Document Title

Summary of the toxicological studies for Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)

Data Requirement(s)

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

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Section 7: Toxicological studies

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

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on behalf of

Bayer AG

Crop Science Division

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Version history

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

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

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Fluopicolide (AE C638206) was included in Annex I to Council Directive 91/414/EEC in 2010 (Commission Directive 2010/15/EU, Entry into Force on June 1, 2010). The expiration of approval of fluopicolide is May 31, 2023 (Commission Implementing Regulation (EU) 2017/1527). The Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer AG (former Bayer CropScience) for the Annex I inclusion under Council Directive 91/414/EEC are contained in the Draft Assessment Report (DAR) and its Addenda, and are included in the Baseline Dossier provided by Bayer AG.

The formulation Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L), abbreviation FLC+PCH SC 687.5, is a suspension concentrate formulation (SC) containing 62.5 g/L of fluopicolide. This formulation is registered throughout Europe under trade names such as Infinito and Volare. FLC+PCH SC 687.5 was already a representative formulation of Bayer AG for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC.

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

Fluopicolide has a long track record of safe use in a large number of targeted crops within horticulture, e.g. cucumbers, lettuce and on arable crops (e.g. potato).

Fluopicolide is active against a wide range of Oomycete fungi, the causal agents of devastating plant diseases of economic importance in EU-27 such as potato late blight (*Phytophthora infestans*) or downy mildew diseases in a broad range of crops.

It provides effective, long lasting protection at low application rates against Oomycetes diseases at different stage of development of the fungi, giving flexibility of use to the farmer.

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

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

By reducing the Oomycete damages, applications of Fluopicolide + Propamocarb SC 687.5 on target crops contribute to the achievement of optimum yield and quality, thus securing sufficient supply of high-quality potatoes and horticultural produces for European consumer destinations and markets abroad, being it fresh or for the processing industry.

CP 7.1 Acute toxicity

Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) is not acutely toxic *via* the oral route (LD_{50} >2000 mg/kg bw), the dermal route (LD_{50} >4000 mg/kg bw) or the inhalation route (LC_{50} >3195 mg/m^3) and was not irritating to the skin or eyes. Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) was not sensitising to the skin in a modified Beuhler test; however, a mouse LLNA revealed a skin sensitising potential. Based on the doses administered it was possible to exclude category 1A for skin sensitisation. Overall, therefore, Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) should be classified with skin sensitisation category 1B (H317).

Table 7.1- 1: Acute toxicity studies with FLC+PCH SC 687.5

Study Type	Species (sex)	Results	Reference
Acute oral toxicity	Rat (M & F)	LD50 > 2000 mg/kg bw	M-220883-02-1
Acute dermal toxicity	Rat M & F)	LD50 > 4000 mg/kg bw/d	M-220889-02-1
Acute inhalation toxicity	Rat (M & F)	LC50 > 3195 mg/m^3	M-231342-01-1
Acute skin irritation	Rabbit (M)	Not irritating	M-224065-01-1
Acute eye irritation	Rabbit (M)	Not irritating	M-224035-01-1
Skin sensitisation (modified Beuhler)	Guinea pig (M & F)	Non-sensitising	M-237614-01-1
Skin sensitisation (LLNA)	Mice (F)	Skin sensitiser category 1B	M-237614-01-1

CP 7.1.1 Oral toxicity

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fluopicolide. One acute oral toxicity study is available for FLC+PCH SC 687.5, a short summary of which is presented below.

Data Point:	KCP 7.1.1/01
Report Author:	[redacted]
Report Year:	2004
Report Title:	AE B066752 04 SC61 A1-EXP11120A - Study for acute oral toxicity in rats
Report No:	C036530
Document No:	M-220883-02-1
Guideline(s) followed in study:	Directive 67/548/EEC, Annex IV B, Part B, B.1; OECD 423 (1996); US-EPA 712-C-98-190, OPPTS 870.1100 (1998)
Deviations from current test guideline:	6 animals (3 males and 3 females) were dosed concurrently rather than sequentially.
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

Three male and three female fasted rats were administered a single oral gavage dose of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L), in demineralized water at a dose level of 2000 mg/kg bw. The animals were observed daily for mortality and clinical signs (several times on the day of dosing) and body weights were measured weekly. Animals were sacrificed following a 14-day observation period and were subject to a gross necropsy.

There were no deaths; in 3/3 females, reduced motility was observed from 10 minutes to three hours following dosing. There were no clinical signs observed in males. Body weight development was considered normal for rats of this age and strain and there were no unusual findings on necropsy.

The acute oral LD_{50} of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) in rats was therefore greater than 2000 mg/kg bw. No classification for acute oral toxicity is warranted.

I. Materials and Methods

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220159

2. Vehicle and/or positive control

Vehicle:	Demineralized water

3. Test animals

Species:	Rat
Strain:	HsdCpb:WU
Age:	8-9 weeks
Weight at start:	195 – 196 g (males), 162 – 164g (females)
Source:	[redacted]
Acclimation period:	5 days
Identification:	Cage cards and individual markings
Diet:	PROVIMI KLIBA 3883.0.15, Switzerland
Water:	Available *ad libitum*
Housing:	Polycarbonate cages
Temperature:	22° ± 2° C
Humidity:	Approx. 55 ± 5%
Air changes:	Approx. 10 times/hour
Photoperiod:	12-hours

B. Study design

1. In-life dates: 6 November 2002 to 22 November 2002

2. Animal assignment and treatment

No. of animals (group size)	3/sex
Dose(s)	2000 mg/kg bw
Exposure	Once *via* gavage
Post exposure observation period	14 days

Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) was administered to fasted male and female rats (3/sex) at a dose of 2000 mg/kg bw and a volume of 10 ml/kg bw. Food was reintroduced two hours following dosing. The day of dose administration was designated day 1 of the test.

C. Methods

1. Observations

Animals were examined for clinical signs and mortality several times on the day of treatment and at least once daily thereafter. Body weights were recorded prior to dosing, once weekly and on sacrifice or death.

2. Necropsy

Animals were anesthetized by diethyl ether and sacrificed at the end of the observation period. All animals were subject to a gross necropsy.

II. Results and Discussion

A. Results

1. Dose-response table (LD_{50})

The results of the study for acute oral toxicity in the fasted rat, are summarized in table 7.1.1-1 below.

Table 7.1.1- 1: Dose response

Dose (mg/kg bw)	Toxicological result*	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
2000	0/0/3	-	-	>2000
Female rats				
2000	0/3/3	10 mins to 3 hours	-	>2000

* Number of animals which died /number of animals with signs / total number of animals

The LD_{50} was therefore **> 2000 mg/kg bw**

2. Clinical signs

There were no mortalities and no clinical signs were observed in males. In females, reduced motility was observed from 10 minutes following dosing and had resolved by 3 hours post-dose.

3. Body weights

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

4. Necropsy findings

No unusual gross pathology findings were noted in the animals sacrificed at the end of the observation period.

III. Conclusion

The acute oral LD_{50} of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) in rats was greater than 2000 mg/kg bw. Classification for acute oral toxicity in accordance with regulation (EC) No. 1272/2008 is therefore not required.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the acute oral toxicity of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L). Under the conditions of this study, Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) is of low acute oral toxicity (LD_{50} > 2000 mg/kg bw), and classification for acute oral toxicity is not required.

CP 7.1.2 Dermal toxicity

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fluopicolide. One acute dermal toxicity study is available for FLC+PCH SC 687.5, a short overall summary of which is provided below.

Data Point:	KCP 7.1.2/01
Report Author:	[redacted]
Report Year:	2004
Report Title:	AE B066752 04 SC61 A1-EXP11120A - Study for acute dermal toxicity in rats
Report No:	C036532
Document No:	M-220889-02-1
Guideline(s) followed in study:	Directive 92/69/EEC, Annex V, Part B.3 (1992); OECD 402 (1987); US-EPA EPA 712-C-98-192,: OPPTS 870.1200 (1998)
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) was applied to the shorn back and flanks of 5/sex fasted rats and occluded with a gauze dressing. Following a 24-hour exposure period, the dressing was removed, and the area washed with soap and water. An observation period of 14 days followed. Animals were observed daily for mortality and clinical signs (several times on the day of treatment). Body weights were recorded prior to dosing and once weekly thereafter. All animals were subject to a full gross necropsy.

There were no deaths or clinical signs of systemic toxicity. Local irritation, comprising partial reddening and encrusting of the treatment area was observed in one female from day 5 to day 11 post-application. There was no effect on body weight in males; however, one female showed a small transient reduction in body weight on day 8 of the study only. There were no unusual gross necropsy findings in any animal.

The acute dermal LD_{50} of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) in rats was greater than 4000 mg/kg bw. Classification for acute dermal toxicity in accordance with regulation (EC) No. 1272/2008 is therefore not required.

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220159

2. Vehicle and/or positive control

Vehicle:	None

3. Test animals

Species:	Rat
Strain:	HsdCpb:WU
Age:	9 weeks (males) & 12 weeks (females)
Weight at start:	227-239g (males) & 200-221g (females)
Source:	[redacted]
Acclimation period:	5 days
Identification:	Cage cards and individual markings
Diet:	PROVIMI KLIBA 3883.0.15, Switzerland
Water:	Available *ad libitum*
Housing:	Housed individually in polycarbonate cages
Temperature:	22° ± 2°C
Humidity:	Approx. 55 ± 5%
Air changes:	Approx. 10 times/hour
Photoperiod:	12-hours

B. Study design

1. In-life dates: November 13, 2002 to November 27, 2002

2. Animal assignment and treatment

No. of animals (group size)	5/sex
Dose(s)	4000 mg/kg bw
Exposure	24 hours, dermal
Post exposure observation period	14 days

The test substance was applied to a gauze strip and attached to the shorn back and flanks of the rats (covering an area of 18 cm^2). The test item was left in place for 24 hours, after which the area was washed with soap and water.

