy.

3. Statistics

Group means, and standard deviations of bodyweights were calculated.

II. RESULTS AND DISCUSSION

A. MORTALITY

Limit test

In the limit test of 5 males and 5 females administered the test substance at 2000 mg/kg bw one male, and one female died during the first 30 hours. All other animals survived the 14 days observation period.

Range finding study

In the range-finding study where the test substance was administered at 1590, 2520, 3990, 6320 and 10020 mg/kg bw (1 animal/sex/dose), one female of the highest dose group died during 24 hours, all other animals survived the 14 day observation period.

Main study

In the high dose group (8000 mg/kg bw), 6 of 10 animals died (2 males and 2 females died during first 24 hours after administration; 1 male and 1 female died during the first 2 days after administration).

In the medium dose group (5000 mg/kg bw), 5 of 10 animals died (1 male and 2 females died during the first 2 days; 2 females died during the third day after administration).

In the low dose group (3200 mg/kg bw), 3 of 10 animals died (1 male and 2 females) during the first 30 hours after administration. The mortality is given in the Table below.

Table 7.1.1-01 EXP 4209 - Acute oral toxicity in rats – mortality (main study)

	Dose (mg/kg bw)	Number animals	Number of deaths	Onset of death after
Males	3200	5	1	0-30 hours
Females	3200	5	2	0-30 hours
Males	5000	5	1	0-2 days
Females	5000	5	4	0-3 days

Males	8000	5	3	0-2 days
Females	8000	5	3	0-2 days

B. CLINICAL OBSERVATIONS

Clinical signs were piloerection and lethargy accompanied by a slight dyspnea and sometimes abnormal body carriage (hunched posture). Signs were more marked in high dose group than in low dose groups.

In surviving animals, the signs disappeared during the first 2 to 5 days depending on the dosage. The animals which died during the observation period and the animals of the high dose group had similar clinical signs.

C. BODYWEIGHT

The body weight gain has not been influenced by the treatment. The changes in the body weight in the main study is given in the table below.

Table 7.1.1-02 EXP 4209 - Changes in the body weight in g (mean ± SD) in the main study

Dosage [g/kg bw]	Sex	Initial weight* [g]	Weight after		Weight increase [g]
			One week [g]	Two weeks** [g]	
3.2	M	281 ± 5.2	328 ± 7.3	361 ± 9.4	79 ± 5.0
	F	230 ± 20.0	264 ± 14.2	263 ± 11.7	35 ± 7.6
5.0	M	287 ± 14.3	340 ± 22.4	383 ± 23.2	95 ± 13.4
	F	234 ± 8.7	259 ± ND	264 ± ND	28± ND
8.0	M	280 ±14.9	311 ± 19.8	354 ± 9.9	80 ± ND
	F	232 ± 5.9	258 ± 4.2	257 ± 4.2	25 ± 0.5

*: 1 day of treatment
**: just before necropsy

D. NECROPSY

Autopsy of survivors showed greenish and pale kidneys. In the animals that died beside greenish and pale kidneys the main observation was a yellow to brown or black staining of the content of the GI tract, probably caused by the test substance. This staining also occurred in the bladder and the anogenital area of a few animals.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The oral LD50 of Bandur and its 95 % confidence limits was calculated to be 5596 (3303-9479) mg/kg bw for rats. Aclonifen SC 600 G is therefore not classified as harmful by ingestion according to Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid. The study followed OECD 401, however this guideline was deleted in 2002 and is replaced by guidelines OECD 420, OECD 423 and OECD 425.

Assessment and conclusion by RMS:

CP 7.1.2 Dermal toxicity

Data Point:	KCP 7.1.2.01
Report Author:	[redacted]
Report Year:	1988
Report Title:	Acute dermal toxicity study (or limit test) of EXP4209 in rats
Report No:	C025170
Document No:	M-208819-01-1
Guideline(s) followed in study:	OECD 402, (1982)
Deviations from current test guideline:	Current Guideline: OECD 402, 2017 No significant deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive summary

In an acute dermal toxicity test, groups of Sprague Dawley rats (5/sex) were given a single dermal dose of the test substance EXP 4209, 2000 mg/kg bw, diluted in distilled water, and applied to shaven skin in an area of 5 x 5 cm. The test substance was covered in a semi-occlusive dressing and removed by washing 24 hours after dose administration. The animals were observed for 14 days.

There were no mortalities and no clinical signs of toxicity. The only finding was a compound-related local yellow discolouration of the skin, and a greenish staining of the kidneys at necropsy in 2 males and 2 females.

In conclusion EXP 4209 was found to be of a low order of acute dermal toxicity following exposure in rats.

I. MATERIALS AND METHODS

A. MATERIALS

1.	**Test materials:**	EXP 4209 (Bandur)
	Description:	Suspension Concentrate (SC), colour: yellow
	Lot/Batch:	OP 880633
	Purity:	The theoretical content of active substance aclonifen was 600 +/- 30 g/L and the measured content was 599 g/L (Certificate of analysis N° BA 10013 of 22/06/88).
	Stability of test compound:	Shown to be stable (see MCP2)
2.	**Vehicle:**	None
3.	**Test animals:**	
	Species:	Rat
	Strain:	Sprague Dawley rats
	Age:	Data not given
	Weight at dosing:	Males (312 g ± 20.7) and females (263 g ± 16.4)
	Source:	[redacted]
	Acclimatisation period:	One week
	Diet:	Altromin R+ M, typ 1324. Charge 62, *ad libitum*
	Water:	Tap water, *ad libitum*
	Housing:	1 rat/cage. In macrolon cages type III
4.	**Environmental conditions:**	
	Temperature:	20°C ± 2°C
	Humidity:	50% relative humidity
	Air changes:	12-15 times/hour
	Photoperiod:	Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 18 August 1988 to 12 September 1988

2. Animal assignment and treatment

Animals received by topical application, an effective dose of 2000 mg/kg body weight of the product EXP 4209 or Aclonifen SC 600 G diluted in distilled water, at a volume of 1.60 mL/kg bw (= 2.0 g/kg bw; spec. weight of the test substance:1.25 g/ml). The test substance was applied on the shaved dossal area of the trunk (shaved 24 hours before application). The application area was about 5 x 5 cm. After 24 hours exposure under a semi-occlusive dressing, residual test substance was washed away. The observation period was 14 days after the single application. The study did not include a control group.

All surviving animals were sacrificed on Day 14 and subjected to gross/macroscopic necropsy.

3. Statistics

Group means, and standard deviations of bodyweights were calculated.

II. RESULTS AND DISCUSSION

A. MORTALITY

No deaths occurred during the study.

B. CLINICAL OBSERVATIONS

No clinical signs related to the treatment were observed. Only a yellow to brown coloration of the skin on the application area occurred during the observation period.

C. BODYWEIGHT

The body weight gain has not been influenced by the treatment. The changes in the body weight in the main study is given in the table below.

Table 7.1.2-01 EXP 4209 – acute dermal toxicity - body weight in g (mean ± SD)

Dosage [g/kg bw]	Sex	Initial weight* [g]	Weight after		Weight change [g]
			One week [g]	Two weeks** [g]	
2000	M	312 ± 10.7	347 ± 11.5	378 ± 10.7	65.6 ± 4.8
	F	263 ± 16.4	270 ± 18.1	278 ± 18.3	15.4 ± 6.3

*: 1 day of treatment
**: just before necropsy

D. NECROPSY

The animals killed at the end of the observation period showed no macroscopically visible abnormalities related to the treatment. Only the skin of the treated area was slightly yellow. Kidneys of 2 males and 2 females showed greenish colour.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The acute dermal LD_{50} of the test substance EXP 4209 (Bandur equivalent to Aclonifen SC 600 G) was determined to be > 2000mg/kg bw. The test substance is therefore not classified for acute dermal toxicity under Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

CP 7.1.3 Inhalation toxicity

An inhalation study is not required for an SC formulation, and therefore for animal welfare reasons no acute inhalation study has been conducted on Aclonifen SC 600 G.

The inhalation LC_{50} of aclonifen in the rat (> 5.06 mg/L air) is low, and the vapour pressure of aclonifen is also low, 1.5 x 10^{-4} Pa. None of the coformulants are classified for acute inhalation toxicity. Using the calculation method no classification for acute inhalation toxicity is needed. For further information on the inhalation toxicity of the coformulants please refer to the confidential section JCP.

The product Aclonifen SC 600 G is therefore not classified for acute inhalation toxicity under Regulation (EC) 1272/2008.

CP 7.1.4 Skin irritation

Data Point:	KCP 7.1.4/01
Report Author:	[redacted]
Report Year:	1988
Report Title:	Acute dermal irritation / corrosion toxicity study of EXP4209 in rabbits
Report No:	C025171
Document No:	M-208821-01-1
Guideline(s) followed in study:	OECD: 404, (1982)
Deviations from current test guideline:	Current Guideline: OECD 404, 2015 No significant deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

The fur was clipped from the dorsal area of three male rabbits. The test item EXP 4209 (0.5mL) was applied as supplied by topical application to the exposed skin (of about 6 cm2) and covered by a semi-occlusive dressing for 4 hours. After this time the dressing was removed and the site gently washed with warm water.

The scoring of skin reactions was performed at approximately 0.5, 1, 24, 48 and 72 hours after patch removal. Autopsy was performed after last scoring. The evaluation of scoring was performed according to the EU system.

There were no mortalities and there no signs of erythema or oedema in any of the animals throughout the study.

The test substance EXP 4209 (Bandur, equivalent to Aclonifen SC 600 G) is not classified as a skin irritant under Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: EXP 4209 (Bandur)

Description: Suspension Concentrate (SC), colour: yellow

Lot/Batch: OP 880633

Purity: The theoretical content of active substance aclonifen was 600 +/- 30 g/L and the measured content was 599 g/L (Certificate of analysis N° BA 10013 of 22/06/88).

Stability of test compound:	Shown to be stable (see MCP2)

2. Vehicle: None

3. Test animals:

Species:	Rabbit
Strain:	Albino New Zealand rabbits
Age:	Data not given
Weight at dosing:	2.8 kg ± 6.5
Source:	[redacted]
Acclimatisation period:	14 days
Diet:	Altromin R+M, typ 1324, Charge 62, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Single housing in batteries for rabbits

4. Environmental conditions:

Temperature:	18°C ± 2°C
Humidity:	50% relative humidity
Air changes:	12-15 times/hour
Photoperiod:	Day-night rhythm 12 hours (7 a.m.-7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 18 August 1988 to 19 September 1988

2. Animal assignment and treatment

A single dose of 0.5 mL of the undiluted test substance (or placebo) was applied to the intact shaved skin of 3 male New Zealand White rabbits (to an area of approximately 6 cm2) during 4 hours under semi-occlusive conditions. The cutaneous reactions were observed 0.5, 1, 24, 48 and 72 hours after the exposure period. Autopsy was performed after last scoring.

The evaluation of scoring was performed according to Draize (see Table below). Autopsy was performed after last scoring.

Grading scales:

Erythema and Eschar formation	Oedema
0 …. No erythema	0….. No oedema
1…. Slight (barely perceptible) erythema	1 ….. Slight (barely perceptible) oedema
2 ….. Definite erythema	2 ….. Slight oedema (contour clearly defined)

3 … Moderate to severe erythema	3 ….. Moderate oedema (thickness approx. 1 mm)
4 …. Severe erythema (purple) with formation of eschars (deep lesions) preventing erythema being grading	4 …. Severe oedema (thickness greater than 1 mmm, a surface larger than the zone of application)

II. RESULTS AND DISCUSSION

A. FINDINGS

No mortality occurred during the study. There were no signs of erythema or oedema in any of the animals as shown in the table below.

Table 7.1.4-01 EXP 4209 - Skin irritation scores (erythema and oedema).

Rabbit n.	Parameter	0.5 hour	1 hour	24 hours	48 hours	72 hours	Mean score (24+48+72 hours)
1	Erythema	0	0	0	0	0	0
	Oedema	0	0	0	0	0	0
2	Erythema	0	0	0	0	0	0
	Oedema	0	0	0	0	0	0
3	Erythema	0	0	0	0	0	0
	Oedema	0	0	0	0	0	0

B. NECROPSY

None.

C. DEFICIENCIES

None.

III. CONCLUSIONS

Over an exposure period of 4 hours, the undiluted the test substance EXP 4209 (Bandur equivalent to Aclonifen SC 600 G) was not irritating to skin. EXP 4209 is therefore not classified as skin irritant according to Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

CP 7.1.5 Eye irritation

Data Point:	KCP 7.1.5/01
Report Author:	[redacted]
Report Year:	1988
Report Title:	Acute eye irritation / corrosion toxicity study of EXP4209 in rabbits
Report No:	C025172
Document No:	M-208824-01-1
Guideline(s) followed in study:	OECD: 404, 1982
Deviations from current test guideline:	Current Guideline: OECD 405, 2017 No significant deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

Three White New Zealand male rabbits were administered a single ocular dose of 0.1 mL of undiluted test substance into the conjunctival sac of left eye of each animal. The right eye was treated in the same way by using physiological saline solution. The eyes were rinsed 24 hours after instillation of the test substance/physiological saline solution.

The ocular reactions were observed 0.5, 1, 3, 6, 24, 48 and 72 hours after the instillation. Final examination was performed on day 21 of the study before necropsy.

In conclusion, EXP 4209 (Bandur or Aclofinen SC 600 G) is not classified as an eye irritant under Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: EXP 4209 (Bandur)

Description: Suspension Concentrate (SC), colour: yellow

Lot/Batch: OP 880633

Purity:	The theoretical content of active substance aclonifen was 600 +/- 30 g/L and the measured content was 599 g/L (Certificate of analysis N° BA 10013 of 22/06/88).
Stability of test compound:	Shown to be stable (see MCP2)

2. Vehicle: None

3. Test animals:

Species:	Rabbit
Strain:	White New Zealand- rabbits
Age:	Data not given
Weight at dosing:	2.77 kg ± 3.9%
Source:	[redacted]
Acclimatisation period:	14 days
Diet:	Altromin R+ M, typ 1324. Charge 62 *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Single housing in batteries for rabbits

4. Environmental conditions:

Temperature:	18°C ± 2°C
Humidity:	50% relative humidity
Air changes:	12-15 times/hour
Photoperiod:	Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 18 August 1988 to 26 September 1988

2. Animal assignment and treatment

On the day of treatment, approx. 0.1 mL of the test item was placed in the conjunctival sac of the left eye of each animal. The right eye was left untreated and served as the control.

The eyes of each animal were examined at approximately 0.5, 1, 3, 6, 24, 48 and 72 hours after treatment and were scored according to the OECD guideline 405. Clinical observations were made once daily from the day of treatment. Final examination was performed on day 21 of the study before necropsy.

II. RESULTS AND DISCUSSION

A. MORTALITY

No deaths were observed during the study.

B. CLINICAL OBSERVATIONS

No ocular reaction was observed in any animal (see table below).

Table 7.1.5-01 EXP 4209 - Eye irritation: mean scores

Rabbit n.	Rabbit n.	0.5 hour r/l	1 hour r/l	24 hours r/l	48 hours r/l	72 hours r/l	Mean score (24+48+72 hours) r/l
Cornea	1	0/0	0/0	0/0	0/0	0/0	0/0
	2	0/0	0/0	0/0	0/0	0/0	0/0
	3	0/0	0/0	0/0	0/0	0/0	0/0
Iris	1	0/0	0/0	0/0	0/0	0/0	0/0
	2	0/0	0/0	0/0	0/0	0/0	0/0
	3	0/0	0/0	0/0	0/0	0/0	0/0

C. DEFICIENCIES

None.

III. CONCLUSIONS

Undiluted EXP 4209 (Bandur or Aclonifen SC 600 G) was not irritating to the eyes of rabbit, therefore it is not classified as an eye irritant under Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

CP 7.1.6 Skin sensitization

Data Point:	KCP 7.1.6/01
Report Author:	[redacted]
Report Year:	1995
Report Title:	Skin sensitization test in guinea-pigs (Modified Buehler test: 9 applications) EXP04209
Report No:	R007916
Document No:	M-175869-01-1
Guideline(s) followed in study:	--
Deviations from current test guideline:	Current Guideline: OECD 406, 1992 No deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

The potential of EXP 04209 formulation to cause delayed contact hypersensitivity was investigated in Dunkin-Hartley albino guinea-pigs (10 per sex) according to the modified method by Buehler.

A preliminary study test was performed to define the maximum concentration to be tested and followed by the main study.

In the main study, intradermal injections of 0.5 mL of the undiluted test substance was applied to the skin on the anterior left flank of Dunkin-Hartley Guinea pigs (10 males and 10 females) under occlusive dressing and 3 times a week of 3 consecutive weeks during 6 hours. The control group (5 males and 5 females) received the vehicle (distilled water) under the same experimental conditions.

Challenge treatment: 10 days after the last induction: 0.5 mL of the test substance at a concentration of 50 % (w/w) (right flank) and 0.5 mL of the vehicle (left flank) were applied to a non-treated area of the posterior region of all animals. Cutaneous reactions were evaluated 24 and 48 hours after the removal of the pads of the challenge application by comparing the reactions on both flanks.

No clinical signs and no deaths related to treatment were observed throughout the main study. The body weight gain was not influenced by the treatment.

During the induction period very slight (dryness of the skin, erythema grade 1) cutaneous reactions were observed. No cutaneous reactions were observed 24 and 48 hours after the challenge phase.

It was concluded that EXP 04209 (Bandur or Aclonifen 600SC G) formulation does not exhibit a skin sensitisation potential in Guinea pigs under the conditions of the test and when tested at a concentration of 50% (w/w). Therefore, it was concluded that Aclonifen 600SC G is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: EXP 4209 (Bandur)

Description:	Suspension Concentrate (SC), colour: yellow
Lot/Batch:	OP 940221
Purity:	The theoretical content of active substance aclonifen was 600 +/- 30 g/L and the measured content was 584 g/L (Certificate of analysis N°AGF 94.091 of 23/03/94).
Stability of test compound:	Shown to be stable (see MCP2)

2. Vehicle: Distilled water, Batch Nos. 3303 and 4778 (Fresenius, 93216, France)

3. Test animals:

Species:	Guinea-pigs
Strain:	Dunkin-Hartley
Age:	1-3 months old
Weight at dosing:	Males = 333 ± 44 g; females = 325 ± 25 g
Source:	[redacted]
Acclimatisation period:	At least 5 days
Diet:	Guinea-pigs sustenance reference 106 diet (U.A.R. 91360 Villemoisson-sur-Orge, France)
Water:	Filtered water
Housing:	Individually housed in polycarbonate cages (48 x 27 x 20 cm)

4. Environmental conditions:

Temperature:	21°C ± 2°C
Humidity:	30 to 70% relative humidity
Air changes:	12-15 times/hour
Photoperiod:	Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 07 August 1995 to 07 September 1995

2. Animal assignment and treatment

Pre-study: A preliminary test was performed to define the maximum concentration to be tested.

The test substance was applied as supplied at 0.5 mL/animal to the flank of Dunkin-Hartley Guinea pigs (1 male and 1 female) and maintained under occlusive dressing for 6 hours. Residual test substance was then removed and scoring of cutaneous reactions was performed 24 and 48 h after application.

Main study: Induction treatment: 3 times a week for 3 consecutive weeks, 0.5 mL of the undiluted test substance was applied to the skin on the anterior left flank of Dunkin-Hartley Guinea pigs (10 males and 10 females) during 6 hours under occlusive dressing.

The control group (5 males and 5 females) received the vehicle (distilled water) under the same experimental conditions.

Challenge treatment: 10 days after the last induction: 0.5 mL of the test substance at a concentration of 50 % (w/w) (right flank) and 0.5 mL of the vehicle (left flank) were applied to a non-treated area of the posterior region of all animals. Cutaneous reactions were evaluated 24 and 48 hours after the removal of the pads of the challenge application by comparing the reactions on both flanks.

The sensitivity of the guinea-pigs in C.I.T. experimental conditions was checked in a recent study with a positive sensitizer: 2,4-dinitro-1-chlorobenzene. During the induction period, the test substance was applied at concentration from 0.5 to 0.1%. At cutaneous challenge application, 0.5 5 were tested on right flank and paraffin oil on left flank.

The degree of dermal reaction to treatment was scored on a 4-point scale:

Erythema and eschar formation

No response	**0**
Very slight erythema (barely perceptible)	**1**
Well-defined erythema	**2**
Moderate to severe erythema	**3**
Severe erythema (beet redness) t slight eschar formation (injuries in depth)	**4**

Oedema formation

No response	**0**
Very slight oedema (barely perceptible)	**1**
Slight oedema (visible swelling with well-defined edges)	**2**
Moderate oedema (visible swelling raised more than 1 millimeter)	**3**
Severe oedema (visible swelling raised more than 1 millimeter and extending beyond area of exposure	**4**

All other lesions were noted.

II. RESULTS AND DISCUSSION

A. MORTALITY

No deaths were noted during both studies.

B. SKIN REACTIONS

Pre-study: Twenty-four hours after application of the test substance, a yellow colouration of the skin appeared which could mask an eventual erythema at grade 1. No cutaneous reactions were observed at 48 h.

Concentration chosen for the induction phase was 100 % (w/w) and for the challenge application it was 50 % (w/w) due to a yellow colouration of the skin which could mask an eventual erythema at grade 1 (see Table below).

Table 7.1.6-01 EXP 04209 - Skin sensitisation- pre-study results

Sex	Conc. Substance (%)	Number of animals	Flank	Scoring			
				24 h		48 h	
				E	Oe	E	Oe
Males	100	1	Right	C1	0	0	0
			Left	C1	0	0	0
Females	100	1	Right	C1	0	0	0
			Left	C1	0	0	0

E: erythema; Oe: oedema; C1: yellow colouration of the skin which could mask an eventual erythema at grade 1

Main study: No clinical signs and no deaths related to treatment were observed throughout the study. The body weight gain was not influenced by the treatment.

During the induction period very slight (dryness of the skin, erythema grade 1) cutaneous reactions were observed. No cutaneous reactions were observed 24 and 48 hours after the challenge phase (see Table below).

Table 7.1.6-02 EXP 04209 Main-study results: Number of animals with signs of allergic skin reactions.

Treatment	Animals	24 hours				48 hours			
		Erythema		Oedema		Erythema		Oedema	
		LF	RF	LF	RF	LF	RF	LF	RF
Treated group	10 M	0	0	0	0	0	0	0	0
	10 F	0	0	0	0	0	0	0	0
Control group	5 M	0	0	0	0	0	0	0	0
	5 F	0	0	0	0	0	0	0	0

LF: left flank (control); RF: right flank (treated)

C. DEFICIENCIES

None.

III. CONCLUSIONS

Under current evaluation criteria, EXP 04209 (Bandur or Aclonifen 600SC G) was considered not to be a skin sensitiser in guinea-pigs and therefore is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

Assessment and conclusion by applicant: All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

Data Point:	KCP 7.1.6/02
Report Author:	[redacted]
Report Year:	2004
Report Title:	Bandur Evaluation of potential dermal sensitization in the local lymph node assay (LLNA)
Report No:	C042305
Document No:	M-232345-01-1
Guideline(s) followed in study:	OECD: 429; USEPA (=EPA): OPPTS 870.2600
Deviations from current test guideline:	Current Guideline: OECD 429, 2010 No deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

Sixteen female CBA mice were allocated in 4 groups of four animals each in which three groups received the test substance Bandur at the concentration of 5,10 and 20% and one control group received the vehicle (Dimethylsulfoxide= DMSO). The test substance and the vehicle were applied on external surfaces of each ear (i.e. 50 µl/animal) for three consecutive days (days 0, 1 and 2) at concentrations of 5%, 10% and 20%. On day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine and the obtained values were used to calculate proliferation indices.

No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed in the vehicle as well as in the treated groups. The proliferation index values did not increase 3 times over the control values and were 0.7, 1.1. and 1.7 at treatment concentrations of respectively 5%, 10% and 20%

It was concluded that Bandur (Aclonifen 600 SC G) formulation showed no potential for sensitisation under the conditions of the test. Therefore, it was concluded that Bandur is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: Bandur (EXP 10854 B)

Description: Not given

Lot/Batch: OP220331

Purity: Not given

Stability of test compound: Shown to be stable (see MCP2)

2. Vehicle: DMSO

3. Test animals:

Species: Mice

Strain: CBA strain

Age: 8-9 months old

Weight at dosing: Not given

Source: [redacted]

Acclimatisation period: At least 5 days

Diet: Certified rodent pellet diet, A04C-10 from U.A.R. (Usine D' Alimentation Rationelle Villemoisson-sur Orge, France)- *ad libitum*

Water: Filtered and softened tap water-*ad libitum*

Housing: Housed individually in suspended, stainless steel, wire-mesh cages

4. Environmental conditions:

Temperature: 20°C – 24°C

Humidity: 40 to 70% relative humidity

Air changes: 10-15 times/hour

Photoperiod: Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: Date of the report: 12 Jun 2004; Date of experimental work is not indicated.

2. Animal assignment and treatment

Bandur is a Suspension Concentrate; Batch number: OP220331. The theoretical content of active substance aclonifen is 600 g/L.

Dosing formulations were prepared daily by dissolving the test substance in Dimethylsulfoxide (DMSO) to produce the required dosing concentration (w/v).

Sixteen female CBA/IFFA CREDO mice were allocated in four groups of four animals each:

- three groups receiving the test substance at the concentration of 5 %, 10 % and 20 %,

- one control group receiving the vehicle (Dimethylsulfoxide = DMSO),

The test substance and the vehicle were applied to external surfaces of each ear (i.e. 50 µL/animal) for three consecutive days (days 0, 1 and 2) at concentrations of 5 %, 10 % and 20 %. On day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl-thymidine and the values obtained were used to calculate proliferation indices.

II. RESULTS AND DISCUSSION

A. MORTALITY

No deaths were observed during this study.

B. FINDINGS

No systemic clinical signs were observed during the study. No cutaneous reactions were observed in the vehicle and in all treated groups. Negative lymphoproliferative responses (PI < 3) were noted at all tested concentrations.

Table 7.1.6-03 Bandur - local lymph node assay - results of proliferation assay

Compounds	Treatment concentration (%)	Disintegrations per minute (DPM)	Disintegrations per node (DPM)	Proliferation index (PI)
DMSO	-	4610	576	-
Bandur	5	3121	390	0.7
Bandur	10	4889	611	1.1
Bandur	20	7916	990	1.7

C. DEFICIENCIES

None.