C. Methods

1. Observations

The animals were examined for mortality and clinical signs several times on the day of dosing and then daily thereafter for the remainder of the observation period. Body weights were recorded prior to dosing and then weekly thereafter. Animals were also weighed upon death or sacrifice.

2. Necropsy

Animals were sacrificed by diethyl ether inhalation following the 14-day observation period. All animals (including intercurrent deaths) were subject to a full gross necropsy examination.

II. Results and Discussion

A. Results

1. Dose-response table (LD_{50})

Dose (mg/kg bw)	Toxicological result*	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
4000	0/0/5	-	-	>4000
Female rats				
4000	0/1/5	5 days to 11 days	-	>4000

* Number of animals which died /number of animals with signs / total number of animals

The LD_{50} was therefore **> 4000 mg/kg bw**

2. Clinical signs

There were no deaths or clinical signs of systemic toxicity. Local signs of toxicity (partly reddened and encrusted treatment area) were observed in one female from day 5 until day 11 of treatment.

3. Body weights

A slight, transient decrease in body weight was observed on day 8 of the study. The body weight development of males was not affected.

4. Necropsy findings

No unusual gross pathology findings were noted in the animals sacrificed at the end of the observation period.

III. Conclusion

The acute dermal LD_{50} of Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L) in rats was greater than 4000 mg/kg bw. Classification for acute dermal toxicity in accordance with regulation (EC) No. 1272/2008 is therefore not required.

<u>Assessment and conclusion by applicant:</u>
The study is valid and acceptable to determine the acute dermal toxicity of FLC+PCH SC 687.5.
Under the conditions of this study, FLC+PCH SC 687.5 is of low acute dermal toxicity (LD_{50} > 4000 mg/kg bw), and classification for acute dermal toxicity is not required.

CP 7.1.3 Inhalation toxicity

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fluopicolide. One acute inhalation study is available for FLC+PCH SC 687.5, a short overall summary of which is provided below.

Data Point:	KCP 7.1.3/01
Report Author:	[redacted]
Report Year:	2003
Report Title:	AE C638206 and Propamocarb SC 62,5 + 625 - Study on acute inhalation in rats according to OECD No. 403
Report No:	C032394
Document No:	M-231342-01-1
Guideline(s) followed in study:	Directive 92/69/EEC., B2 (1992); OECD 403 (1981; US-EPA 712C-98-193, OPPTS 870.1300 (1998)
Deviations from current test guideline:	None
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

The acute inhalation toxicity of FLC+PCH SC 687.5 was investigated by exposing groups of five male and five female rats to an aerosol atmosphere of the test substance, for a 4-hour continuous nose-only exposure. The target concentration was the limit concentration 5000 mg/m³; however, the maximum technically obtainable concentration was 3195 mg/m3. The mass median aerodynamic diameters (MMAD) was in the recommended range of 1 to 4 µm with a geometric standard deviation (GSD) of 1.5 to 3 (2.96±2.43 µm).

Animals were then subject a 14-day observation period in which they were examined for mortality and clinical signs several times on the day of exposure and daily thereafter. Body weights were recorded prior to exposure, on days 3 and 7 and then weekly for the duration of the study. At the end of the observation period, the animals were sacrificed, and a full gross necropsy was performed (with a particular emphasis on the respiratory tract).

There were no deaths or clinical signs of toxicity and body weights were not affected by treatment (a slight decrease in body weight gain in females during the observation was considered to be incidental and not related to treatment with FLC+PCH SC 687.5). there were no unusual findings on gross necropsy.

The 4-hour acute inhalation LC_{50} of FLC+PCH SC 687.5 in rats was >3195 mg/m³ (the maximum attainable concentration); therefore, classification for acute inhalation toxicity is not required.

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	QP220159

2. Vehicle and/or positive control

Vehicle:	None

3. Test animals

Species:	Rat
Strain:	HsdCpb:WU
Age:	Approximately 2 months
Weight at start:	Weight range was within ± 10% of the mean
Source:	[redacted]
Acclimation period:	5 days
Identification:	Cage cards and individual markings
Diet:	PROVIMI KLIBA 3883.0.15, Switzerland
Water:	Available *ad libitum*
Housing:	Housed individually in conventional Makrolon type III cages
Temperature:	22° ± 2° C
Humidity:	Approx. 40-60%
Air changes:	Approx. 10 times/hour
Photoperiod:	12-hours

B. Study design

1. In-life dates: November 20, 2002 to December 04, 2002

2. Animal assignment and treatment

No. of animals (group size)	5/sex
Dose(s)	0 (control) and 5000 mg/kg bw (target concentration)
Exposure	4 hours, nose-only
Post exposure observation period	14 days

The acute inhalation toxicity of FLC+PCH SC 687.5 was investigated by exposing groups of five male and five female rats to an aerosol atmosphere of the test substance for a 4-hour continuous nose-only exposure. The target concentration was the limit concentration 5000 mg/m³; however, the maximum technically obtainable concentration was 3195 mg/m3. Animals were then subject a 14-day observation period, following which the animals were sacrificed and a full gross necropsy was performed.

Table 7.1.3-1: Concentrations of the test substance

Mean concentration (mg/m³)	Nominal concentration (mg/m³)	MMAD ± GSD (µm)	Resp. fraction (% < 3 µm)
3195	14931	2.96 ±2 .43	50.8

The mass median aerodynamic diameters (MMAD) was in the recommended range of 1 to 4 µm with a geometric standard deviation (GSD) of 1.5 to 3 (2.96±2.43 µm).

C. Methods

1. Observations

The animals were examined for mortality and clinical signs several times on the day of exposure and at least once daily thereafter. Body weights were recorded prior to exposure, on days 3 and 7 and then on a weekly basis.

2. Necropsy

All rats were subject to a gross necropsy; the respiratory tract was examined in detail.

II. Results and Discussion

A. **Results**

The results of the acute inhalation toxicity study with FLC+PCH SC 687.5 are summarised in the table below.

1. Dose-response table (LD_{50})

Target concentration (mg/m³)	Toxicological result*	Duration of signs	Time of death	LD_{50} (mg/m³)
Male rats				
0	0/0/5	-	-	-
5000	0/0/5	-	-	>5000
Female rats				
0	0/0/5	-	-	-
5000	0/0/5	-	-	>5000

* Number of animals which died /number of animals with signs / total number of animals

The LD_{50} was therefore **> 3195 mg/m³**

2. Clinical signs

There was no deaths or clinical signs of toxicity and no animals experienced any abnormal reflexes in a battery of reflex measurements performed on day one following exposure.

3. Body weights

There were no effects on body weights in the treated animals in comparison with controls. A slight decrease in body weight gain in treated females during the observation period, was considered to be incidental and not an effect of treatment with FLC+PCH SC 687.5.

4. Necropsy findings

There were no unusual gross necropsy findings in animals sacrificed at the end of the observation period.

III. Conclusion

The 4-hour acute inhalation LC_{50} of FLC+PCH SC 687.5 in rats was 3195 mg/m³ (the maximum attainable concentration); therefore, classification for acute inhalation toxicity is not required.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the acute inhalation toxicity of FLC+PCH SC 687.5.

Under the conditions of this study, FLC+PCH SC 687.5 is of low acute inhalation toxicity (LC_{50} > 3195 mg/m³) and classification for acute inhalation toxicity is not required.

CP 7.1.4 Skin irritation

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline

Dossier of fluopicolide. One skin irritation study is available for FLC+PCH SC 687.5, a short overall summary of which is provided below.

Data Point:	KCP 7.1.4/01
Report Author:	[redacted]
Report Year:	2003
Report Title:	AE B066752 04 SC61 A1 (EXP11120A) - Acute dermal irritation in rabbits
Report No:	C038035
Document No:	M-224065-01-1
Guideline(s) followed in study:	Directive 92/69/EEC, B.4 (1992) - OECD 404 (1992)
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

The potential of FLC+PCH SC 687.5 to irritate the skin was investigated in three male New Zealand White rabbits. Approximately 24 hours prior to treatment, both flanks of each animal were shorn with electric clippers and the skin examined; animals with healthy intact skin were selected for the study. The undiluted test item (0.5 mL) was applied to the right flank of three animals, via application onto a gauze pad, and held *in situ* with a semi-occlusive dressing for four hours. The untreated skin served as a control. After the 4-hour exposure period, the dressings were removed, and the area wiped with a moistened cotton pad.

The treated skin was examined approximately 1-, 24-, 48- and 72-hours following removal of the dressing. Local dermal irritation was evaluated for each animal and assigned a numerical value.

The mean scores over 24, 48 and 72 hours for each animal were 0.3, 0.3 and 0.3 for erythema and 0.0, 0.0 and 0.0 for oedema. The slight erythema observed, had recovered by day 2 of the observation period in all animals.

Therefore, FLC+PCH SC 687.5 is not irritating to the skin of rabbits following a 4-hour exposure period and no classification for dermal irritation is thus required.

I. Materials and Methods

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220159

2. Vehicle and/or positive control

Vehicle:	None

3. Test animals

Species:	Rabbit
Strain:	New Zealand White
Age:	2-4 months old
Weight at start:	2.6±0.3 kg
Source:	[redacted]
Acclimation period:	At least 5 days
Identification:	Metal ear tag
Diet:	110 pelleted diet, UAR, Villemoisson, France
Water:	Provided *ad libitum*
Housing:	Individually in polystyrene cages
Temperature:	18 ± 3˚C
Humidity:	30 to 70%
Air changes:	Approximately 12 cycles
Photoperiod:	12 hours light/12 hours dark

B. Study design

1. In-life dates: Not stated

2. Animal assignment and treatment

No. of animals (group size)	3 males
Dose(s)	0.5 mL
Exposure	4 hours, semi-occlusive
Post exposure observation period	4 days

Approximately 24-hours prior to treatment, both flanks of each animal were shorn with electric clippers and the skin examined; animals with healthy intact skin were selected for the study. The undiluted test item (0.5mL) was applied to the right flank of 3 animals, via application onto a gauze pad, and held in situ with a semi-occlusive dressing for 4 hours. The untreated skin served as a control. After the 4-hour exposure period, the dressings were removed, and the area wiped with a moistened cotton pad.