III. CONCLUSIONS

Under current evaluation criteria, Bandur (Aclonifen 600SC G) was considered not to be a sensitizing formulation in the Local Lymph Node Assay and therefore is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

Data Point:	KCP 7.1.6/03
Report Author:	[redacted]
Report Year:	2005
Report Title:	Aclonifen SC600 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse
Report No:	SA05215
Document No:	M-259889-01-1
Guideline(s) followed in study:	OECD 429
Deviations from current test guideline:	Current Guideline: OECD 429, 2010 No deviations
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

Twenty-four female CBA/J mice were allocated in 6 groups of four animals each in which four groups received the test substance at the concentration of 10, 25, 50 or 100% in vehicle, one positive control group received 0.25%p-Benzoquinone in 50% Aclonifen SC600 and 50% of aqueous pluronic acid at 1%, and one control group received the vehicle, 1% pluronic acid in water. The mentioned concentrations were chosen based on result of preliminary screening test.

The test substance, aclonifen SC600 and the vehicle were applied on external surfaces of each ear (i.e. 50 µl/animal) for three consecutive days (days 0, 1 and 2) at concentrations of 5%, 10% and 20%. On day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine and the obtained values were used to calculate proliferation indices.

No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed in the vehicle as well as in the treated groups. The proliferation index values were 1.4, 1.8, 2.3 and 1.6 at treatment concentrations of 10, 25, 50 and 100%, respectively. The proliferation index value of the positive control was 5.0 at a treatment concentration of 0.25% of p-Benzoquinone in 50% Aclonifen SC600 and 50% aqueous Pluronic acid at 1%.

Under these test conditions Aclonifen SC600 was found to be non-sensitizing formulation in the Local Lymph Node Assay.

Therefore it is concluded that Aclonifen 600SC G is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test materials: Aclonifen SC 600

Description:	Yellow liquid
Lot/Batch:	V465035144
Purity:	99.6%
Stability of test compound:	Shown to be stable (see MCP2)

2. Vehicle: Pluronic acid

3. Test animals:

Species:	Mice
Strain:	CBA/J strain
Age:	7 weeks old
Weight at dosing:	18.3 g to 19.4 g (mean values)
Source:	[redacted]
Acclimatisation period:	At least 5 days
Diet:	Certified rodent pellet diet, AO4C-10 from S.A.F.E. (Scientific Animal food and Engineering Route de Saint Bris, Augy, France)- *ad libitum*
Water:	Filtered and softened tap water-*ad libitum*
Housing:	Housed individually in suspended, stainless steel, wire-mesh cages

4. Environmental conditions:

Temperature:	20°C – 24°C
Humidity:	40 to 70% relative humidity
Air changes:	10-15 times/hour
Photoperiod:	Day-night rhythm 12 hours (7 a.m.- 7 p.m.)

B. STUDY DESIGN AND METHODS

1. In life dates: 19 August 2005 to 01 September 2005

2. Animal assignment and treatment

The dermal contact sensitisation potential of Aclonifen SC600 containing the active substance aclonifen (batch V465035144) was tested using the murine Local Lymph Node Assay.

Twenty-four female CBA/J mice were allocated to 6 groups of four animals each:

- four groups received the test substance at a concentration of 100, 50, 25 or 10 % in vehicle,

- one positive control group received 0.25 % p-benzoquinone in 50 % Aclonifen SC600 and 50 % pluronic acid at 1 % in water. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive control.

- one control group received the vehicle, 1 % pluronic acid in water.

The test substance, positive control or the vehicle were applied on external surfaces of each ear (50 µL/animal) for three consecutive days (days 0, 1 and 2) at the appropriate concentrations. 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.

II. RESULTS AND DISCUSSION

A. MORTALITY

No deaths were observed during this study.

B. FINDINGS

No systemic clinical signs were observed during the study. No cutaneous reactions were observed in the vehicle and in all treated groups. No significant body weight change. The proliferation index values of the test substance were 1.4, 1.8, 2.3 and 1.6 at treatment concentrations of 10, 25, 50 and 100 % respectively. The proliferation index value of the positive control was 5.0 at treatment concentration of 0.25 % of p-benzoquinone.

Table 7.1.6-04 Aclonifen SC600 – Local lymph node assay -results of proliferation assay

Group number	Test group number	Disintegrations per minute (DPM)	Proliferation index (PI)
1	Control 1% aqueous pluronic acid	309	--
2	Bandur 10% 1% aqueous pluronic acid	439	1.4
3	Bandur 25% 1% aqueous pluronic acid	543	1.8
4	Bandur 50% 1% aqueous pluronic acid	719	2.3
5	Bandur 100%	487	1.6
6	p-denzoquinone 0.25% Bandur 50% and 50% aqueous pluronic acid at 1%	1537	5.0

C. DEFICIENCIES

None.

III. CONCLUSIONS

Under current evaluation criteria, Aclonifen SC600 was considered not to be a sensitizing formulation in the Local Lymph Node Assay and therefore is not classified as a potential dermal sensitiser according to Regulation (EC) 1272/2008.

Assessment and conclusion by applicant:

All validity criteria were satisfied and therefore this study can be considered to be valid.

Assessment and conclusion by RMS:

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 aclonifen or other components in Aclonifen SC 600 G that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since Aclonifen SC 600 G 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 aclonifen when used in the Aclonifen SC 600 G are provided in the following sections.

Acute non-dietary risk assessment is not included in this submission because an AAOEL is not relevant for aclonifen.

The Plant Protection Product Aclonifen SC 600 G containing 600 g/L of aclonifen is intended to be used on peas as an herbicide. Usage information pertinent to the assessment of exposure is summarised in the table below.

Table 7.2-01 Summary of critical uses patterns (i.e. worst case).

Crop (indoor / field)	Application rate (Kg/ha per application)		Spray dilution (L/ha)	Application equipment	Number applications
Peas	0.600 kg as/ha	1 kg product/ha	150-300	Spraying (broadcast, overall	1
Peas	0.300 kg as/ha	1 kg product/ha	100-300	Spraying (broadcast, overall	1

These critical use patterns have been defined following the evaluation of the individual GAPs for the mentioned crop in each relevant Member State. The estimations were based on the dermal penetration values obtained from one comparative *in vitro* dermal penetration study through human and rat skin performed with Aclonifen SC 600 G and a further *in vivo* study through rat skin dermal penetration study is provided as supportive data.

Table 7.2-02 Proposed values for EU endpoints used on the non-dietary human risk assessment.

Endpoints used in risk assessment	Result
Dermal penetration Concentrate (%) Spray dilution (%)	 **2.5** **35***
AOEL (mg/kg body weight/day)	**0.07**

*Pro-rata calculation for the highest in-use dilution from a value of 1.5g/L (tested dilution)

Note Dermal penetration data derived from the results of [redacted] S. 2003, M-232331-01-1. Please refer to section M-CP 7.3 for further detail. Pro-rata calculation for the highest in-use dilution from a value of 1.5g aclofinen/L (tested dilution) was conducted. The AOEL value was derived from NOAEL from 2-year rat supported by the multigeneration study and sub-chronic studies in the rat and applying a safety factor of 100. Please refer to Doc N1 for further detail.

CP 7.2.1 Operator exposure

Operator exposure to Aclonifen SC 600 G was not evaluated as part of the EU review of the active substance aclonifen. Therefore, all relevant data and risk assessments are provided here and are considered adequate. The current EFSA modelling tool on the assessment of exposure of operators, workers, residents, and bystanders, was used to estimate the respective exposures from the application

of Aclonifen SC 600 G on peas. The AOEM calculator released on 30 March 2015 supports the EFSA guidance document[1] that was last updated on 24 April 2015.

CP 7.2.1.1 Estimation of operator exposure

Table 7.2.1-01 Input parameters considered for the estimation of operator exposure for peas (outdoor use).

Formulation type	SC		Crop type	Peas
Application rate (AR)	0.300 0.600	kg a.s./ha	Application method	downward spraying
Minimum water volume (V)	100 150	L/ha	Application equipment	Vehicle-mounted
Area treated per day (A)	50	ha	Indoor/outdoor	Outdoor
Dermal absorption (DA)	2.5	% (concentrate)	Closed cabin	No
	35	% (dilution)	Drift reduction	No
Inhalation absorption (IA) Oral Absorption (%)	100 100	% %	Cultivation	Normal
Body weight (BW)	60	kg/person	Water soluble bag	No
AOEL	0.07	mg/kg bw/d		
AAOEL		mg/kg bw/d		

The input parameter "RVNAS" (Reference value non-acutely toxic active substance) is equivalent to the AOEL value (= 0.07 mg/kg body weight/day, please refer DocN1, 2019). The "RVAAS" (Reference value acutely toxic active substance) was not applied. "DFR" (Dislodgeable foliar residue) was assumed to be 3 µg a.s./ cm^2 /kg a.s./ha. This is a default value and it is assumed as a worst-case scenario for the intended uses of Aclonifen SC 600 G as no specific studies determining this parameter were available. The same principle is applicable to the "DT_{50}" (50% Dissipation Time) which was assumed to be 30 days, assumed as a worst-case scenario by EFSA.

The following sections show the summary results from the calculator. An attached appendix depicts the related full output pages from the calculator.

An AAOEL was not allocated during the peer review for the renewal of approval of aclonifen (EFSA, 2017). Therefore, estimates of acute exposure to workers have not been conducted.

[1] 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)

Table 7.2.1-02 Summary of the assessment of longer-term operator exposure from the use of Aclonifen SC 600 G in peas (outdoor uses).

		Active: aclonifen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% systemic AOEL**
Spraying (broadcast, overall), peas Application rate: 1x 0.300 kg a.s. /ha, 100 L/ha			
Downward spray (AOEM; 75th percentile) Body weight: 60 kg	Potential exposure	0.0334	47.77
	Work wear M/L and A	0.0225	32.13
	Work wear M/L and A + gloves M/L	0.0063	9.00
Spraying (broadcast, overall), peas Application rate: 1x 0.600 kg a.s. /ha, 150 L/ha			
Downward spray (AOEM; 75th percentile) Body weight: 60 kg	Potential exposure	0.0861	122.93
	Work wear M/L and A	0.0559	79.87
	Work wear M/L and A + gloves M/L	0.0283	40.41

The maximum exposure to operators is estimated to be approximately 80% of the RVNAS (AOEL value; 0.07 mg/kg bw/day) when protected workwear is worn. Therefore, the risk to operators from the use of Aclonifen SC 600 G in peas crops is considered acceptable.

Conclusion

According to the AOEM estimations, it can be concluded that the risk for the operator towards long-term use of Aclonifen SC 600 G is acceptable when standard protected workwear is worn (e.g. coveralls and working footwear). The use of gloves is recommended during mixing/ loading and when handling contaminated surfaces.

CP 7.2.1.2 Measurement of operator exposure

Not required as assessments demonstrated safe use using the accepted models. A modelling study (reference KCP 7.2.1.2/01, M-216939-01-1, [redacted], 2003) submitted in the Annex I inclusion dossier was not needed or used.

CP 7.2.2 Bystander and resident exposure

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

Bystanders and residents are not involved in application or 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.

Bystanders 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.

Residents may live or work near areas of the application of plant protection products (e.g. standing, working or sitting in a garden in the 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).

CP 7.2.2.1 Estimation of bystander and resident exposure

Bystanders

Because no AAOEL value has been set bystanders are assumed to be protected by the resident risk assessment.

Residents

The resident exposure assessment was conducted following the EFSA calculator. The common parameters used for resident exposure risk assessment are presented in the Table below.

Table 7.2.2.1-01 Default input parameters considered for the estimation of resident exposure.

Intended use(s)	**Peas (outdoor)**		Drift percentage mean (DR)	4.10 (highest)	%
Application rate (AR)	0.600	kg a.s./ha	Transfer coefficient surface deposits (TC)	7500	cm²/h (adult)
				2250	cm²/h (child)
Minimum water volume (V)	100	L/ha	Drift on surface (D) - 75th perc.		
Buffer strip	2-3	m	Drift on surface (D) - mean		
Number of applications (NA)	1		Turf Transferable Residues (TTR)		
Interval between applications	365	days	Exposure duration dermal (H_D)		
The half-life of active substance	2	days	Exposure duration inhal. (H_I)		
Multiple application factor (MAF)			Exposure duration entry into treated crops (H_E)		
Body weight (BW)	60	kg/person (adults)	Airborne Concentration		

	10	kg/person (children)	of Vapour (VC)		
Dermal absorption (DA)	35	% ('worst case')	Dislodgeable foliar residue (DFR) from model	1.8 (highest)	µg/cm²/kg a.s.
Inhalation absorption (IA)	100	%	Light clothing adjustment factor (CF)	18	%
Oral absorption (OA)	100	%	Saliva Extraction Factor (SE)	50	%
AOEL	0.07	mg/kg bw/d	Surface Area of Hands (SA)	20	cm²
Spray drift dermal (SD) - 75th perc.	0.47	mL spray dilution (adult)	Frequency of Hand to Mouth (Freq)	9.5	events/h
	0.327	mL spray dilution (child)			
Spray drift inhal. (SI) - 75th perc.	0.00010	mL spray dilution (adult)	Dislodgeable residues object to mouth (DR_{OM})	20	%
	0.00022	mL spray dilution (child)			
Spray drift dermal (SD) - mean	0.22318	mL spray dilution (adult)	Ingestion Rate for Mouthing of Grass (IgR)	25	cm²/d
	0.18	mL spray dilution (child)			
Spray drift inhal. (SD) - mean	0.00009	mL spray dilution (adult)	TC entry into treated crops - 75th perc.	7500	cm²/h (adult)
	0.00017	mL spray dilution (child)		2250	cm²/h (child)
Inhalation rate (IR)	0.23	m³/d /kg (adult)	TC entry into treated crops - mean:	5980	cm²/h (adult)
	1.07	m³/d /kg (child)		1794	cm²/h (child)

Based on the above parameters, the total systemic exposure for residents is shown in the Tables below.

Table 7.2.2.1-02 Estimation of resident exposure from the use of Aclonifen SC 600 G in peas (outdoor uses).

Model data	**Level of PPE**	**Active: aclonifen**	
		Total absorbed dose (mg/kg bw/day)	**% systemic AOEL**
Spraying (broadcast, overall), peas Drift reduction technology: No (default values DT_{50} = 30 days and Initial DFR: 3 µg/cm²/kg a.s./ha) Interval between treatments:1 day Buffer strip: 2-3 meters			
Number of applications and application rate:		1 x 0.6 Kg a.s./ha	
Resident child	Drift (75th perc.)	0.0250	35.77

Body weight: 10 Kg	Vapour (75th perc.)	0.0011	1.53
	Deposits (75th perc.)	0.0015	2.08
	Re-entry (75th perc.)	0.0354	50.63
	Sum (mean)	0.0443	63.28
Resident adult Body weight: 60 kg	Drift (75th perc.)	0.0046	6.51
	Vapour (75th perc.)	0.0002	0.33
	Deposits (75th perc.)	0.0006	0.84
	Re-entry (75th perc.)	0.0197	28.13
	Sum (mean)	0.0187	26.77

It is expected that the risks to residents is acceptable when Aclonifen SC 600 G is applied under the worse-case field conditions (e.g., buffer zone- 2 to 3 meters) to peas crops according to the supported GAP.

Conclusion
According to the EFSA model estimations, it can be concluded that the risk for residents (children and adults) towards long-term use of Aclonifen SC 600 G is acceptable

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 aclonifen following application of Aclonifen SC 600 G formulation for the representative use on crop. The estimation is provided in the following sections.

CP 7.2.3.1.1 Estimation of worker exposure

For peas, the main re-entry activity after treatment is related to maintenance and/or reaching/picking. The common parameters used for worker exposure risk assessment are presented in the Table below. The indicative transfer coefficient values from EFSA calculator for dermal exposure, are presented in the table below and are considered for the worker exposure risk assessment (first-tier assessment) following the use of the product in peas crops.

Table 7.2.3.1.1-01 Common parameter considered for the estimation of worker exposure from the use of Aclonifen SC 600 G.

Intended use(s)	**Outdoor activities**		Dislodgeable foliar residue (DFR)	3	µg/cm²/kg a.s./ha
Application rate (AR)	0.6	kg a.s./ha	Dermal absorption (DA)	35	% (worst case)
Number of applications (NA)	1		Inhalation absorption (IA)	100	%

Interval between applications	365	days	Work rate per day (WR)	8	h/d
Half-life of active substance	30	days	TC dermal (potential)	5800	cm^2/h
Multiple application factor (MAF)	1		TC dermal (work wear)	2500	cm^2/h
Body weight (BW)	60	kg/person	TC dermal (work wear, gloves)	580	cm^2/h
AOEL	0.07	mg/kg bw/d	Task specific factor inhalation (TSF)	n/a	ha/h x 10^{-3}

Aclonifen shows a low vapour pressure of 1.5 x 10^{-4} Pa. Therefore, contamination of workers through inhalation of aclonifen in open field activities was considered negligible and consequently not used in the calculations.

An AAOEL is not allocated for the approval of aclonifen (EFSA, 2008). Therefore, estimates of acute exposure to workers have not been conducted.

Table 7.2.3.1.1-02 Estimation of longer-term worker exposure from the use of Aclonifen SC 600 G in peas.

		Active: aclonifen	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% systemic AOEL**
Task: reaching and picking, peas MAF: 1.0 Work rate: 8 hours/day (default values DT_{50}= 30 days and Initial DFR: 3 µg/cm²/kg a.s./ha) Interval between treatments: 365 days			
Number of applications and application rate:		1 x 0.6 Kg a.s./ha, 100 L/ha	
Body weight: 60 kg	Workwear (arms, body, and legs covered) TC: 5800 cm²/person/h	0.2100	300.00
	Workwear (hands, arms, body, and legs covered) TC: 2500 cm²/person/h	0.0487	69.60

For the use of Aclonifen SC 600 G in peas, workers will be involved in reaching and picking activities at the time of harvest. In this case, systemic exposure is estimated to be approximately 70% of the AOEL based on normal use of workwear and gloves. Therefore, the risks to workers from exposure to Aclonifen SC 600 G is considered acceptable. Also, the inhalation of aclonifen in open field activities was considered negligible.

CP 7.2.3.1.2 Measurement of worker exposure

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

CP 7.3 Dermal absorption

Summary of dermal absorption

Two dermal absorption studies were available, comprising an *in vivo* rat study and a comparative *in vitro* study using human and rat skin. The EFSA guidance on dermal absorption 2017 (section 3.1) allows for the provision to base the dermal absorption value on the results of one well conducted *in vitro* study through human skin; therefore, only the comparative *in vitro* study through human skin has been used to calculate the final dermal absorption values for the concentrate and the aqueous dilution. This study was found to be well-conducted, of enough quality and has been re-evaluated to the requirements of the EFSA 2017 guidance.

The *in vivo* rat study is not relevant for the derivation of the final dermal absorption value for aclonifen and therefore has been included in the dossier as supplementary information and not considered relevant for renewal approval.

Summary of dermal absorption values (according to 2017 EFSA guidance)

Aclonifen content	*in vitro* dermal absorption study [redacted] (2003) M-232331-01-1		*in vivo* dermal absorption study [redacted] (2003) M-232328-01-1
	Human skin	Rat Skin	Rat skin
600 g/L:	2.5%	5.3%	10%
1.5 g/L:	23%	70%	41%

The necessary adjustments have been made to the data evaluation in this summary to comply with the 2017 EFSA guidance. Overall, the estimated amount of aclonifen considered to be absorbed from the concentrate and aqueous spray dilution was 2.5 % and 23% of the total applied dose, respectively.

Pro-rata adjustment

For spray dilutions lower than 1.5g/L aclonifen a pro-rata adjustment should be made in accordance with the 2017 EFSA guidance on dermal absorption.

The highest dilution rate for use in field peas is a 1 in 600 dilution (1g/L aclonifen) (assuming a maximum application rate of 0.5 kg/ha aclonifen in a maximum water volume of 300L/ha). The tested dilution was a 1 in 400 dilution (1.5 g/L aclonifen).

Pro-rata adjustment calculation from a 1 to 400 dilution to a 1 in 600 dilution = 23 x 600/400 = 34.5% (rounded to 35%).

The dermal absorption of aclonifen in a 1g/L dilution is 35%. This value is used as the most conservative value for the operator exposure calculations for the spray dilutions.

The data for the rat is presented for information only but was not used for the calculations of dermal absorption values.

***In vivo* dermal absorption study**

Data Point:	KCP 7.3/01
Report Author:	[redacted]
Report Year:	2003
Report Title:	In vivo dermal absorption study in the male rat (14C)-Aclonifen
Report No:	C032940
Document No:	M-232328-01-1
Guideline(s) followed in study:	OECD: 417 (1984), Draft doc. 5 (2000 + 2002)
Deviations from current test guideline:	Current Guideline: OECD 427, 2004 No significant deviations. EFSA dermal absorption guideline 2017 - study not evaluated to current EFSA guidance on dermal absorption so needs to be re-evaluated to the current guidance.
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary

The percutaneous absorption of aclonifen was evaluated following dermal application of EXP04209E (Bandur®) to male rats (Sprague-Dawley, Crl:CD®BrR strain, n=5) at two dose levels, i.e., a nominal 600 g aclonifen/L and a diluted formulation (low level: 1.5 g/L).

The doses were applied on the skin at a rate of 120 µl formulation over an area of *ca* 3x 4 cm of shaved skin using a positive displacement pipette. At 8 hours after dose application, the treated area of skin was washed, to remove non-absorbed dose. The swabs were taken for analysis. Urine and faces were collected during the study. At sacrifice the treated skin was washed again to remove any remaining dose. The treated skin was then removed for analysis (tape stripping was not conducted). The main study involved three groups of five male rats at each dose level. The duration of exposure was 8 hours and a group of animals was sacrificed 8, 24, and 72 hours after dose application. The radioactivity was measured in all animal samples by liquid scintillation analysis.

Originally, this study was not fully evaluated according to the 2017 EFSA Guidance on dermal absorption therefore it is not relevant to the derivation of the dermal absorption values of aclonifen, which is based solely on a comparative *in vitro* study through human skin (as recommended in the EFSA 2017 guidance on dermal absorption). Therefore, the study summary has been submitted in the dossier for transparency reasons, but it was not considered relevant for renewal approval.

Using the new EFSA guidance 2017 the dermal absorption is 41% for the dilution (1.5g/L aclonifen) and 10% for the concentrate (600 g/L aclonifen).

I. MATERIALS AND METHODS

A. MATERIALS

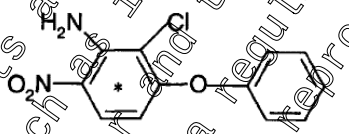
1. Test material (non-radiolabelled): Alonifen (formulated as EXP04209E, Bandur)

Description:	Yellow solid
Lot/Batch:	BES1572 and 2250019
Purity:	996 g/kg
Stability of test compound:	April 2008. Non-radiolabeled formulation shown to be stable (see MCP2)

2. Husbandry:

Temperature:	21±2 °C
Humidity:	4-0-70%
Photocycle:	Alternating 12 hour light/dark
Air changes:	Approximately 15 per hour
Diet:	Pelleted laboratory rodent diet (VRFIC, Batch n. 20723, Charles River UK Ltd.) - *ad libitum*
Water:	Tap water- *ad libitum*

3. Test material (labelled):



* Denotes position of ^{14}C-radiolabel

Lot/Batch:	OR1765 (radiolabeled aclonifen); 0131JCZ02 (formulated product concentrate); 012JCZ02 (formulated product as aqueous dilution)
Concentration:	600 g Aclonifen/L (conc.) 1.5 g aclonifen/L (dil.)
Specific activity:	8.24 MBq/g formulation (conc.); 5.70 MBq/g formulation (dil)
Purity:	> 97% (radiochemical purity)

4. Test skin:

Species:	Rat
Strain:	Sprague-Dawley (Crl:CD®BrR)
Sex and sex of donors:	male
Site of skin samples:	Skin on dorsal area of trunk
Body weights:	184 -239 g
Source:	[redacted]

B. STUDY DESIGN AND METHODS

1. In life dates: 17 October 2002 to 14 February 2003

2. Animal assignment and treatment

The rate and extent of absorption of radioactivity following dermal application of the herbicide aclonifen has been studied using a [14C]-aclonifen formulation, EXP04209E (BANDUR®). [14C]-aclonifen was administered (120 µL) in a concentrate formulation (high level; 600 g/L), and a diluted formulation (low level; 1.5 g/L).

The absorption process was monitored using [^{14}C]-aclonifen, which was incorporated into the dose preparations prior to application. Animals were dosed at a rate of 120 µl formulation over an area of *ca* 3x 4 cm of shaved skin using a positive displacement pipette. The treated area was protected by a plastic saddle attached by adhesive dressing to prevent loss and disturbance. The cover was not in contact with the treated area so that the area was open to air. At 8 hours after dose application, the treated area of skin was washed, with cotton wool swabs soaked in Tween 80 (1% v/v) in aqueous sodium chloride (0.9 g/L) to remove non-absorbed dose. The swabs were taken for analysis. The protective plastic saddle was kept in place over the treated area and animals were then returned to the cages until be taken for measurement of radioactivity after sacrifice. Urine, blood and faeces were collected separately from each animal for measurement of radioactivity. At sacrifice the treated area of skin was washed with cotton swabs in Tween 80 (1% v/v) in aqueous sodium chloride (0.9 g/L) to remove any remaining dose. The treated area of skin was the removed and taken for analysis (tape stripping was not conducted). Two further skin samples were also taken for analysis, namely the area (~1 cm wide) immediately surrounding the treated site and a control sample. Dressing and covers removed from the animals were retained and taken for analysis.

The study involved three groups of five male rats at each dose level. The duration of exposure was 8 hours and a group of animals was sacrificed 8, 24, and 72 hours after dose application.

The radioactivity was measured in all animal samples by liquid scintillation analysis using Wallac 1409 automatic liquid scintillation counters ([redacted]). Th radiochemical purity of 14C-aclonifen in all dose formulations was determined by high performance liquid chromatography (HPLC) and, for the preliminary study only, by thin-layer chromatography (TLC).

3. Analytical techniques

Liquid scintillation counting (LSC) conditions were:

Sampling:	at least duplicate
Units	dpm/g
Counting period:	4 minutes or until 900,000 counts
Scintillation fluid:	Wallac Oy 1409

II. RESULTS AND DISCUSSION

A. FINDINGS

The distribution of radioactivity 72 hours after dermal application (expressed as % of dose administered) is given in Table below.

At the low level about 33.04 % of the applied dose was absorbed. At the high level only 1.71 % of the applied dose was absorbed.

The treated skin at the application site contained 4.54 % and 3.87 % of the applied dose at low and high dose levels respectively. Based on the information of [14C]-aclonifen distribution in the skin obtained in the preliminary study (see study report for details) it is assumed that about 1 % of the dose in the treated skin is still available for absorption.

Table 7.3-1 Dermal absorption in the rat- Distribution of radioactivity 72 hours after dermal application- main study.