C. Methods

1. Observations

The treated skin was examined approximately 1-, 24-, 48- and 72-hours following removal of the dressing. Local dermal irritation was evaluated for each animal using the following numerical scale:

Erythema and Eschar formation

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

Oedema formation

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (edges raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

II. Results and Discussion

1. Dermal reactions

The observed dermal reactions for each animal, and the mean scores for 24, 48 and 72 hours for each animal are provided in the table below:

Table 7.1.4-1: Dermal irritation scores

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
287	Erythema	1	1	0	0	0.3	2
	Oedema	0	0	0	0	0.0	
288	Erythema	1	1	0	0	0.3	2
	Oedema	0	0	0	0	0.0	
289	Erythema	1	1	0	0	0.3	2
	Oedema	0	0	0	0	0.0	

The mean scores over 24, 48 and 72 hours for each animal were 0.3, 0.3 and 0.3 for erythema and 0.0, 0.0 and 0.0 for oedema. The slight erythema observed, had recovered by day 2 of the observation period in all animals.

III. Conclusion

Under the conditions of this study, FLC+PCH SC 687.5 is not irritating to the skin of rabbits following a 4-hour exposure; therefore, no classification for dermal irritation is required.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the dermal irritation potential of FLC+PCH SC 687.5.

Under the conditions of this study, FLC+PCH SC 687.5 is not irritating to the skin of the rabbit, and classification for dermal irritation is not required.

CP 7.1.5 Eye irritation

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline Dossier of fluopicolide. One eye irritation study is available for FLC+PCH SC 687.5, a short overall summary of which is provided below.

Data Point:	KCP 7.1.5/01
Report Author:	[redacted]
Report Year:	2002
Report Title:	AE B066752 04 SC61 A1 (EXP11120A) - Acute eye irritation in rabbits
Report No:	C038025
Document No:	M-224035-01-1
Guideline(s) followed in study:	EC Directive No. 92/69/EEC,, B.5 (1992); OECD 405 (1987)
Deviations from current test guideline:	A systemic and topical analgesic was not applied
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

The eye irritating potential of FLC+PCH SC 687.5 was investigated in three male New Zealand White rabbits only animals without irritation, ocular defects or pre-existing injury were used). A single dose (0.1 mL) of the undiluted test item was installed into the conjunctival sac of the left eye of each animal. No irrigation of the eyes was performed. The untreated (right) eye served as the control.

The eyes were examined 1-, 24-, 48- and 72-hours following administration of the test item. Conjunctival reactions, iritis and corneal opacity were evaluated daily for each animal; the detection of the presence or absence of corneal opacity was aided with fluorescein. The ocular reactions were assigned a numerical score.

The mean scores for each animal over 24, 48 and 72 hours were 1.0, 0.7 and 1.0 for conjunctivae chemosis, 0.3, 0.3 and 0.3 for conjunctivae redness, 0.0, 0.0 and 0.0 for iritis and 0.3, 0.0 and 0.0 for corneal opacity.

Very slight chemosis (grade 1 or 2) and very slight redness (grade 1) were observed in all animals from day 1 and had fully reversed by day 2. Similarly, a very slight corneal opacity (grade 1) observed in 2/3 animals on day 2 had fully reversed by day 3. Other findings comprised a clear discharge and alopecia around the eyes in 2/3 animals on day 1 only.

Under the conditions of this study, FLC+PCH SC 687.5 is not irritating to the eyes of rabbits; therefore, no classification for acute eye irritation is required.

I. Materials and Methods

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220159

2. Vehicle and/or positive control

Vehicle:	None

3. Test animals

Species:	Rabbit
Strain:	New Zealand White
Age:	2-4 months old
Weight at start:	2.9 ± 0.3 kg
Source:	[redacted]
Acclimation period:	At least 5 days
Identification:	Metal ear tag
Diet:	110 pelleted diet, UAR, Villemoisson, France
Water:	Provided *ad libitum*
Housing:	Individually in polystyrene cages
Temperature:	18 ± 3˚C
Humidity:	30 to 70%
Air changes:	Approximately 12 cycles
Photoperiod:	12 hours light/12 hours dark

B. Study design

1. In-life dates: Not stated

2. Animal assignment and treatment

No. of animals (group size)	3 males
Dose(s)	0.1 mL
Exposure	Single instillation in conjunctival sac
Irrigation	No
Post exposure observation period	4 days

Approximately 24 hours prior to treatment, the eyes of each animal were examined. Only animals without irritation, ocular defects or pre-existing injury were selected. A single dose of 0.1 mL of the test item was installed into the conjunctival sac of the left eye of each animal. The lower and upper eyelids were held together for approximately one second to ensure the test item was retained in the eye and the eyes were not rinsed following administration of the test item. The untreated (right) eye served as the control.

C. Methods

1. Observations

The eyes were examined 1-, 24-, 48- and 72-hours following administration of the test item. Conjunctival reactions, iritis and corneal opacity were evaluated daily for each animal; the presence or absence of corneal opacity was aided with a UV lamp following the addition of one or two drops of 0.5% sodium fluorescein to the eye (performed on day 1 and day 2 in animal 287 and 288 and on day 1 in animal number 289). The ocular reactions were assigned a score in accordance with the following numerical scale:

Conjunctival lesions and discharge

Chemosis (lids and/or nictitating membranes):	
No swelling	0
Any swelling above normal (includes nictitating membranes)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids half closed	3
Swelling with lids more than half closed	4
Redness (refers to palpebral and bulbar conjunctivae, cornea and iris):	
Blood vessels normal	0
A number of blood vessels definitely hyperemic (injected)	1
Diffuse, crimson colour, individual vessels not easily discernible	2
Diffuse, beefy red	3
Discharge:	
Absence of discharge	0
Slight discharge	1
Discharge with moistening of lids and hairs adjacent to lids	2
Discharge with moistening of lids and hairs on wide area around eyes	3

Iris lesions

Normal	0
Markedly deepened rugae, congestion, swelling, moderate circum-corneal hyperemia, or injection (any combination), iris still reacting to light	1
No reaction to light	2

Corneal lesions

Degree of opacity:	
No ulceration or opacity	0
Scattered or diffuse areas of opacity, details of iris clearly visible	1
Easily discernible translucent area, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Opaque cornea, iris not discernible through the opacity	4
Area of opacity	
One quarter (or less) but not zero	1
Greater than one quarter but less than a half	2
Greater than one half but less than three quarters	3
Greater than three quarters up to whole area	4

II. Results and Discussion

1. Ocular reactions

The observed ocular reactions for each animal, and the mean scores for 24, 48 and 72 hours for each animal are provided in the table below:

Table 7.1.5-1: Ocular irritation scores

Animal No.	Region of eye	Description	Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
			1 h	24 h	48 h	72 h		
287	Conjunctiva	Chemosis	2	2	1	0	1.0	3
		Redness	1	1	0	0	0.3	
		Discharge	1	1	0	0	0.3	
	Iris	Lesions	0	0	0	0	0.0	
			0	1	0	0	0.3	
	Cornea	Opacity intensity	0	1	0	0	0.3	
		Opacity area						
288	Conjunctiva	Chemosis	1	1	1	0	0.7	3
		Redness	1	1	0	0	0.3	
		Discharge	0	0	0	0	0.0	
	Iris	Lesions	0	0	0	0	0.0	
	Cornea	Opacity intensity	0	0	0	0	0.0	
		Opacity area	0	0	0	0	0.0	
289	Conjunctiva	Chemosis	2	2	1	0	1.0	3
		Redness	1	1	0	0	0.3	
		Discharge	1	1	0	0	0.3	
	Iris	Lesions	0	0	0	0	0.0	
	Cornea	Opacity intensity	0	0	0	0	0.0	
		Opacity area	0	0	0	0	0.0	

The mean scores for each animal over 24, 48 and 72 hours were 1.0, 0.7 and 1.0 for conjunctivae chemosis, 0.3, 0.3 and 0.3 for conjunctivae redness, 0.0, 0.0 and 0.0 for iritis and 0.3, 0.0 and 0.0 for corneal opacity.

Very slight chemosis (grade 1 or 2) and very slight redness (grade 1) were observed in all animals from day 1 and had fully reversed by day 2. Similarly, a very slight corneal opacity (grade 1) observed in 2/3 animals on day 2 had fully reversed by day 3. Other findings comprised a clear discharge and alopecia around the eyes in 2/3 animals on day 1 only.

III. Conclusion

Under the conditions of this study, FLC+PCH SC 687.5 is not irritating to the eyes of rabbits; therefore, no classification for acute eye irritation is required.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the eye irritating potential of FLC+PCH SC 687.5.

Under the conditions of this study, FLC+PCH SC 687.5 is not irritating to the eyes of the rabbit, and classification for acute eye irritation is therefore not required.

CP 7.1.6 Skin sensitization

All studies for this endpoint were presented and evaluated during the EU process for the Annex I inclusion of fluopicolide under Council Directive 91/414/EEC. Please refer to the DAR and the Baseline

Dossier of fluopicolide. Two skin sensitisation studies are available for FLC+PCH SC 687.5 (a modified Beuhler test in guinea pigs and a mouse LLNA). A short overall summary of these studies is provided below.

Data Point:	KCP 7.1.6/01
Report Author:	[redacted]
Report Year:	2003
Report Title:	AE B066752 04 SC61 A1 (EXP11120A) - Skin sensitization test in guinea pigs (Modified Buehler test: 9 applications)
Report No:	C038042
Document No:	M-224078-01-1
Guideline(s) followed in study:	EC Directive No. 96/54/EEC, B.6 (1996); OECD 406 (1992)
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

A preliminary test was conducted in which the test item was applied at concentrations of 100% and 50% (w/w) to the shaved flanks of 2 male and 2 female Hartley guinea pigs (4 applications).

The highest concentration selected for the induction phase of the main study should cause weak/moderate skin reactions, whilst the highest concentration for the challenge phase should cause no irritant effect; therefore, as no dermal effects were noted with 50% (w/w) and only mild irritation effects were noted with undiluted test substance, the undiluted test substance (100%) was selected for the main study.

For the main study, concentrations of 100% were applied to the animals of the treated group on days 1 and 3; this was reduced to 50% for days 5, 8, 10, 12, 15, 17 and 19 owing to the severity of skin reactions observed. Animals of the control group received purified water under the same experimental conditions.

On day 29, a challenge application of 100% was applied to the clipped posterior right flank, whilst vehicle only was applied to the posterior left flank of the same animal. As equivocal reactions were noted, a second challenge was performed after an interval of 14-days (day 44) in which 50% (w/w) was applied to the left flank and vehicle to the right flank.

There were no deaths or clinical signs of toxicity and body weight development was normal.

Following the first challenge application, discrete erythema (grade 1) was observed at the 24-hour reading in 6/10 and 9/20 of the control and treated groups respectively, persisting until the 48-hour reading in 3/10 and 6/10 animals, respectively. Following the second challenge application, no dermal reactions were noted. Therefore, it is considered that the dermal reactions following the first challenge were secondary to irritation and not elicitation.

Under the conditions of this modified Beuhler test, FLC+PCH SC 687.5 is not a skin sensitiser, therefore no classification for skin sensitisation is warranted.

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220159

2. Vehicle and/or positive control

Vehicle:	Purified water

3. Test animals

Species:	Guinea pigs
Strain:	Hartley Crl: (HA) BR
Age:	1 to 2 months old
Weight at start:	453 ± 30 g (males) and 432 ± 32 g (females)
Source:	[redacted]
Acclimation period:	At least 5 days
Identification:	Individual ear tattoo
Diet:	106 pelleted diet, SAFE, Villemoisson, France
Water:	Provided *ad libitum*
Housing:	Housed individually in polycarbonate cages with stainless steel lids
Temperature:	22 ± 2°C
Humidity:	30 to 70%
Air changes:	Approximately 12 hours
Photoperiod:	12 hours light/12 hours dark

B. Study design

1. In-life dates: November 18, 2002 to January 3, 2003

2. Animal assignment and treatment

No. of animals (group size)	Test substance group: 15 and 15 female guinea pigs Vehicle control group: 5 male and 5 female guinea pigs
Range finding	Yes (preliminary study with 2 male and 2 female guinea pigs)
Exposure (concentration(s), no. of applications)	Induction phase: 100% on days 1 & 3 and 50% (w/w) on days 5, 8, 10, 12, 15, 17 and 19 Challenge 1: 100% on day 29 Challenge 2: 50% (w/w) on day 44
Reliability check	Regularly assessed with Mercaptobenzothiazole

For the preliminary and main tests, the application sites of each animal were clipped and shaved the day before application of the induction phase and challenge phase and again before the 48-hour reading of the challenge phase. Appropriate concentrations of the test substance were loaded on to a filter paper (approximately 8cm²) which was applied to the shaved skin of the flank and held in place with an occlusive dressing for 6 hours.

For the preliminary induction phase, concentrations of 100% and 50% were applied (one concentration per flank). The treatment was repeated to obtain a total of 4 applications (with an interval of 2 or 3 days between applications). Cutaneous reactions were evaluated approximately 24 hours after each treatment. A challenge was performed at 100% and 50% using the same method and skin examined for reactions

24- and 48-hours following dressing removal. The highest concentration selected for the induction phase of the main study should cause weak/moderate skin reactions, whilst the highest concentration for the challenge phase should cause no irritant effect.

For the main study, concentrations of 100% were applied to the animals of the treated group on days 1 and 3; this was reduced to 50% for days 5, 8, 10, 12, 15, 17 and 19 owing to the severity of skin reactions observed. Animals of the control group received purified water under the same experimental conditions.

On day 29 a challenge application of 100% was applied to the clipped posterior right flank, whilst vehicle only was applied to the posterior left flank of the same animal. As equivocal reactions were noted, a second challenge was performed after an interval of 14-days.

On day 44, a second challenge of 50% (w/w) was applied to the left flank and vehicle to the right flank. No residual test item was noted on removal of the dressing for the induction or challenge phases.

C. Methods

1. Observations

Animals were observed at least once daily for mortality and clinical signs. Animals were weighed on the day of group allocation, and on days 1, 31 and 46 of the study.

2. Dermal observations

Twenty-four hours after each application of the induction phase, before the second challenge and 24 and 48 hours after removal of the dressing in each challenge application, both flanks of the treated and control animals were examined and any dermal reactions were evaluated according to the following numerical scale:

No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema	3

In addition, any observed oedema or other lesions were recorded. Any reactions in the treated group (score ≥ 1) persisting for at least 48-hours and/or appearing after 24-hours are considered positive reactions. If a positive reaction is observed in the control animals, only reactions in the treated animals with a greater intensity and/or duration of those in the control animals are considered positive.

II. Results and Discussion

A. Results

1. Clinical signs

There were no mortalities or clinical signs of toxicity and the body weight development of the treated animals was comparable to that of the controls.

2. Dermal reactions

In the preliminary study, No, irritation was noted at scoring (induction phase) with 50% (w/w) test item. A scoring of 1 was noted on day 2 in the female animal and on day 9 in the male animal with the undiluted test item. No dermal reactions were noted during the preliminary challenge phase with either

concentration. Therefore 100% was selected as the concentration for the induction and challenge phases of the main study.

In the main study, dermal reactions were noted during the induction phase, following application of the undiluted test item on days 1 and 3. Therefore, the concentration was reduced to 50% (w/w).

The scoring of the dermal reactions during the challenge phase of the main study are summarised in the table below.

Table 7.1.6-1: Scoring of dermal reaction during the challenge phase of the main study

	24 hours				48 hours				Total number of animals affected	
After first challenge										
	Male		**Female**		**Male**		**Female**		**Male**	**Female**
	LF	**RF**	**LF**	**RF**	**LF**	**RF**	**LF**	**RF**		
Control	0/5	5/5	0/5	1/5	0/5	2/5	0/5	1/5	5/5	1/5
Treated	0/10	6/10	0/10	3/10	0/10	4/10	0/10	2/10	6/10	4/10
After second challenge										
Control	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Treated	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10

*Number of animals with positive dermal response (scores of 1-3) /number of animals in dose group, LF = Left flank (vehicle), RF = right flank (test item)

Following the first challenge application, discrete erythema (grade 1) was observed at the 24-hour reading in 6/10 and 9/20 of the control and treated groups respectively, persisting until the 48-hour reading in 3/10 and 6/10 animals, respectively. As the challenge results were equivocal, a second challenge application was administered (following an interval of 14-days).

Following the second challenge application, no dermal reactions were noted. Therefore, it is considered that the dermal reactions following the first challenge were secondary to irritation and not elicitation.

III. Conclusion

Under the conditions of this modified Beuhler test, FLC+PCH SC 687.5 is not a skin sensitiser, therefore no classification for skin sensitisation is warranted on the basis of this study.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the skin sensitising potential of FLC+PCH SC 687.5.

Under the conditions of this study, FLC+PCH SC 687.5 is not a skin sensitiser, and classification for skin sensitisation is therefore not required on the basis of this study.

Data Point:	KCP 7.1.6/02
Report Author:	[redacted]
Report Year:	2004
Report Title:	EXP11120A (AE B066752 04 SC61 A1) (AE C638206 62.5 g/l + propamocarb HCl 625 g/l) - Evaluation of potential dermal sensitization in the local lymph node assay
Report No:	C046056
Document No:	M-237614-01-1
Guideline(s) followed in study:	OECD 429 (2002)
Deviations from current test guideline:	None
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Executive Summary:

The skin sensitising potential of FLC+PCH SC 687.5 was investigated in a mouse local lymph node assay (LLNA). Groups of 4 female CBA mice were topically administered control item or test substance at concentrations of 10, 25, 50 or 100 %; 1% aqueous Pluronic acid provided the vehicle/vehicle control whilst p-Benzoquinone 0.1% in 50:50 test-substance: vehicle provided the positive control. The test substance or control was applied to the dorsal surface of each ear, daily on days 0, 1 and 2 of the study. The test site was examined for dermal reactions and animals were examined daily for mortality and clinical signs; body weights were recorded at the start of the study and at sacrifice. Following injection with ^{3}H methyl thymidine, the nodes of each group of mice were removed and pooled and prepared for the determination of proliferation indices. A proliferation index of ≥3 is considered a positive response.

There were no deaths or clinical signs of toxicity and the animals gained the expected amount of weight. No local dermal irritation was seen at the application site. Simulation index values were 0.96, 0.66, 1.6 and 6.3 at concentrations of 10, 25, 50 and 100% respectively. As the simulation index at 100% was >3 FLC+PCH SC 687.5 is considered a mild sensitiser. The solvent and positive controls gave the expected results thus confirming the validity of the assay.

As the EC3 value was >2 and the lower concentrations showed no positive proliferative response, FLC+PCH SC 687.5 should be classified for skin sensitisation category 1B (H317).