Sample	Dilute formulation (% of dose)	Concentrate formulation (% of dose)
Urine	16.31 ± 1.81	0.72 ± 0.24
[redacted] wash	1.71 ± 0.65	0.14 ± 0.03
Faeces	14.55 ± 2.98	0.58 ± 0.23
Carcass	0.47 ±0.07	0.30 ± 0.50
Total absorbed	33.04 ± 2.39	1.71 ± 0.50
Treated skin (fur, stratum corneum and epidermis)	4.54 ± 0.43	3.87 ± 1.44
Skin surrounding dose site	0.15 ± 0.06	0.63 ± 0.57
Dose site swabs		
8 hours	53.14 ± 6.61	82.87
Sacrifice [a]	5.21 ± 1.74	5.40 ± 2.67
Total recovery	96.07 ± 5.53	94.48 ± 1.91

[a] Taken at sacrifice and includes saddle and bandages.

The total absorbed dose can be calculated to be 33.04 + 1 % = 34.04 %, assumed to be conservatively at 35 % for diluted formulation. Following the same approach for concentrate, total absorbed dose is 1.71 + 1 % = 2.71 %, conservatively approximated to 3 %.

The table below shows the dermal absorption calculated using the new EFSA guidance 2017. These give a dermal absorption of 41% for the dilution (1.5g/L aclonifen) and 10% for the concentrate (600 g/L aclonifen).

Study Evaluated to new EFSA guidance 2017

Table 7.3-2 Dermal absorption of aclonifen in rats - sacrificed 72 hours after dose application

IN VIVO STUDY	Concentrate		Dilution 1	
Dilution	None		(1:400)	
Number of replicates	5		5	
Target concentration [mg/mL]	600		1.5	
Target dose [µg/cm2]	6180		15	
Mean actual applied dose [µg/cm2]	6180		14.7	
Recovery [% applied dose]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 hrs	82.87	3.14	53.14	6.61
Skin wash at sacrifice	2.55	0.95	4.20	1.64
Skin covering	2.85	2.12	1.00	0.18
Total dislodgeable dose	**88.26**	**1.10**	**58.348**	**5.90**

Skin associated dose				
Treated skin[a]	3.87	1.44	**4.54**	**0.43**
Skin surrounding dose site	0.63	0.57	**0.15**	**0.06**
Total skin associated dose	**4.50**	**1.84**	**4.684**	**0.456**
Absorbed dose				
Urine	0.72	0.24	**16.31**	**1.81**
Cage wash	0.11	0.03	**1.71**	**0.65**
Faeces	0.58	0.23	**14.55**	**2.98**
Carcass	0.30	0.05	**0.47**	**0.07**
Blood	ND	ND	ND	ND
Total absorbed dose	**1.71**	**0.50**	**33.04**	**2.39**
Total recovery	**94.48**	**1.91**	**96.07**	**5.53**
LLC of t_0.5 absorption	not relevant		not relevant	
Number of replicates	5		5	
Absorption complete?	NA	NA	NA	NA
Measured absorption, if LLC of t_0.5<=75%[b]	6.21	1.97	37.73	2.51
Measured absorption, if LLC of t_0.5>75%[c]	NA	NA	NA	NA
Measured absorption corrected (total absorbed in treated skin and surrounding site) with normalisation and missing data added where relevant	7.78	2.12	37.73	2.51
Relevant absorption estimate (adjusted for *k x SD*)	10.32		40.74	
Final estimate (rounded)	**10**		**41**	

ND = not detected
NA = not applicable
SD = standard deviation
K = 1.2
a: sum of treated skin, surrounding skin and control skin
b: sum of directly absorbed radioactivity and the radioactivity found in the skin.
c: The tape strips were not performed in the main study and therefore cannot be subtracted from the potentially absorbable value.

B. DEFICIENCIES

Originally, this study was not fully evaluated according to the 2017 EFSA Guidance on dermal absorption, therefore the dermal absorption has been recalculated to the current guidance.

III. CONCLUSIONS

The study calculated the absorption of [14C]-aclonifen in the male rat following a single dermal application of the formulation EXP04209E (BANDUR®) was lower than 35 % of the applied dose

at the low level (equivalent to operator exposure level during application) and lower than 3 % of the applied dose at the high dose level (equivalent to operator exposure level during mixing and loading).

Using the new EFSA guidance 2017 the dermal absorption was recalculated as 41% for the dilution (1.5g/L aclonifen) and 10% for the concentrate (600 g/L aclonifen).

Assessment and conclusion by applicant:

The *in vivo* rat study is not relevant for the derivation of the final dermal absorption value for aclonifen and therefore has been included in the dossier as supplementary information and not considered relevant for renewal approval. The original study was not conducted to the current EFSA guidelines on dermal absorption therefore in this summary the data has been re-calculated to the new 2017 EFSA guidance on dermal absorption.

The study used same formulation as in the *in vitro* study ([redacted] 2003, M-232231-01-1), the same dilution, the same strain of rats, and the same washing technique and same exposure period.

Using the new EFSA guidance 2017 the dermal absorption was recalculated as 41% for the dilution (1.5g/L aclonifen) and 10% for the concentrate (600 g/L aclonifen).

Assessment and conclusion by RMS:

Data Point:	KCP 7.3/02
Report Author:	[redacted]
Report Year:	2003
Report Title:	Comparative in vitro dermal penetration study using human and rat skin (14C)-Aclonifen
Report No:	C032941
Document No:	M-232231-01-1
Guideline(s) followed in study:	-
Deviations from current test guideline:	Current Guideline: OECD 428, 2004 2 human donors were used for the skin samples for the concentrate and dilution, which is below the recommended number of 4, but does not invalidate the study. EFSA dermal absorption guideline 2017 - study evaluated to the 2012 EFSA guidance on dermal absorption so needs to be re-evaluated to the current guidance.
Previous evaluation:	yes, evaluated and accepted Source: [redacted]
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

***in vitro* dermal absorption study**

Executive Summary

The percutaneous absorption of aclonifen, formulated as Bandur (containing 600 g/L aclonifen) was evaluated in two groups of human (male/female) and male rats using two target dose levels: a low dose (1.5 g/L), corresponding to one in-use application rate of the product, and a high dose (600 g/L), equivalent to the commercially supplied concentrate.

Flow-through diffusion cells were prepared for each skin type at each dose level. Dermatomed membranes (approximately 300 µm thickness) were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested in tritiated water ($^3H_20$). After removal of residual $^3H_20$, the [14C]-Aclonifen was applied to the unoccluded skin samples at the rate of 10 µl/cm^2.

The skin samples were exposed to the test material for 8 hours, then remaining dose was washed off the skin. Receptor fluid samples were collected at hourly intervals for the duration of 24 hours. The solubility of aclonifen in the receptor fluid was demonstrated to be sufficient for the study and not to be rate limiting to the absorption process. At the end of the study, the skin samples were tape stripped to remove residual surface dose and the stratum corneum.

Radioactivity was measured by Liquid Scintillation Counting (LSC).

By 24 hours after application, the total amount of radioactive material absorbed was 3.02 times greater for rat skin than for human skin at the high dose level, and 5.95 times greater for rat skin than human skin following application of the low dose. The results also indicated that the rat is over-predictive of the dermal penetration of aclonifen in man.

The necessary adjustments have been made to the data evaluation in this summary to comply with the 2017 EFSA guidance. Overall, the estimated amount of aclonifen considered to be absorbed from the concentrate and aqueous spray dilution was 2.5 % and 23% of the total applied dose, respectively.

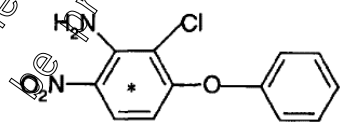
I. MATERIALS AND METHODS

A. MATERIALS

1. Test material (non-radiolabelled): Aclonifen (formulated as Bandur)

Description:	Yellow solid
Lot/Batch:	OP 2250019
Purity:	920 g/kg
Stability of test compound:	Jan 2003. Non-radiolabeled formulation shown to be stable (see MCP2)

2. Test material (labelled):



* Denotes position of ^{14}C-radiolabel

Lot/Batch:	Batch SEL/1202
Concentration:	600 g Aclonifen/L (conc); 1.5 g aclonifen/L (dil.)
Specific activity:	7.51 MBq/mg

Purity:	> 99%

3. Rat skin:

Species, strain:	Rat, Sprague-Dawley CD
Source:	[redacted]
Sex:	Male.
Number:	8 rats, three donors for the concentrate, 5 donors for the dilution
Anatomical site:	Dorsal
Skin Preparation:	Each animal was killed by cervical dislocation or overdose with carbon dioxide. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of *ca* 300 to 400 µm in thickness.

4. Human skin:

Source: [redacted]

Number and sex: 2 donors, one male, one female.
Anatomical region: male abdomen, female back.

Thickness: dermatomed to 300 to 400 µm.

5. Receptor fluid:

Phosphate buffered saline, supplemented with Bovine Serum

Albumin (5% w/v), adjusted to pH 7.4.

B. STUDY DESIGN AND METHODS

1. In life dates: 14 Jun 2002 to 17 February 2003

2. Animal assignment and treatment

The rate and extent of absorption was investigated following topical application of the herbicide aclonifen to excised human and rat skin in an emulsifiable concentrate formulation (trade name BANDUR), at two dose concentrations, a high level of 600 g/L, equivalent to the commercially supplied concentrate, and a low level of 1.5 g/L, corresponding to one in-use application rate of the product.

Flow-through diffusion cells were used, with a flow-rate of 1.5 mL/hr allowed approximately 6 receptor chamber content changes per hour.

Dermatomed membranes (approximately 300 to 400 µm thickness) were maintained in the cells at approximately 32 °C. The integrity of the membranes was first tested using tritiated water ($3H_2O$). After removal of the residual ^3H_2O, the [^{14}C]-Aclonifen was applied to the unoccluded skin samples at a rate of 10 µL/cm2 to an exposure area of 0.64 cm^2 skin (6.4 µL dose volume).

The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid samples were collected at hourly intervals for the duration of the study (24 hours). The solubility of aclonifen in the receptor fluid was demonstrated to be sufficient for the study and not to be rate limiting to the absorption process. At the end of the study, the skin samples were tape stripped to remove residual surface dose and the stratum corneum.

II. RESULTS AND DISCUSSION

A. FINDINGS

The amount of radioactivity recovered in the receptor fluid at the end of the study and the amount of radioactivity remaining in the skin after tape stripping was considered the absorbed fraction. The amount recovered in the skin swabs, in surface tape strips and in the stratum corneum was considered non-absorbed.

The distribution patterns of radioactivity following the application of high and low dose level formulations (nominally 600 g/L and 1.5 g/L respectively) to human and rat skin were broadly similar at each dose level.

The distribution of radioactivity can be summarised as follows, expressed as percent of applied dose of radio-labelled material.

Table 7.3-4 Dermal absorption *in vitro*- Distribution of radioactivity after 24 hours.

Group		**1**	**2**	**3**	**4**
Dose Level		**High**	**High**	**Low**	**Low**
Species		**Human**	**Rat**	**Human**	**Rat**
TOTAL ABSORBED					
Receptor fluid	%	0.095	0.209	4.654	23.87
Skin	%	0.076	0.309	1.893	15.10
Total	%	0.172	0.519	6.547	38.97
TOTAL NON-ABSORBED					

Skin surface (Skin swabs + surface tape strips)	%	96.09	96.03	79.75	35.72
Stratum corneum	%	1.225	3.282	8.480	24.94
Remaining on cell (Donor + receptor chambers)	%	2.353	0.840	2.976	0.484
Total	%	99.67	100.1	91.21	61.14
TOTAL RECOVERY	%	99.85	100.7	97.76	100.1

Rat skin was more permeable than human skin following application of either high or low dose.

The total absorbable dose over 24 hours was calculated as the sum of the amount in the remaining skin (absorbable at 24 hours) and that present in the receptor fluid (cumulative amount absorbed by 24 hours) and was 0.172 % and 0.519 % for human and rat skin respectively following application of the aclonifen high level dose, and 6.547 % and 38.97 % for human and rat skin respectively following application of the low dose formulation. The total amount of material absorbed is therefore 3.02 times greater for rat skin than for human skin at the high dose level, and 5.95 times greater for rat skin than human skin following application of the low dose.

The estimated steady-state absorption rate for [^{14}C]-aclonifen (measured between 7 and 24 hours after application) was 2.38 times faster through rat skin than human skin for the high dose, and 6.40 times faster for the low dose.

The group mean distributions of radioactivity are summarise in the following table.

Table 7.3-5 Group mean distributions of radioactivity for concentrate and diluted aclonifen formulation.

Group number **Dose levels** **Species**	**1** **High** **Human**	**2** **High** **Rat**	**3** **Low** **Human**	**3** **Low** **Rat**
Total % Absorbed	0.172	0.519	6.547	38.97
Total % Non-absorbed	99.67	100.1	91.21	61.14
Total % Recovered	99.85	100.7	97.76	100.1
Absorption rate (ng/cm²/hr)	304.1	724.7	35.03	224.1

B. RECALCULATIONS

Originally, this study was not evaluated according to the new EFSA Guidance on dermal absorption (2017). The following tables summarize the data as prepared in accordance with the EFSA guidance (2017) (using the accompanying spreadsheet). The calculations consider the main requirements of the guidance, including whether or not absorption is complete, tape stripping procedures and rounding of values. Please see Appendix 2 for the original calculations.

Table 7.3-6 Human skin: A summary of the total amount of aclonifen absorbed (% applied dose) in human skin from the concentrate and the aqueous spray dilution after 24 hours- according to the BfR template.