A. Materials

1. Test material

Test substance:	Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity:	Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.:	OP220829

2. Vehicle and/or positive control

Vehicle	Pluronic acid
Positive control	p-Benzoquinone

3. Test animals

Species:	Mice
Strain:	CBA/J
Sex:	Female
Age:	At least 8 weeks old
Weight at start:	Not stated
Source:	[redacted]
Acclimation period:	At least 5 days
Identification:	Cage card
Diet:	Certified rodent pellet diet AO4C-10, SAFE, France
Water:	Provide *ad libitum*
Housing:	Individually housed in suspended, stainless steel, wire mesh cages
Temperature:	20˚C to 24˚C
Humidity:	40% to 70%
Air changes:	10 to 15 changes per hour
Photoperiod:	12 hours light/12 hours dark

B. Study design

1. In-life dates: October 20, 2004 to October 26, 2004

2. Animal assignment and treatment

No. of animals (group size)	4 female/group
Range finding	No
Exposure (concentration(s), no. of applications)	0 (vehicle control), 10, 25, 50 & 100% and 0.1% p-Benzoquinone in a 50:50 test substance: vehicle mixture

Each mouse was topically dosed on the dorsal surface of each ear, once daily on days 0,1 and 2 with 25µl of the test substance using an Eppendorf pipette; the applied dose remained on the ear reflecting realistic exposure to the test substance.

C. Methods

1. Observations

The animals were examined daily for mortality and clinical signs of toxicity. Body weights were recorded at the start of the test and at sacrifice.

2. Dermal observations

The site of application was examined for signs of local irritation.

3. Proliferation assay

On day 5 of the study, the tail vein of each mouse was injected with 250 µl of sodium chloride (0.9%) containing 20µCi of ^{3}H methyl thymidine; the mice were retained in a plastic cage for 5 hours. The nodes form each group of 4 mice were pooled in a tube of physiological saline and disaggregated with a plastic piston to obtain a connective-tissue-free cell suspension.

Cell suspensions were washed with 10 mL of 0.9% physiological saline, centrifuged for 20 minutes at 1800 rpm. The resulting pellets were resuspended in 4 L of 5% trichloroacetic acid (TCA) and stored

overnight at approximately +4˚V. following a final centrifugation, the pellets were resuspended in 1 mL of saline. Mixed and placed in an ultrasonic bath for 25 minutes. The dispersed cell suspensions were then added to 10 mL of scintillation fluid and assayed in a beta counter. Results were expressed as disintegrations per minute (DPM) per animal. Stimulation indices (SI) were calculated according to the formula SI = DPM of treated group/DPM of control group.

4. Evaluation criteria

A test substance is regarded as a skin sensitiser if one concentration of the test substance results in an increase of ^{3}H-TdR incorporation of 3-fold or greater (i.e. an SI of 3), when compared with control values. A dose response should be excluded, and no skin irritation should be seen. The concentration causing the 3-fold increase is known as the EC3.

II. Results and Discussion

A. Results

1. Clinical signs

There were no deaths or clinical signs of toxicity. Animals of the treated and control groups gained the expected amount of weight during the study.

2. Dermal reactions

No cutaneous reactions were observed at the treatment site in either the treated, negative control or positive control groups.

3. Proliferation assay

Table 5.1.6-2: mean DPM and simulation index

Group No.	Concentration	Mean DPM	Simulation index
1	Control*	792	-
2	10%	764	0.96
3	25%	524	0.66
4	50%	1261	1.6
5	100%	4961	6.3
6	Positive control**	3511	4.4

*1% Aqueous Pluronic acid **0.1% p-Benzoquinone in 50% test substance & 50% vehicle

A positive lymphoproliferative response was noted for 100% FLC+PCH SC 687.5 which gave an SI>3 (6.3). The positive and negative controls gave the expected results, thus confirming the validity of the assay. According to the guidance on the application of the CLP criteria, it is possible to sub categorise a substance into either 1A or 1B based on the EC3 value. As the EC value was >2%, and no positive proliferative responses were seen at the lower doses, FLC+PCH SC 687.5 should be classified as H317 subcategory 1B for skin sensitisation.

III. Conclusion

A positive proliferative was seen at a concentration of 100% test substance. Therefore, classification for skin sensitisation 1B (H317) is warranted for FLC+PCH SC 687.5 based on this mouse LLNA.

Assessment and conclusion by applicant:

The study is valid and acceptable to determine the skin sensitising potential of FLC+PCH SC 687.5.

Under the conditions of this study, FLC+PCH SC 687.5 is a mild skin sensitiser, and classification for skin sensitisation category 1B (H317) is appropriate.

CP 7.1.7 Supplementary studies on the plant protection product

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the active substance(s) or other components in FLC+PCH SC 687.5 that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since FLC+PCH SC 687.5 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 fluopicolide when used in the FLC+PCH SC 687.5 formulation are provided in the following sections.

For operators, exposure estimates predict acceptable risks for all the intended use of FLC+PCH SC 687.5, with no PPE required for outdoor uses on potatoes or lettuce only normal workwear (with arms, legs, torso covered). For glasshouse use acceptable exposure on cucumbers requires gloves and coveralls to be worn. Exposure estimates for residents predict acceptable risks for all intended uses of FLC+PCH SC 687.5. Since no AAOEL has been set for either active, the exposure estimate for residents also covers bystanders; therefore, exposure estimates for bystanders are also considered acceptable for all intended uses. Regarding worker exposure, exposure estimates predict acceptable risks for workers for all intended uses of FLC+PCH SC 687.5, provided normal workwear covering arms, body and legs are worn for outdoor uses on potatoes or lettuce. For glasshouse use acceptable exposure on cucumbers requires workwear covering arms, body and legs and protective gloves to be worn. As the product is a mixture of two active substances, a combined exposure assessment is required. Only long-term combined exposure needs to be considered as neither active is acutely toxic. Exposure estimates predict acceptable risk for operators, residents, and workers for all intended uses of FLC+PCH SC 687.5 from combined long-term exposure to fluopicolide and propamocarb. Propamocarb and fluopicolide are not acutely toxic therefore a combined acute exposure risk assessment is not needed.

FLC+PCH SC 687.5 is a fungicide for the control of oomycete phytopathogens, especially in potato plants, but also in vegetables (indoors and outdoors). It combines fluopicolide (FLC), a fungicide with a novel mode of action and propamocarb-hydrochloride (PCH), a well-known anti-fungal compound. It is a suspension concentrate (SC) formulation containing 62.5 g/L fluopicolide (FLC) and 625 g/L propamocarb-hydrochloride (PCH) for the control of foliar, stem and tuber blight. It is applied by spraying, up to 4 applications per crop with a minimum spraying interval of 7 days between repeat applications.

Uses supported in this renewal are field crops of potatoes and lettuces and indoor crops of cucumbers. Details of supported uses are presented in Appendix 1 at the end of this document and summarised in the table below.

Table 7.2-01: Summary of critical uses patterns (i.e. worst case) of FLC+PCH SC 687.5

Crop	Application max rate of formulation (L/ha)	Application rate (Kg as/ha per application)		Spray dilution water (L/ha)	Application equipment	Number of applications
		Fluopicolide	Propamocarb			
Field Crops						
Potato	1.6	0.1	1	100-1000	Field Crop Sprayer	1-4
Potatoes treated with a tractor boom (Field Crop Sprayer). AOEM model used. This scenario also covers potatoes treated with 1-3 applications and 1-2 applications per crop.						
Lettuce	1.6	0.1	1	200-1000	Handheld Sprayer	1-2
Lettuce treated with a manual hand-held and knapsack sprayer. AOEM model used. This scenario also covers lettuces treated with only 1 application per crop.						

Greenhouse Crop						
Cucumber (high tech glasshouse)	1.6	0.1	1	1000-1250	Handheld Sprayer	1-3
Cucumbers treated with manual sprayer, and worker re-entry after roof-fogger. Up to 3 applications per crop. The Dutch greenhouse model used for operators and AOEM model used for workers.						

Estimations of potential operator exposure have been undertaken for fluopicolide and propamocarb-hydrochloride using the list of intended uses (Appendix 2 of this document) and the following predictive models:

Field crops: 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 FLC+PCH SC 687.5 on potatoes and lettuces. The AOEM calculator released on 30 March 2015 supports the EFSA guidance document[1] that was last updated on 24 April 2015.

Glasshouse crops: The Dutch greenhouse model has been used[2].

Dermal absorption and AOEL values

The estimations of human dermal penetration of fluopicolide and propamocarb which are the active substances in the mixed formulation FLC+PCH SC 687.5 were obtained from two *in vitro* dermal absorption studies using human skin conducted by [redacted] 2003; M-222382-01-1 and [redacted]; 2015; M-516805-01-1 respectively. The proposed values including the AOEL values are summarised below. The vapour pressures of both actives are below $5x10^{-3}$ Pa.

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

Endpoints used in risk assessment	Fluopicolide	Propamocarb
Dermal penetration		
Concentrate % (g/L of active)	0.26 % (62.5 g/L)	2% (625 g/L)
Spray dilution % (g/L of active)	13 %* (0.1 g/L outdoor use) 16 %* (0.08 g/L indoor use)	8.6%** (1 g/L outdoor use) 8.6%** (0.8 g/L indoor use)
Reference	Study M-222382-01-1 *in vitro* human	Study M-516805-01-1 *in vitro* human
Reference values		
AOEL (mg/kg body weight/day)	0.07 (based on 90 day rat study NOAEL of 7.4 mg/kg bw/day)	0.29 (EFSA Scientific Report (2006) 78, 1-80)

[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)

[2] Available from Ctgb https://english.ctgb.nl/documents/assessment-framework-ppp/2016/10/27/calculation-model-operator-nl-greenhouse

AAOEL (mg/kg bw/day)	None proposed for the renewal of fluopicolide	Not set (EFSA Scientific Report (2006) 78, 1-80)

*Pro-rata calculation for the highest in-use dilution from a value derived from the tested dilution of 0.25g/L with a dermal absorption of 5.1%
**Tested dilution was 0.3 g/L therefore no pro-rata adjustment needed

Summary of estimates

Exposure assessments pertinent to the assessment of non-dietary exposure are summarized below.