	Concentrate	Dilution 1
Dilution	N/A	(1:400)

Number of replicates	7		7	
Target concentration [mg/ml]	600		1.5	
Target dose [µg/cm²]	6000		15	
Mean actual applied dose [µg/cm²]	5810		14.41	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 hours	94.10	1.94	68.32	10.35
Donor chamber wash	2.24	1.91	2.98	1.98
Skin-associated dose				
Tape strips 1-2	2.00	0.81	11.43	5.07
Tape strips 3x	1.23	1.13	8.48	6.28
Skin preparation	0.08	0.03	1.89	1.07
Absorbed dose				
Receptor fluid	0.10	0.05	4.65	2.86
Receptor chamber wash	0.11	0.16	0.00	0.00
Total recovery	**99.85**	**0.71**	**97.76**	**4.68**
LLC of t_0.5 absorption	0.74	0.54	0.01	0.02
Is absorption complete?	No		No	
Measured absorption, if LLC of t_0.5 ≤ 75%	1.51	1.10	15.03	9.19
Measured absorption, if LLC of t_0.5 > 75%	N/A	N/A	N/A	N/A
Measured absorption corrected	1.51	1.10	15.03	9.19
Relevant absorption estimate	2.523		23.481	
Final estimate (rounded)	**2.5**		**23**	

Note: receptor fluid values at 12 hrs not available but graphs of absorption over 24 hrs show it is not 75% complete at 12hrs (dummy low values for T0.5 have been entered in the tables to ensure the tape strips are included in the absorbed dose).

Table 7.3-7 Rat skin: A summary of the total amount of aclonifen absorbed (% applied dose) in rat skin from the concentrate and the aqueous spray dilution after 24 hours- according to the BfR template.

	Concentrate		Dilution 1	
Dilution	N/A		(1:400)	
Number of replicates	7		9	
Target concentration [mg/mL]	600		1.5	
Target dose [µg/cm²]	6000		15	
Mean actual applied dose [µg/cm²]	5810		14.41	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after 8 hours	94.04	2.63	29.86	5.15
Donor chamber wash	0.84	0.34	0.45	0.14
Skin associated dose				
Tape strips 1-2	1.98	0.81	5.86	3.14
Tape strips 3-x	3.28	1.66	24.94	9.74
Skin preparation	0.31	0.13	15.10	4.23
Absorbed dose				
Receptor fluid	0.21	0.12	23.87	6.82
Receptor chamber wash	0.00	0.00	0.03	0.04

Total recovery	**100.67**	**1.40**	**100.12**	**3.94**
LLC of t_0.5 absorption	0.25	0.43	0.00	0.00
Absorption complete?	No		No	
Measured absorption, if LLC of t_0.5<=75%	3.80	1.68	63.94	7.95
Measured absorption, if LLC of t_0.5>75%	N/A	N/A	N/A	N/A
Measured absorption corrected	3.80	1.68	63.94	7.95
Relevant absorption estimate	5.342		70.062	
Final estimate (rounded)	**5.3**		**70**	

Note: receptor fluid values at 12 hrs not available but graphs of absorption over 24 hrs show it is not 75% complete at 12hrs (dummy low values for T0.5 have been entered in the tables to ensure the tape strips are included in the absorbed dose)

According to the new EFSA guidance[2] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met by any of the dose groups in this study. There is also the provision that a standard deviation should be added to the mean (adjusted with a multiplication factor *k* according to the number of replicates. Additionally, where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. The application of the guidance results in the following values for [^{14}C]-aclonifen in the ACL SC 600 formulation:

Human skin		Rat Skin	
600 g/L:	2.5%	600 g/L:	5.3%
1.5 g/L:	23%	1.5 g/L:	70%

III. CONCLUSIONS

In this well-conducted GLP and guideline compliant *in vitro* study, using the formulation aclonifen SC 600 g/L, evaluated according to the 2017 EFSA guidance on dermal absorption, the dermal absorption of aclonifen through human skin was 2.5% in the concentrate (600 g/L aclonifen) and 23% in the spray dilution (1.5g/L aclonifen).

In rat skin the dermal absorption of aclonifen was 5.3% in the concentrate (600 g/L aclonifen) and 70% in the spray dilution (1.5g/L aclonifen).

Assessment and conclusion by applicant:

[2] EFSA; Guidance on Dermal Absorption. EFSA Journal 2017;15(6):4873

All validity criteria were satisfied and therefore this study can be considered to be valid. The necessary adjustments have been made to the data evaluation in this summary to comply with the 2017 EFSA guidance. Overall, the estimated amount of aclonifen considered to be absorbed from the concentrate and aqueous spray dilution was 2.5 % and 23% of the total applied dose, respectively.

For spray dilutions lower than 1.5g/L aclonifen a pro-rata adjustment should be made in accordance with the 2017 EFSA guidance on dermal absorption.

The highest dilution rate for use in field peas is a 1 in 600 dilution (1g/L aclonifen) (assuming a maximum application rate of 0.5 kg/ha aclonifen in a maximum water volume of 300L/ha).

The dermal absorption of aclonifen in a 1g/L dilution is 35%. This value is used as the most conservative value for the operator exposure calculations for the spray dilutions.

The data for the rat is presented for information only but was not used for the calculations of dermal absorption values.

Assessment and conclusion by RMS:

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information – data provided separately (Document MCP).

Appendix 1 Exposure calculator output

Appendix 1.1 Operator exposure for Aclonifen SC600G outdoor spray application in peas crops.

Operator exposure for outdoor spray applications

Application rate of active substance	0.3	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	15	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	2.50%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	35.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	39062	146484	AOEM	
	Body	23935	153834	AOEM	
	Head	778	4268	AOEM	
	Protected hands (gloves)	201	2972	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	262	4194	AOEM	
	Protected head (hood and face shield)	12	242	AOEM	
	Inhalation	7	107	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	941	4836	AOEM	
	Body	193	197	AOEM	
	Head	8	16	AOEM	
	Protected hands (gloves)	14	74	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	7	8	AOEM	
	Inhalation	4	6	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Potential exposure		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	2.0065	2.0065	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0334	0.0334	
% of RVAAS	47.77%	47.77%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	9.2643	9.2643	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.1544	0.1544	
% of RVAAS	#DIV/0!	#DIV/0!	

Operator exposure for outdoor spray applications

Application rate of active substance	0.6 kg a.s./ha		*i_AppRate*
Assumed area treated	50 ha/day		*d_AreaTreated*
Amount of active substance applied	30 kg a.s./day		*i_AmoutAS*
Dermal absorption of the product	2.50%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	35.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

OutdoorSoluble concentrates, emulsifiable concentrate, etc.Downwardspraying Vehicle-mounted

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	66603	251478	AOEM	
	Body	38962	194812	AOEM	
	Head	1557	4539	AOEM	
	Protected hands (gloves)	315	5942	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	484	4369	AOEM	
	Protected head (hood and face shield)	25	483	AOEM	
	Inhalation	70	319	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Application	Hands	4422	27671	AOEM	
	Body	2488	13825	AOEM	
	Head	118	355	AOEM	
	Protected hands (gloves)	266	4955	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	68	167	AOEM	
	Inhalation	6	21	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	No			
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	Yes		vehicle mounted upward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	5.1633	3.3544	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0861	0.0559	
% of RVNAS	122.93%	79.87%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	25.6867	16.5292	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.4281	0.2755	
% of RVAAS	#DIV/0!	#DIV/0!	

Appendix 1.2 Worker exposure for Aclonifen SC600G outdoor spray application in peas crops.

Worker exposure from residues on foliage for		
Crop type	Fruiting vegetables	
Indoor or outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Worker's task	Reaching/Hoeing	
Main body parts in contact with foliage	Hand and body	
Application rate of active substance	0.6	kg a.s./ha
Number of applications	1	
Interval between multiple applications	365	days
Half-life of active substance	30	days
Multiple application factor	1.0	
Dermal absorption of the product	2.50%	
Dermal absorption of the in-use dilution	25.00%	
Dislodgeable foliar residue (i_AppRate*i_DFR)	1.8	µg a.s./cm²
Working hours	8	hr
Dermal transfer coefficient - Total potential exposure	4300	cm²/hr
Dermal transfer coefficient - arms, body and legs covered	2500	cm²/hr
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm²/hr
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves
Total systemic exposure (mg a.s./day)	29.0320	12.6000	2.9232
Total systemic exposure per kg body weight (mg/kg bw/day)	0.4872	0.2100	0.0487
% of RVNAS	696.00%	300.00%	69.60%

Appendix 1.3 Resident exposure for Aclonifen SC600G outdoor spray application in peas crops.

Resident exposure for			
Croptype	Fruiting vegetables		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Buffer strip	5	m	
Application rate of the product	0.6	kg a.s./ha	
Concentration of active substance (in-use dilution for liquid applications)	4	g a.s./l	
Dermal absorption of product	2.50%		
Dermal absorption of in-use dilution	35.00%		
Oral absorption	100.00%		
Dislodgeable foliar residue (i_AppRate*i_DFR)	1.8	µg a.s./cm²	
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure < 5*10-3	Pa	
Concentration in air	0.001	mg/m³	
Resident dermal spray drift exposure 75th percentile - adult	0.23798	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.2175	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.00002	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00017	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.12748	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.12	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.00008	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00014	ml spray dilution/person	
Exposure duration dermal	2	hours	
Exposure duration inhalation	24	hours	
Exposure duration entry into treated crops	0.25	hours	
Light clothing adjustment factor	18.0%		
Breathing rate adult	0.23	m³/day/kg	
Breathing rate child (1-3 year old)	1.17	m³/day/kg	
Drift percentage on surface (75th percentile)	2.00%		
Drift percentage on surface (mean)	1.80%		
Turf transferable residues percentage	5.00%		
Transfer coeff. of surface deposits-adult	7300	cm²/hour	
Transfer coeff. of surface deposits-child (1-3 year old)	2400	cm²/hour	
Saliva extraction percentage	50.0%		
Surface area of hands mouthed	20	cm²	
Frequency of hand to mouth activity	9.5	events/hour	
Ingestion rate for mouthing of grass per day	25	cm²	
Dislodgeable residues percentage transferability for object to mouth	20.0%		
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm²/h	
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm²/h	
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm²/h	
Transfer coefficient for entry into treated crops (mean) - child	1794	cm²/h	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0250	% of RVNAS	35.77%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	1.53%
	Surface deposits (75th percentile) mg/kg bw/day	0.0015	% of RVNAS	2.08%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0354	% of RVNAS	50.63%
	All pathways (mean) mg/kg bw/day	0.0443	% of RVNAS	63.28%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0046	% of RVNAS	6.51%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.33%
	Surface deposits (75th percentile) mg/kg bw/day	0.0006	% of RVNAS	0.84%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0197	% of RVNAS	28.13%
	All pathways (mean) mg/kg bw/day	0.0187	% of RVNAS	26.77%

Appendix 2 Accompanying spreadsheet with dermal absoprtion data from BfR template (from EFSA dermal absorption guidance, 2017)

***In vitro* human dermal absorption data.**

Comparative in vitro dermal penetration study using human and rat skin (14C)-Aclonifen.

For some data with values below 0% a low number, zero has been added to aid in the excel formulas which give an error if 0 is used.

M-232331-01-1. [redacted] 2003.

Tested doses		
	Concentrate	Dilution 1
Target concentration [mg/mL]	600	1.5
Surface area dose [µg/cm²]	6000	15
Total dose [µg/cell]	3840	9.6
Specific activity [kBq/mL]	4110	4092
No. of donors	2	2
No. of replicates used/valid replicates*	7	7
Justification for excluded replicates, if applicable		

Test system			
Diffusion cell	Type of diffusion cell	Flow-through	
	(If dynamic) Flow rate	1.5	mL/h
	Exposed skin area	0.64	cm²
	Cover		
Skin sample	Skin type	Dermatomed	
	Skin thickness range	300-400	µm
	Skin donor age	60-69	years
	Skin donor sex	Male and female	

	Site	Abdomen and back		
	Source	Unknown		
	Integrity test	Yes		
Receptor	Receptor medium	phosphate buffered saline, supplemented with Bovine Serum Albumin (5% w/v)		
	Solubility in receptor medium	acceptable- found to be at least 118.3 µg/mL. Sufficient to dissolve 100% of applied dose of the concentrate in receptor fluid (107.7µg/mL).		
Sampling	Exposure time		8	hours
	Sampling duration		24	hours
	Sample intervals		1	hours
	Skin wash/Swabbing	1 % v/v Tween 80 in aqueous sodium chloride solution		
Tape strips	Tape stripping	Yes		
	Type of tape strips used	3M Scotch Magic tape		
	TS 1-2 analysed seperately?	Yes		

Concentrate:

Replicate	1	2	3	4	5	6	7	n	MEAN	SD	MAX
T0.5 <= 75 %											
Absorbed dose	0.155	0.108001	0.132001	0.173001	0.504	0.246	0.114		0.20	0.14	0.504
Tape strips 3-x	1.626	1.912	0.893	3.289	0.247	0.337	0.275		1.23	1.13	3.289
Skin preparation	0.106	0.091	0.094	0.105	0.042	0.048	0.049		0.08	0.03	0.106
Sum	1.887	2.111001	1.119001	3.567001	0.793	0.631	0.438		1.51	1.10	3.567001
Relevant data normalised	1.887	2.111001	1.119001	3.567001	0.793	0.631	0.438		1.51	1.10	3.567001
Relevant data added	1.887	2.111001	1.119001	3.567001	0.793	0.631	0.438		1.51	1.10	3.567001
Relevant data	1.887	2.111001	1.119001	3.567001	0.793	0.631	0.438	7	**1.51**	**1.10**	**3.567001**
T0.5 > 75 %											
Absorbed dose	0.155	0.108001	0.132001	0.173001	0.504	0.246	0.114		0.20	0.14	0.504
Skin preparation	0.106	0.091	0.094	0.105	0.042	0.048	0.049		0.08	0.03	0.106
Sum	0.261	0.199001	0.226001	0.278001	0.546	0.294	0.163		0.28	0.13	0.546
Relevant data normalised	0.261	0.199001	0.226001	0.278001	0.546	0.294	0.163		0.28	0.13	0.546
Relevant data added	0.261	0.199001	0.226001	0.278001	0.546	0.294	0.163		0.28	0.13	0.546
Relevant data	0.261	0.199001	0.226001	0.278001	0.546	0.294	0.163	7	**0.28**	**0.13**	**0.546**
Non-absorbed dose	97.667	98.171	99.921	96.296	99.164	98.107	99.056		98.34	1.18	99.921
Total Recovery	**99.554**	**100.282001**	**101.040001**	**99.865001**	**99.957**	**98.738**	**99.494**		**99.85**	**0.71**	**101.040001**
T0.5	1.09999911	0.92592593	0.75757576	0.57803468	1.88679245	1.58730159	2.08333333	7	1.27	0.58	2.08333333
								Mean lower li	**0.74**		
								k*SD	**0.53533801**		

Replicate	1	2	3	4	5	6	7	MEAN	SD	MAX
Donor ID										
Receptor fluid	0.091	0.108	0.132	0.173	0.053	0.063	0.048	0.10	0.05	0.173
Receptor compartment wash	0.064	0.000001	0.000001	0.000001	0.451	0.183	0.066	0.11	0.16	0.451
Donor compartment wash	2.035	0.448	1.215	0.832	1.454	5.634	4.091	2.24	1.91	5.634
	2.662	1.313	1.996	2.244	3.33	1.223	1.235	2.00	0.81	3.33
	1.626	1.912	0.893	3.289	0.247	0.337	0.275	1.23	1.13	3.289
										0
										0
										0
										0
										0
										0
										0
										0
										0
										0
										0
										0
Skin wash	92.97	96.41	96.71	93.73	94.38	91.25	93.73	94.10	1.94	96.71
Stripped skin	0.106	0.091	0.094	0.105	0.042	0.048	0.049	0.08	0.03	0.106
										0
Receptor fluid after 12 hours	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.00	0.00	0.001
Receptor fluid after 24 hours	0.091	0.108	0.132	0.173	0.053	0.063	0.048	0.10	0.05	0.173

Dilution:

T0.5 <= 75 %											
Absorbed dose	9.041001	7.341001	6.250001	3.342001	2.517001	2.136001	1.954001		4.65	2.86	9.041001
Tape strips 3-x	20.65	6.478	4.336	13.45	5.555	3.498	5.387		8.48	6.28	20.65
Skin preparation	3.693	2.702	2.42	1.514	1.182	0.795	0.946		1.89	1.07	3.693
Sum	33.384001	16.521001	13.006001	18.306001	9.254001	6.429001	8.287001		15.03	9.19	33.384001
Relevant data normalised	33.384001	16.521001	13.006001	18.306001	9.254001	6.429001	8.287001		15.03	9.19	33.384001
Relevant data added	33.384001	16.521001	13.006001	18.306001	9.254001	6.429001	8.287001		15.03	9.19	33.384001
Relevant data	33.384001	16.521001	13.006001	18.306001	9.254001	6.429001	8.287001	7	**15.03**	**9.19**	**33.384001**
T0.5 > 75 %											
Absorbed dose	9.041001	7.341001	6.250001	3.342001	2.517001	2.136001	1.954001		4.65	2.86	9.041001
Skin preparation	3.693	2.702	2.42	1.514	1.182	0.795	0.946		1.89	1.07	3.693
Sum	12.734001	10.043001	8.670001	4.856001	3.699001	2.931001	2.900001		6.55	3.92	12.734001
Relevant data normalised	12.734001	10.043001	8.670001	4.856001	3.699001	2.931001	2.900001		6.55	3.92	12.734001
Relevant data added	12.734001	10.043001	8.670001	4.856001	3.699001	2.931001	2.900001		6.55	3.92	12.734001
Relevant data	12.734001	10.043001	8.670001	4.856001	3.699001	2.931001	2.900001	7	**6.55**	**3.92**	**12.734001**
Non-absorbed dose	83.102	76.871	80.561	84.531	83.819	95.334	94.785		82.73	10.98	95.334
Total Recovery	**96.786001**	**93.192001**	**93.567001**	**102.837001**	**93.073001**	**101.763001**	**103.072001**		**97.76**	**4.68**	**103.072001**
T0.5	0.0111731	0.0137817	0.01626016	0.03045062	0.04026003	0.04741584	0.05202914	7	0.03	0.02	0.05202914
								Mean lower limit	**0.01**		
								k*SD	**0.01548153**		

[%]	Replicate / Donor ID								MEAN	SD	MAX
Receptor fluid	Receptor fluid	9.041	7.341	6.25	3.342	2.517	2.136	1.954	4.65	2.86	9.041
Receptor chamber	Receptor compartment wash	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001	0.00	0.00	0.000001
Donor chamber wa	Donor compartment wash	1.099	1.116	2.361	3.681	1.51	5.031	6.035	2.98	1.98	6.035
											0
Tape strips 1+2		9.033	7.235	17.82	18.66	6.849	7.593	12.84	11.43	5.07	18.66
Tape strips 3-x		20.65	6.478	4.336	13.45	5.555	3.498	5.387	8.48	6.28	20.65
											0
											0
											0
											0
											0
											0
											0
											0
											0
											0
											0
											0
											0
Skin wash	Skin wash	57.27	69.33	60.38	62.19	75.46	82.71	75.91	68.32	10.35	82.71
Skin preparation	Stripped skin	3.693	2.702	2.42	1.514	1.182	0.795	0.946	1.89	1.07	3.693
											0
T0.5 Receptor fluid	Receptor fluid after 12 hours	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.00	0.00	0.001
T1 Receptor fluid	Receptor fluid after 24 hours	8.95	7.256	6.15	3.284	2.487	2.109	1.922	4.59	2.83	8.95

Results and discussion

	Concentrate	Dilution 1
		(1:xxx)

Target concentration [mg/mL]	600		1.5	
Target dose [µg/cm²]	6000		15	
Mean actual applied dose [µg/cm²]	5810		14.41	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after x hours	94.10	1.94	68.32	10.35
Donor chamber wash	2.24	1.91	2.98	1.98
Skin associated dose				
Tape strips 1-2	2.00	0.81	11.43	5.07
Tape strips 3-x	1.23	1.13	8.48	6.28
Skin preparation	0.08	0.03	1.89	1.07
Absorbed dose				
Receptor fluid	0.10	0.05	4.65	2.86
Receptor chamber wash	0.11	0.16	0.00	0.00
Total recovery	99.85	0.71	97.76	4.68
LLC of t_0.5 absorption	0.74	0.54	0.01	0.02
Absorption complete?	No		No	
Measured absorption, if LLC of t_0.5<=75%	1.51	1.10	15.03	9.19
Measured absorption, if LLC of t_0.5>75%	N/A	N/A	N/A	N/A
Measured absorption corrected	1.51	1.10	15.03	9.19
Relevant absorption estimate	2.523		23.481	
Final estimate (rounded)	2.5		23	
Remarks				
receptor fluid values at 12 hrs not available but graphs of absorption over 24 hrs show it is not 75% complete at 12hrs (dummy low values for T0.5 have been entered in the tables to ensure the tape strips are included in the absorbed dose.				

***In vitro* rat dermal absorption data.**

Comparative in vitro dermal penetration study using human and rat skin (14C)-Aclonifen.

M-232331-01-1. [redacted] 2003.

For some data with values below 0% a low number > zero has been added to aid in the excel formulas which give an error if 0 is used.

Tested doses:

	Concentrate	Dilution 1
Target concentration [mg/mL]	600	1.5
Surface area dose [µg/cm²]	6000	15
Total dose [µg/cell]	3840	9.6
Specific activity [kBq/mL]	4110	4032
No. of donors	3	5
No. of replicates used/valid replicates*	7	9
No outliers		

General information:

General information			
	Species	Rat	
	Method	In vitro	
Test material			
Active substance	Name (Lot/Batch No.)	[aniline-UL-14C]aclonifen	
	Test preparation	Spiking into blank product	
	Radiochemical purity	99	%
Product	Name (Lot/Batch No.)	AE F068300 00 SC50 A2	
	Company code		
	Concentration a.s.	600	g/L or g/kg
	Type of formulation	SC	
	Vehicle used (if any)		
Blank product	Name (Lot/Batch No.)	AE F068300 00 SC50 A2	
	Concentration a.s.	600	g/L or g/kg
	Type of formulation	SC	
Test system			
Diffusion cell	Type of diffusion cell	Flow-through	
	(If dynamic) Flow rate	1.5	mL/h
	Exposed skin area	0.64	cm^2
	Cover		
Skin sample	Skin type	Dermatomed	
	Skin thickness range	300-400	µm
	Skin donor age	60-69	years
	Skin donor sex	Male	
	Site	Dorsal	
	Source	Post mortem	
	Integrity test	Yes	
Receptor	Receptor medium	phosphate buffered saline, supplemented with Bovine Serum Albumin (5% w/v)	
	Solubility in receptor medium	acceptable- found to be at least 118.3 µg/mL. Sufficient to dissolve 100% of applied dose of the concentrate in receptor fliud (107.7µg/mL).	
Sampling	Exposure time	8	hours
	Sampling duration	24	hours
	Sample intervals	1	hours
	Skin wash/Swabbing	1 % v/v Tween 80 in aqueous sodium chloride solution	
Tape strips	Tape stripping	Yes	
	Type of tape strips used	3M Scotch Magic tape	

	TS 1-2 analysed seperately?	Yes
Remarks		
Sprague-Dawley rats		

Concentrate:

Replicate	1	2	3	4	5	6	7	n	MEAN	SD	MAX
T0.5 <= 75 %											
Absorbed dose	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001		0.21	0.12	0.392001
Tape strips 3-x	4.736	4.81	2.616	5.197	1.349	1.224	3.042		3.28	1.66	5.197
Skin preparation	0.166	0.221	0.155	0.376	0.339	0.39	0.517		0.31	0.13	0.517
Sum	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001		3.80	1.68	5.720001
Relevant data normalised	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001		3.80	1.68	5.720001
Relevant data added	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001		3.80	1.68	5.720001
Relevant data	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001	7	**3.80**	**1.68**	**5.720001**
T0.5 > 75 %											
Absorbed dose	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001		0.21	0.12	0.392001
Skin preparation	0.166	0.221	0.155	0.376	0.339	0.39	0.517		0.31	0.13	0.517
Sum	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001		0.52	0.04	0.579001
Relevant data normalised	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001		0.52	0.04	0.579001
Relevant data added	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001		0.52	0.04	0.579001
Relevant data	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001	7	**0.52**	**0.04**	**0.579001**
Non-absorbed dose	96.272	94.782	97.662	96.507	99.547	99.025	94.269		96.87	2.00	99.547
Total Recovery	**101.566001**	**100.089001**	**100.754001**	**102.227001**	**101.363001**	**100.780001**	**97.890001**		**100.67**	**1.40**	**102.227001**
T0.5	0.25510139	0.36231753	0.31152551	0.68026748	0.7812439	0.70921483	1.61287721	7	0.67	0.47	1.61287721
								Mean lower limit of confidence	**0.25**		
								k*SD	**0.42795274**		

Replicate	1	2	3	4	5	6	7		MEAN	SD	MAX
Donor ID											
Receptor fluid	0.392	0.276	0.321	0.147	0.128	0.141	0.062		0.21	0.12	0.392
Receptor compartment wash	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001		0.00	0.00	0.000001
Donor compartment wash	0.726	1.482	0.609	0.835	1.101	0.585	0.544		0.84	0.34	1.482
Tape strips											0
	3.426	2.72	1.763	1.552	1.076	1.48	1.875		1.98	0.81	3.426
	4.736	4.81	2.616	5.197	1.349	1.224	3.042		3.28	1.66	5.197
Skin wash	92.12	90.58	95.29	94.12	97.37	96.96	91.85		94.04	2.63	97.37
Stripped skin	0.166	0.221	0.155	0.376	0.339	0.39	0.517		0.31	0.13	0.517
											0
Receptor fluid after 12 hours	0.001	0.001	0.001	0.001	0.001	0.001	0.001		0.00	0.00	0.001
Receptor fluid after 24 hours	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001		0.21	0.12	0.392001

Replicate	1	2	3	4	5	6	7
T0.5 <= 75 %							
Absorbed dose	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001
Tape strips 3-x	4.736	4.81	2.616	5.197	1.349	1.224	3.042
Skin preparation	0.166	0.221	0.155	0.376	0.339	0.39	0.517
Sum	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001
Relevant data normalised	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001
Relevant data added	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001
Relevant data	5.294001	5.307001	3.092001	5.720001	1.816001	1.755001	3.621001
T0.5 > 75 %							
Absorbed dose	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001
Skin preparation	0.166	0.221	0.155	0.376	0.339	0.39	0.517
Sum	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001
Relevant data normalised	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001
Relevant data added	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001
Relevant data	0.558001	0.497001	0.476001	0.523001	0.467001	0.531001	0.579001
Non-absorbed dose	96.272	94.782	97.662	96.507	99.547	99.025	94.269
Total Recovery	**101.566001**	**100.089001**	**100.754001**	**102.227001**	**101.363001**	**100.780001**	**97.890001**