Crop	Model	Summary
Potatoes (Field)	AOEM	Can be used safely with vehicle-mounted sprayers provided normal workwear is worn (arms, legs, torso covered). Acceptable risk to bystanders and residents.
Lettuce (Field)	AOEM	Can be used safely with manual hand-held sprayers and manual knapsack sprayers provided normal workwear is worn (arms, legs, torso covered). Acceptable risk to bystanders and residents.
Cucumber (glasshouse)	Dutch Greenhouse (operators) AOEM (workers)	Can be used safely with hand-held sprayers provided workers wear gloves and protective coveralls. Can be used safely for worker re-entry following roof fogging provided normal workwear (arms, legs, torso covered) and gloves are worn. Acceptable risk to bystanders and residents.

Overall conclusion

Exposure estimates predict acceptable risks for all the intended use of FLC+PCH SC 687.5 as long as normal workwear (arms, legs, torso covered) is worn for all uses and in addition protective gloves should be used by operators and workers in glasshouses.

CP 7.2.1 Operator exposure

CP 7.2.1.1 Estimation of operator exposure

Potatoes

Table 7.2.1-01: Input parameters considered for the estimation of operator exposure for potatoes

AOEM EFSA calculator		
Product name and code	**FLC+PCH SC 687.5**	
Formulation type	SC soluble or suspension concentrate	
Category	Fungicide	
Crop type	Potatoes	
Indoor/outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Minimum water volume	100 L/ha	
DT50	30 days	
DFR	3 µg/cm2	
Buffer strip	2-3 metres	
Number of applications	1-4	
Interval between multiple applications	7 days	
Assumed area treated	50 ha/day	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	None	None
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Concentrate: 0.26% Dilution: 13% *For more information please refer to section 7.3*	Concentrate: 2% Dilution: 8.6% *For more information please refer to section 7.3*

The scenario of a tractor mounted sprayer in low crops was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.1-02: Estimated operator exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on potatoes

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Potato Field Crop Application, vehicle-mounted sprayer **Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH)** **Body weight 60 kg**					
4 applications a crop, 7 days between applications*					
AOEM 75th percentile **longer term** systemic exposure	no PPE; work wear - arms, body and legs covered during mixing/loading and during application.	0.0026	**3.65**	0.0454	**15.66**
AOEM 75th percentile **acute** systemic exposure	no PPE work wear - arms, body and legs covered during mixing/loading and during application.	0.0197	**NA**	0.1918	**N/A**
*** This scenario also applies to the following:** 3 applications a crop, 7 days between applications 2 applications a crop, 7 days between applications					

Lettuce

Table 7.2.1-03: Input parameters considered for the estimation of operator exposure for lettuce

AOEM EFSA calculator	
Product name and code	**FLC+PCH SC 687.5**
Formulation type	SC soluble or suspension concentrate
Category	Fungicide
Crop type	Lettuce
Indoor/outdoor	Outdoor
Application method	Downward spraying
Application equipment	Manual-Knapsack and Manual Hand-held
Minimum water volume	1000 L/ha
DT50	30 days
DFR	3 µg/cm2
Buffer strip	2-3 metres
Number of applications	1-2

Interval between multiple applications	7 days	
Assumed area treated	1 ha/day for manual-knapsack 4 ha/day for manual hand-held	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	none	none
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Concentrate: 0.26% Dilution: 13% *For more information please refer to section 7.3*	Concentrate: 2% Dilution: 8.6% *For more information please refer to section 7.3*

The scenario of a manual-knapsack sprayer and manual hand-held sprayer in low crops (lettuces) was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.1-04: Estimated operator exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on lettuce

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Lettuce Field Crop Application Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH) Body weight 60 kg 2 applications a crop, 7 days between applications (these scenarios also cover 1 application a crop)					
Manual-knapsack sprayer 1 ha/day					

AOEM 75th percentile **longer term** systemic exposure	Potential exposure (no clothing)	0.197	**281.74**	0.1339	**46.17**
	no PPE: work wear - arms, body and legs covered during mixing/loading and during application.	0.0239	**34.18**	0.0190	**6.56**
AOEM 75th percentile **acute** systemic exposure	Potential exposure (no clothing)	0.308	**N/A**	0.2128	**N/A**
	no PPE: work wear - arms, body and legs covered during mixing/loading and during application.	0.1470	**N/A**	0.1053	**N/A**
Manual hand-held 4 ha/day					
AOEM 75th percentile **longer term** systemic exposure	Potential exposure (no clothing)	0.1966	**280.84**	0.3548	**122.34**
	no PPE: work wear - arms, body and legs covered during mixing/loading and during application.	0.0232	**33.21**	0.0460	**15.87**
AOEM 75th percentile **acute** systemic exposure	Potential exposure (no clothing)	0.3098	**N/A**	0.5955	**N/A**
	no PPE: work wear - arms, body and legs covered during mixing/loading and during application.	0.1463	**N/A**	0.2755	**N/A**

Cucumber:
The Dutch Glasshouse Model has been used to estimate exposure to operators applying the product to cucumbers in glasshouses. The following assumptions are made:

Table 7.2.1.05: Input parameters considered for the estimation of operator exposure for cucumbers grown under glass

Dutch Glasshouse Model	
Product name and code	**FLC+PCH SC 687.5**

Formulation type	SC soluble or suspension concentrate
Category	Fungicide
Crop type	Cucumber
Indoor/outdoor	Indoor
Application method	Spraying
Application equipment	Manual sprayer
Minimum water volume	1000 L/ha
Number of applications	1-3
Interval between multiple applications	7 days
Assumed area treated	1 ha/day
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L
	Propamocarb (PCH) 625 g/L
Maximum application rate of active substance	0.1 kg/ha
	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day
	0.29 mg/kg bw/day
AAOEL	none
	none
Inhalation absorption	100%
	100%
Oral absorption	100%
	100%
Dermal absorption	Concentrate: 0.26% Dilution: 16% *For more information please refer to section 7.3*
	Concentrate: 2% Dilution: 8.6% *For more information please refer to section 7.3*

The following sections show the summary results from the Dutch Glasshouse model calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.1-06: Estimated operator exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on cucumbers

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Cucumber glasshouse application, manual-knapsack sprayer Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH) Body weight 60 kg					
3 applications a crop, 7 days between applications*					

DUTCH GLASSHOUSE MODEL **longer term** systemic exposure	**None**	0.055	**78.6**	0.30	**104.6**
	Gloves and coveralls	0.007	**10**	0.0453	**15.6**
*** This scenario also applies to the following:** 2 applications a crop, 7 days between applications 1 application a crop					

Overall conclusion on operator exposure

Exposure estimates predict acceptable risks for all the intended use of FLC+PCH SC 687.5, with no PPE required for outdoor uses on potatoes or lettuce only normal workwear (with arms, legs, torso covered). For glasshouse use acceptable exposure on cucumbers requires gloves and coveralls to be worn.

CP 7.2.1.2 Measurement of operator exposure

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

CP 7.2.2 Bystander and resident exposure

CP 7.2.2.1 Estimation of bystander and resident exposure

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

Bystanders and residents are not involved in application or 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. Handheld application is considered to be worse case compared to field crop sprayer.

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

Bystander exposure

Propamocarb: No AAOEL has been set for propamocarb as it does not present an acute toxicity hazard. For plant protection products with no potential acute systemic toxicity the long-term risk assessment for bystander may be considered to be covered by the risk assessment for residents.

For fluopicolide: No AAOEL is proposed for this renewal as it does not present and acute toxicity hazard. For plant protection products with no potential acute systemic toxicity the long-term risk assessment for bystander may be considered to be covered by the risk assessment for residents.

Therefore, no bystander exposure assessment is required for FLC+PCH SC 687.5 as bystanders are considered to be covered by the risk assessment for residents.

Resident exposure

The assessment of potential resident exposure has been conducted using the EFSA AOEM model.

Potatoes

Table 7.2.2-01: Input parameters considered for the estimation of resident exposure for potatoes

AOEM EFSA calculator	
Product name and code	**FLC+PCH SC 687.5**
Formulation type	SC soluble or suspension concentrate
Category	Fungicide
Crop type	Potatoes
Indoor/outdoor	Outdoor
Application method	Downward spraying
Application equipment	Vehicle-mounted
Minimum water volume	100 L/ha
DT50	30 days
DFR	3 µg/cm2
Buffer strip	2-3 metres
Number of applications	1-4
Interval between multiple applications	7 days
Assumed area treated	50 ha/day
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L
Maximum application rate of active substance	0.1 kg/ha
AOEL systemic	0.07 mg/kg bw/day
AAOEL	none
Inhalation absorption	100%
Oral absorption	100%
Dermal absorption	Concentrate: 0.26% Dilution: 13%

	For more information please refer to section 7.3

The scenario of a tractor mounted sprayer in low crops was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.2-02: Estimated resident exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on potatoes

Model data	Exposure route	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	**% of AOEL**	**Total absorbed dose (mg/kg bw/day)**	**% of AOEL**
Potato Field Crop Application, vehicle-mounted sprayer **Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH)** **Body weight 60 kg**					
4 applications a crop, 7 days between applications*					
AOEM 75th percentile systemic exposure **1-3-year-old child**	Spray drift	0.0035	**5.01**	0.0233	**8.03**
	Vapour	0.0011	**1.53**	0.0011	**0.37**
	Surface deposits	0.0009	**1.23**	0.0066	**2.27**
	Entry into treated crops	0.0070	**10.00**	0.0463	**15.96**
	All pathways (mean)	0.0092	**13.17**	0.0557	**19.19**
AOEM 75th percentile systemic exposure **Adult**	Spray drift	0.0008	**1.20**	0.0055	**1.91**
	Vapour	0.0002	**0.33**	0.0002	**0.08**
	Surface deposits	0.0003	**0.40**	0.0019	**0.64**
	Entry into treated crops	0.0039	**5.55**	0.0257	**8.87**
	All pathways (mean)	0.0039	**5.62**	0.0247	**8.53**
*** This scenario is worst case so also applies to the following application rates:** 3 applications a crop, 7 days between applications 2 applications a crop, 7 days between applications					

Lettuce

Table 7.2.2-03: Input parameters considered for the estimation of resident exposure for lettuce

AOEM EFSA calculator	
Product name and code	**FLC+PCH SC 687.5**
Formulation type	SC soluble or suspension concentrate
Category	Fungicide
Crop type	Lettuce

Indoor/outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Manual-Knapsack and Manual Hand-held	
Minimum water volume	200 L/ha	
DT50	30 days	
DFR	3 µg/cm2	
Buffer strip	2-3 metres	
Number of applications	1-2	
Interval between multiple applications	7 days	
Assumed area treated	1 ha/day for manual-knapsack 4 ha/day for manual hand-held	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	none	none
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Concentrate: 0.26% Dilution: 13% *For more information please refer to section 7.3*	Concentrate: 2% Dilution: 8.6% *For more information please refer to section 7.3*

The scenario of a manual-knapsack sprayer, and manual hand-held sprayer in low crops (lettuces) was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.2-04: Estimated resident exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on lettuces

Model data	Exposure route	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Lettuce Field Crop Application - manual-knapsack-sprayer Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH) 2 applications a crop, 7 days between applications (this scenario is worst case so also cover 1 application a crop)					
AOEM 75th percentile systemic exposure **1-3-year-old child**	Spray drift	0.0018	**2.51**	0.0116	**4.01**
	Vapour	0.0011	**1.53**	0.0011	**0.37**
	Surface deposits	0.0005	**0.72**	0.0038	**1.32**
	Entry into treated crops	0.0041	**5.80**	0.0269	**9.26**
	All pathways (mean)	0.0056	**8.06**	0.0317	**10.94**
AOEM 75th percentile systemic exposure **Adult**	Spray drift	0.0004	**0.60**	0.0028	**0.96**
	Vapour	0.0002	**0.33**	0.0002	**0.08**
	Surface deposits	0.0002	**0.23**	0.0011	**0.37**
	Entry into treated crops	0.0023	**3.22**	0.0149	**5.15**
	All pathways (mean)	0.0023	**3.35**	0.0142	**4.91**

Cucumber

Resident exposure to cucumbers grown in glasshouses will not occur so no exposure estimate is necessary.

Overall conclusion on resident exposure

Exposure estimates predict acceptable risks for residents for all intended uses of FLC+PCH SC 687.5.

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 and resident exposure was not necessary and was therefore not carried out.

CP 7.2.3 Worker exposure

CP 7.2.3.1 Estimation of worker exposure

The worker re-entry exposure has been calculated for fluopicolide following application of FLC+PCH SC 687.5 formulation for the representative use(s) on potatoes (field), lettuce (field) and cucumbers (indoor). The estimation(s) is / are provided in the following sections.

FLC+PCH SC687.5 is a fungicide that is applied to various crops. Work activities are tasks like pruning/thinning or harvesting which are done by workers usually throughout the growing season. For some crops (potato) harvesting is fully automatized. For lettuce and cucumber, harvesting may be a manual or semi-manual operation. Re-entry exposure is therefore evaluated and compared with the AOEL of fluopicolide (FLC) and propamocarb-hydrochloride (PCH). Predicted exposures are calculated from a cumulative foliar deposit based on a maximum number of applications made at the maximum dose and 8 hours contact with foliage per day. Systemic exposure values are calculated using worst case dermal absorption values.

Potatoes

The AOEM EFSA calculator has been used to estimate exposure to workers for crop inspection and irrigation activities. The following assumptions were made:

Table 7.2.3-01: Input parameters considered for the estimation of worker exposure for potatoes

AOEM EFSA calculator		
Product name and code	**FLC+PCH SC 687.5**	
Formulation type	SC soluble or suspension concentrate	
Category	Fungicide	
Crop type	Potatoes	
Indoor/outdoor	Outdoor	
DT50	30 days	
DFR	3 µg/cm2	
Buffer strip	2-3 metres	
Number of applications	1-4	
Interval between multiple applications	7 days	
Work rate per day	2 hours/day	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	none	none
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Dilution: 13% (worst case) *For more information please refer to section 7.3*	Dilution: 8.6% (worst case) *For more information please refer to section 7.3*

The scenario of inspection and irrigation in low crops was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.3-02: Estimated worker exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on potatoes

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Potato Field Crop Application, worker inspection, irrigation 2 hours **Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH)** **Body weight 60 kg**					
4 applications a crop, 7 days between applications*					
AOEM **longer term** systemic exposure	Potential exposure (no clothing)	0.0518	**74.05**	0.3429	**118.25**
	Workwear covering arms, body, and legs	0.0058	**8.29**	0.0384	**13.24**
*** This scenario is worst case so also applies to the following application rates:** 3 applications a crop, 7 days between applications 2 applications a crop, 7 days between applications					

Lettuce

The AOEM EFSA calculator has been used to estimate exposure to workers for reaching and picking. The following assumptions were made:

Table 7.2.3-03: Input parameters considered for the estimation of worker exposure for lettuces

AOEM EFSA calculator		
Product name and code	**FLC+PCH SC 687.5**	
Formulation type	SC soluble or suspension concentrate	
Category	Fungicide	
Crop type	Lettuces	
Indoor/outdoor	Outdoor	
DT50	30 days	
DFR	3 µg/cm2	
Buffer strip	2-3 metres	
Number of applications	1-2	
Interval between multiple applications	7 days	
Work rate per day	8 hours/day	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	none	none
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Dilution: 13% (worst case) *For more information please refer to section 7.3*	Dilution: 8.6% (worst case) *For more information please refer to section 7.3*

The scenario of workers reaching and picking in low crops was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.3-04: Estimated worker exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on lettuces

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Lettuce Field Crop Application, worker reaching and picking 8 hours Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH) Body weight 60 kg					
2 applications a crop, 7 days between applications*					
AOEM **longer term** systemic exposure	Potential exposure (no clothing)	0.0558	**79.74**	0.3692	**127.33**
	Workwear covering arms, body, and legs	0.0241	**34.37**	0.1592	**54.88**
	Workwear covering arms, body and legs and protective gloves	0.0056	**7.9**	0.0369	**12.73**
*** This scenario is worst case so also applies to the following application rates:** 1 application a crop					

Cucumbers

The AOEM EFSA calculator has been used to estimate exposure to workers where the product is applied to cucumbers in glasshouses assuming the roof-fogger as the worst-case for indoor application method. The following assumptions are made:

Table 7.2.3-05: Input parameters considered for the estimation of operator exposure for cucumbers grown under glass

AOEM EFSA calculator		
Product name and code	**FLC+PCH SC 687.5**	
Formulation type	SC soluble or suspension concentrate	
Category	Fungicide	
Crop type	Cucumber	
Indoor/outdoor	Indoor	
DT50	30 days	
DFR	3 µg/cm2	
Number of applications	1-3	
Interval between multiple applications	7 days	
Work rate per day	8 hours/day	
Active substance(s) (incl. content)	**Fluopicolide (FLC)** 62.5 g/L	**Propamocarb (PCH)** 625 g/L
Maximum application rate of active substance	0.1 kg/ha	1 kg/ha
AOEL systemic	0.07 mg/kg bw/day	0.29 mg/kg bw/day
AAOEL	none	none
Inhalation absorption	100%	100%
Oral absorption	100%	100%
Dermal absorption	Concentrate: 0.26% Dilution: 16% *For more information please refer to section 7.3*	Concentrate: 2% Dilution: 8.6% *For more information please refer to section 7.3*

The scenario of reaching and picking fruiting vegetables in glasshouse crops was assessed and the defaults settings of the EFSA calculator was used with no refinements. The following sections show the summary results from the calculator. An attached appendix 2 depicts the related full output pages from the calculator.

Table 7.2.3-06: Estimated worker exposure to fluopicolide (FLC) and propamocarb-hydrochloride (PCH) on lettuces

Model data	Level of PPE	Fluopicolide		Propamocarb	
		Total absorbed dose (mg/kg bw/day)	% of AOEL	Total absorbed dose (mg/kg bw/day)	% of AOEL
Cucumber Glasshouse Application - Roof fogger, worker reaching and picking 8 hours Application rate 1.6 L/ha PPP (0.1 kg/ha FLC and 1.0 kg/ha PCH) Body weight 60 kg					
3 applications a crop, 7 days between applications					
AOEM **longer term** systemic exposure	Potential exposure (no clothing)	0.0976	**139.37**	0.9756	**184.01**
	Workwear covering arms, body and legs	0.0432	**61.70**	0.4319	**83.24**
	Workwear covering arms, body and legs and protective gloves	0.0116	**16.51**	0.1156	**24.61**

Overall conclusion on worker exposure

Exposure estimates predict acceptable risks for workers for all intended uses of FLC+PCH SC 687.5, provided normal workwear covering arms, body and legs are worn for outdoor uses on potatoes or lettuce. For glasshouse use acceptable exposure on cucumbers requires workwear covering arms, body and legs and protective gloves to be worn.

CP 7.2.3.2 Measurement of worker exposure

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

The following study has been conducted to determine the dislodgeable foliar reside of fluopicolide and propamocarb on cucumbers. The study may be used to refine the default DFR.

Data Point:	KCP 7.2.3.2/01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Determination of the dislodgeable foliar residues (DFR) of fluopicolide and propamocarb in/on cucumber after spraying of fluopicolide & propamocarb-hydrochloride SC 687.5 in the greenhouse in Italy - FLC+PCH SC 62,5+625 GU-WW
Report No:	12-2903
Document No:	M-460022-01-1
Guideline(s) followed in study:	US EPA OCSPP 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a))
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted fluopicolide DAR 2006
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities.
Acceptability/Reliability:	Yes

Executive Summary:

The GLP study is valid and acceptable to determine the dislodgeable foliar residue (DFR) of fluopicolide and propamocarb on cucumber leaves from a glasshouse study conducted in Italy.