T0.5	0.25510139	0.36231753	0.31152551	0.68026748	0.7812439	0.70921483	1.61287721

Replicate	1	2	3	4	5	6	7
Donor ID							
Receptor fluid	0.392	0.276	0.321	0.147	0.128	0.141	0.062
Receptor compartment wash	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001
Donor compartment wash	0.726	1.482	0.609	0.835	1.101	0.585	0.544
Tape strips							
	3.426	2.72	1.763	1.552	1.076	1.48	1.875
	4.736	4.81	2.616	5.197	1.349	1.224	3.042
Skin wash	92.12	90.58	95.29	94.12	97.37	96.96	91.85
Stripped skin	0.166	0.221	0.155	0.376	0.338	0.39	0.517
Receptor fluid after 12 hours	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Receptor fluid after 24 hours	0.392001	0.276001	0.321001	0.147001	0.128001	0.141001	0.062001

Dilution:

Replicate	1	2	3	4	5	6	7	8	9		MEAN	SD	MAX
T0.5 <= 75 %													
Absorbed dose	23.634	32.796001	35.564	14.962	18.029	18.698001	25.106001	25.608001	20.690001		23.90	6.81	35.564
Tape strips 3-x	9.753	13.84	32.78	30.04	43.92	25.11	27.01	23.93	28.04		24.94	9.74	43.92
Skin preparation	11.37	14.56	7.775	19.72	12.04	20.83	14.69	17.91	17.03		15.10	4.23	20.83
Sum	44.757	61.196004	66.119	64.722	73.989	64.638001	66.806001	67.448001	65.760001		63.94	7.95	73.989
Relevant data normalised	44.757	61.196001	66.119	64.722	73.989	64.638001	66.806001	67.448001	65.760001		63.94	7.95	73.989
Relevant data added	44.757	61.196001	66.119	64.722	73.989	64.638001	66.806001	67.448001	65.760001		63.94	7.95	73.989
Relevant data	44.757	61.196001	66.119	64.722	73.989	64.638001	66.806001	67.448001	65.760001	9	**63.94**	**7.95**	**73.989**
T0.5 > 75 %													
Absorbed dose	23.634	32.796001	35.564	14.962	18.029	18.698001	25.106001	25.608001	20.690001		23.90	6.81	35.564
Skin preparation	11.37	14.56	7.775	19.72	12.04	20.83	14.69	17.91	17.03		15.10	4.23	20.83
Sum	35.004	47.356001	43.339	34.682	30.069	39.528001	39.796001	43.518001	37.720001		39.00	5.31	47.356001
Relevant data normalised	35.004	47.356001	43.339	34.682	30.069	39.528001	39.796001	43.518001	37.720001		39.00	5.31	47.356001
Relevant data added	35.004	47.356001	43.339	34.682	30.069	39.528001	39.796001	43.518001	37.720001		39.00	5.31	47.356001
Relevant data	35.004	47.356001	43.339	34.682	30.069	39.528001	39.796001	43.518001	37.720001	9	**39.00**	**5.31**	**47.356001**
Non-absorbed dose	55.617	37.765	32.064	47.457	53.805	33.685	30.985	31.072	31.156		36.18	7.77	55.617
Total Recovery	**100.374**	**98.961001**	**98.183**	**102.179**	**109.794**	**88.323001**	**97.791001**	**98.520001**	**96.916001**		**100.12**	**3.94**	**109.794**
T0.5	0.00423119	0.00304915	0.00281183	0.0066836	0.00564682	0.00534817	0.00398311	0.00390503	0.00483325	9	0.00	0.00	0.0066836
										Mean lower	**0.00**		
										k*SD	**0.00095636**		

Replicate	1	2	3	4	5	6	7	8	9		MEAN	SD	MAX
Donor ID													
Receptor fluid	23.582	32.796	35.481	14.883	17.965	18.698	25.106	25.608	20.69		23.87	6.82	35.481
Receptor compartment wash	0.052	0.000001	0.083	0.079	0.064	0.000001	0.000001	0.000001	0.000001		0.03	0.04	0.083
Donor compartment wash	0.727	0.473	0.41	0.355	0.414	0.308	0.293	0.542	0.556		0.45	0.14	0.727
													0
	13.16	6.842	2.724	3.292	6.871	6.127	3.972	4	5.76		5.86	3.14	13.16
	9.753	13.84	32.78	30.04	43.92	25.11	27.01	23.93	28.04		24.94	9.74	43.92
Skin wash	41.78	32.45	28.92	33.81	28.52	27.25	26.72	26.53	24.84		29.86	5.15	41.73
Stripped skin	11.37	14.56	7.775	19.72	12.04	20.83	14.69	17.91	17.03		15.10	4.23	20.83
													0
Receptor fluid after 12 hours	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001		0.00	0.00	0.001
Receptor fluid after 24 hours	23.634	32.796001	35.564	14.962	18.029	18.698001	25.106001	25.608001	20.690001		23.90	6.81	35.564

Results and discussion:

	Concentrate		Dilution 1 (1:400)	
Target concentration [mg/mL]	600		1.5	
Target dose [µg/cm²]	6000		15	
Mean actual applied dose [µg/cm²]	5810		14.44	
Recovery [%]	Mean	SD	Mean	SD
Dislodgeable dose				
Skin wash after x hours	94.04	2.63	29.86	5.15
Donor chamber wash	0.84	0.34	0.45	0.14
Skin associated dose				
Tape strips 1-2	1.98	0.81	5.86	3.14
Tape strips 3-x	3.28	1.66	24.94	9.74
Skin preparation	0.31	0.43	15.10	4.23
Absorbed dose				
Receptor fluid	0.21	0.12	23.87	6.82
Receptor chamber wash	0.00	0.00	0.03	0.04
Total recovery	100.67	1.40	100.12	3.94
LLC of t_0.5 absorption	0.25	0.43	0.00	0.00
Absorption complete?	No		No	
Measured absorption, if LLC of t_0.5<=75%	3.80	1.68	63.94	7.95
Measured absorption, if LLC of t_0.5>75%	N/A	N/A	N/A	N/A
Measured absorption corrected	3.80	1.68	63.94	7.95
Relevant absorption estimate	5.342		70.062	
Final estimate (rounded):	5.3		70	

***In vivo* rat dermal absorption data.**

In vivo dermal penetration study in rats (14C)-Aclonifen.

For some data with values below 0% a low number > zero has been added to aid in the excel formulas which give an error if 0 is used.

M-232328-01-1. [redacted] 2003.

Tested doses

	Concentrate	Dilution 1
Target concentration [mg/mL]	600	1.5
Surface area dose [µg/cm²]	6180	15
Total dose [µg/cell]	74.16	0.176
Specific activity [kBq/mL]	1230	690
No. of donors	15	15
No. of replicates used/valid replicates	5	5
Justification for excluded replicates, if applicable: Target dose actual applied dose per animal. Applied to an area of 12cm2.		

Materials and methods

General information			
	Species	Rat Sprague-Dawley	
	Method	In vitro	
Test material			
Active substance	Name (Lot/Batch No.)	[aniline-UL-14C]aclonifen	
	Test preparation	Spiking into blank product	
	Radiochemical purity	98.3	%
Product	Name (Lot/Batch No.)	Bandur	
	Company code		
	Concentration a.s.	600	g/L or g/kg
	Type of formulation	SC	
	Vehicle used (if any)		
Blank product	Name (Lot/Batch No.)		
	Concentration a.s.	600	g/L or g/kg
	Type of formulation	SC	
Test system			
Diffusion cell	Type of diffusion cell		
	(If dynamic) Flow rate		mL/h
	Exposed skin area	12	cm²
	Cover		
Skin sample	Skin type	Full-thickness	
	Skin thickness range		µm
	Skin donor age	6-8 weeks	years
	Skin donor sex	Male	
	Site	Abdomen and back	
	Source		
	Integrity test		
Receptor	Receptor medium		
	Solubility in receptor medium		
Sampling	Exposure time	8	hours
	Sampling duration	72	hours
	Sample intervals	also 24	hours

	Skin wash/Swabbing	1 % v/v Tween 80 in aqueous sodium chloride solution
Tape strips	Tape stripping	No
	Type of tape strips used	
	TS 1-2 analysed seperately?	Yes
Remarks		
skin shaved 24 hr prior to application. Dose applied to 3 x 4 cm protected with plastic saddle attached by adhesive dressing. Urine and faeces and blood collected.		

Concentrate:

Sample	43M	44M	45M	46M	47M	mean	SD
Urine							
0 - 8 hours	0.03	0.05	0.05	0.04	0.06	**0.046**	**0.011402**
8 - 24 hours	0.11	0.13	0.11	0.17	0.21	**0.146**	**0.043359**
24 - 48 hours	0.18	0.25	0.21	0.33	0.4	**0.274**	**0.090167**
48 - 72 hours	0.16	0.18	0.19	0.36	0.37	**0.252**	**0.103779**
Subtotal	0.48	0.61	0.56	0.9	1.04	**0.718**	**0.289833**
Cage wash	0.14	0.12	0.07	0.14	0.09	**0.112**	**0.031145**
Faeces							
0 - 8 hours	0.03	0.02	0.01	ND	0.01	**0.0175**	**0.009574**
8 - 24 hours	0.1	0.12	0.09	0.18	0.14	**0.126**	**0.035777**
24 - 48 hours	0.13	0.16	0.11	0.35	0.27	**0.204**	**0.102372**
48 - 72 hours	0.13	0.18	0.18	0.33	0.37	**0.238**	**0.105214**
Subtotal	0.39	0.48	0.39	0.86	0.79	**0.582**	**0.226208**
Carcass	0.31	0.24	0.26	0.3	0.37	**0.296**	**0.050299**
Whole-blood							
(sacrifice)	ND	ND	ND	ND	ND		
Total absorbed	1.32	1.45	1.28	2.2	2.29	**1.708**	**0.495247**
Total in treated skin	2.23	3.33	5.86	4.78	3.16	**3.872**	**1.438183**
Skin surrounding dose site	0.23	0.32	0.66	1.61	0.34	**0.632**	**0.570412**
Skin (control)	ND	ND	ND	ND	ND		
Saddle and bandages	1.2	1.18	2.01	6.17	3.68	**2.848**	**2.11709**
Dose site swabs							
8 hours	86.17	84.15	83.03	77.71	83.28	**82.868**	**3.136386**
Sacrifice	1.77	1.7	3.87	3.21	2.19	**2.548**	**0.95374**
Total recovery	92.92	92.13	96.71	95.68	94.94	**94.476**	**1.909222**
total absorbed and in skin*	3.78	5.1	7.8	8.59	5.79	**6.212**	**1.968875**
* total absorbed, in treated skin and surrounding site							

total absorbed and in skin						**mean**	**sd**
normalised	4.068015	5.535656	8.06535	8.977843	6.098589		
missing data added	10.86	12.97	11.09	12.91	10.85		
value to use	10.86	5.535656	7.8	8.59	6.098589	**7.776849**	**2.121737**
Dermal absorption adjustments							
Mean recovery <95%	yes						
absorption <5%	yes in some replicates						
k	1.2						
1.2 SD	2.546085						
Dermal abs + 1.2SD	10.32293						
rounded value	**10%**						

Dilution:

Sample	23M	24M	25M	26M	27M	mean	SD
Urine							
0 - 8 hours	2.36	1.98	3.25	1.97	2.34	**2.38**	**0.521296**
8 - 24 hours	9.18	11.57	7.77	8.78	8.38	**9.136**	**1.456925**
24 - 48 hours	4.01	4.05	3.19	3.7	3.08	**3.606**	**0.452471**
48 - 72 hours	0.95	1.74	1.24	1.06	0.93	**1.184**	**0.33426**
Subtotal	16.5	19.34	15.45	15.51	14.73	**16.306**	**1.809207**
Cage wash	2.42	2.21	1.05	1.85	1.03	**1.712**	**0.646467**
Faeces							
0 - 8 hours	0.01	0.01	0.05	0.1	0.07	**0.048**	**0.038987**
8 - 24 hours	5.65	7.69	6.67	10.79	8.77	**7.914**	**1.982897**
24 - 48 hours	3.24	4.72	8.33	5.65	6.07	**5.602**	**1.872183**
48 - 72 hours	1.2	0.55	1.45	0.79	0.95	**0.988**	**0.350314**
Subtotal	10.1	12.97	16.5	17.33	15.86	**14.552**	**2.981018**
Carcass	0.43	0.58	0.41	0.51	0.43	**0.472**	**0.071554**
Whole-blood							
(sacrifice)	ND	ND	ND	ND	ND		
Total absorbed	29.45	35.1	38.41	35.2	32.05	**33.042**	**2.393443**
Total in treated skin	4.68	4.87	4.79	4.55	3.8	**4.538**	**0.429732**
Skin surrounding dose site	0.24	0.16	0.1	0.13	0.1	**0.146**	**0.058138**
Skin (control)	ND	ND	ND	ND	ND		
Saddle and bandages	1.21	1.09	0.99	0.99	0.73	**1.002**	**0.176975**
Dose site swabs							
8 hours	53.6	44.01	60.9	49.7	57.5	**53.142**	**6.607369**
Sacrifice	3.24	6.18	5.16	4.47	1.97	**4.204**	**1.643877**
Total recovery	92.42	91.41	105.35	95.04	96.15	**96.074**	**5.527742**
total absorbed and in skin*	34.37	40.13	38.3	39.88	35.95	**37.726**	**2.508252**

* total absorbed, in treated skin and surrounding site

Dermal absorption adjustments	
Mean recovery <95%	no
k	1.2
1.2 SD	3.009903
Dermal abs + 1.2SD	40.7359
rounded value	**41%**