Under the conditions of this study, the mean (geometric) DFR on cucumber leaves was 1.1 µg/cm² per kg a.s./ha for fluopicolide and 0.2 µg/cm² per kg a.s./ha for propamocarb.

The DFR from this study may be used to refine the default DFR value in exposure assessments if a higher tier assessment is required.

I. Material and Methods

A. Materials

1. Test material

Test substance: Fluopicolide + Propamocarb-hydrochloride SC 687.5 (62.5+625 g/L)
Purity: Fluopicolide 62.5 g/L, Propamocarb 625 g/L
Batch no.: EVS7000925

B. Study design

The study consisted of one field trial in a glasshouse in Italy.

1. Trial dates, location, crop and plot size

Location	I-00050 Palidoro-Fiumicino, Italy
Type of trial	Indoor, glasshouse
Crop	Cucumber, Marketmore
Date of planting	12-09-2012
Date of harvest	01-10 to 30-11 2012
Number of plants per ha	11110
Soil	Sand

Plot size	194.4 m^2 divided into 3 sub-plots of 64.8 m^2 each

2. Application conditions

Application type	Spraying
Nozzle type	Albuz AVI ISO 11003, size 110 03
Pressure	5.0 bar
Date of application	05-10-2012, 15-10-2012 and 25-10-2012 (3 applications with 10-day interval between spraying)
Water	750 L/ha
Crop height	0.45, 0.8, and 1.2 meters at 1st, 2nd, and 3rd application respectively
Application rate	0.125 kg/ha fluopicolide 1.25 kg/ha propamocarb
Concentration of active substance (%) in spray dilution	0.0167% fluopicolide 0.167% propamocarb
Growth stage [BBCH]	61, 63, 71 at 1st, 2nd and 3rd applications respectively
Air temperature °C	30, 25, 30 at 1st, 2nd and 3rd applications respectively
Relative humidity [%]	36, 54, 43 at 1st, 2nd and 3rd applications respectively

3. Leaf sample collections

Leaf punches were collected using a leaf-punch sampler. Each sample consisted of 40 disks of 2.523 cm diameter and a disk area of 5cm^2. A sample was collected from each of the three sub-plots to provide three replicates at each sampling date. Leaf punches were taken from upper, middle and lower portions of the foliage and interior and exterior positions. Control punch samples were taken prior to the first product application. After the first treatment samples were first taken on the day of application after the spray had dried.

4. Dislodgeable residue collection

Dislodging was performed not later than 4 hours after sample collection. Samples were dislodged by adding a100 mL of a 0.01% aqueous solution of Aerosol OT (a docusate sodium salt surfactant) to the jars containing the leaf punch samples. These were placed on a shaker for 10 minutes. The solution was decanted, and the process repeated by adding a fresh sample of dislodging solution to the leaf samples. Each final dislodged sample consisted of 200 ml of dislodging solution.

5. Control and field recovery samples

Unspiked untreated control samples were collected using the same method as for the treated leaf samples.

Spiked samples were used to demonstrate stability of the samples during the study and the ability of the analytical method to recover an analyte. For spiked samples, fluopicolide and propamocarb were applied in the field and leaf samples collected prior to the first spray application. Spikes were 0.01, 0.1 and 1.0 µg/cm^2 of test substance (corresponding to 20, 200 and 2000 µg/L respectively). Dislodgeable residue was collected from the leaves in the same manner as described for treated crop. In addition,

control samples of dislodged residue solution were also spiked. Three replicate samples were collected for each spike.

6. Analytical method

The method was by Stuke, S. and Diehl, P. (3013), method number 01353.

Acetonitrile and an internal standard solution were added to samples, the samples were filtered and analyzed by HPLC-MS/MS. The limit of quantification (LoQ) was set to 20 µg/L.

II. Results and Discussion

No residues above the LoQ were found in the control samples.

Spiked leaf wash sample recoveries showed acceptability of the analytical method. For fluopicolide mean recovery was 93% at the LOQ of 0.01 µg/cm^2. For propamocarb mean recovery was 98% at the LOQ of 0.01 µg/cm^2.

Mean recovery of spiked field samples were 92% and 83% for fluopicolide and propamocarb respectively which is within acceptability criteria (of 70 to 110%). Relative standard deviation was 11.5% for fluopicolide and 12.8% for propamocarb samples with is within acceptable levels (of ≤ 20%).

The residues from field samples are shown in the table below. To convert to DFR a correction for the application rate the values of the DFR are expressed in µg/cm^2 per kg a.s./ha.

Table 7.2.3-07: Dislodgeable foliar residues of fluopicolide and propamocarb in cucumber leaf punch washing specimens

DA1.T	DA2.T	DA3.T	Fluopicolide µg/cm^2	DFR Fluopicolide µg/cm^2 per kg a.s./ha	Propamocarb µg/cm^2	DFR Propamocarb µg/cm^2 per kg a.s./ha
0			0.373	2.984	3.150	2.52
1			0.262	2.096	1.370	1.096
3			0.230	1.84	0.277	0.2216
7			0.084	0.672	0.075	0.06
10			0.018	0.144	0.018	0.0144
10	0		0.289	2.312	1.825	1.46
11	1		0.213	1.704	0.562	0.4496
13	3		0.184	1.472	0.180	0.144
17	7		0.099	0.792	0.061	0.0488
20	10		0.038	0.304	0.020	0.016
20	10	0	0.228	1.824	1.312	1.0496
21	11	1	0.183	1.464	0.410	0.328
23	13	3	0.141	1.128	0.188	0.1504
27	17	7	0.119	0.952	0.212	0.1696
34	24	14	0.079	0.632	0.060	0.048
Geometric Mean			**0.134**	**1.072**	**0.239**	**0.191**

DA(1.)T = Days after (first) treatment.
DA(2.)T = Days after (second) treatment.
DA(3.)T = Days after (third) treatment; LOQ = 0.01 µg/cm2
Application rate was 0.125 kg/ha fluopicolide and 1.25 kg/ha propamocarb

The mean DFR was 1.1 µg/cm^2 per kg a.s./ha for fluopicolide and 0.2 µg/cm^2 per kg a.s./ha for propamocarb. This value may be used to refine worker exposure assessments if a higher-tier exposure assessment is required.

III. Conclusion

Under the conditions of this study, the mean DFR for fluopicolide was 1.1 µg/cm2 per kg a.s./ha and the mean DFR for propamocarb was 0.2 µg/cm2 per kg a.s./ha. This value may be used to refine worker exposure assessments if a higher tier exposure assessment is required.

Assessment and conclusion by applicant:

The GLP study is valid and acceptable to determine the dislodgeable foliar reside (DFR) of fluopicolide and propamocarb on cucumber leaves.

Under the conditions of this study, the mean DFR for fluopicolide was 1.1 µg/cm^2 per kg a.s./ha, the mean DFR for propamocarb was 0.2 µg/cm^2 per kg a.s./ha.

This value may be used to refine worker exposure assessments if a higher tier exposure assessment is required.

Combined exposure

The product is a mixture of two active substances. Therefore, a combined exposure assessment is provided. Only a long-term combined exposure assessment is required as propamocarb and fluopicolide are not acutely toxic.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL/RVNAS. This is equivalent to the predicted exposure as % of systemic AOEL/RVNAS to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 7.2.3-08: Long-term risk assessment from combined exposure to fluopicolide and propamocarb on potatoes

Scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]
Crop: Potatoes (Field) *Application rate: 0.1 kg/ha fluopicolide, 1 kg/ha propamocarb* ***applied by vehicle-mounted sprayer***		
Operators, normal workwear For details please refer to 7.2.1. Only the worst-case scenario is presented	Fluopicolide	0.0365
	Propamocarb	0.1566
	Cumulative risk Operators (HI)[2]	**0.1931**
Resident – Adult For details please refer to 7.2.2. Only the worst case scenario is presented	Fluopicolide	0.0562
	Propamocarb	0.0853
	Cumulative risk Resident-Adult (HI)[2]	**0.1415**
Resident – Child[1] For details please refer to 7.2.2. Only the worst-case scenario is presented	Fluopicolide	0.1317
	Propamocarb	0.1919
	Cumulative risk Resident-Child (HI)[2]	**0.3236**
Workers, with Workwear For details please refer to 7.2.3. Only the worst-case scenario is presented	Fluopicolide	0.0829
	Propamocarb	0.1324
	Cumulative risk Workers (HI)[2]	**0.2153**

[1] The higher exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI =Hazard Index
[3] HQ = Hazard Quotient

For potato uses the Hazard Index is < 1. Therefore, the combined exposure to all active substances in FLC+PCH SC 687.5 is not expected to present a risk for operators, workers, bystanders, and residents. No further refinement of the assessment is required.

Table 7.2.3-09: Long-term risk assessment from combined exposure to fluopicolide and propamocarb on lettuces

Scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]
Crop: Lettuces (Field) *Application rate: 0.1 kg/ha fluopicolide / 1 kg/ha propamocarb* *Applied by manual hand-held sprayer*		
Operators, normal workwear For details please refer to 7.2.1. Only the worst-case scenario is presented	Fluopicolide	0.3321
	Propamocarb	0.1587
	Cumulative risk Operators (HI)[2]	**0.4908**
Resident – Adult[1] For details please refer to 7.2.2. Only the worst case scenario is presented	Fluopicolide	0.0335
	Propamocarb	0.0491
	Cumulative risk Resident-Adult (HI)[2]	**0.0826**
Resident – Child[1] For details please refer to 7.2.2. Only the worst-case scenario is presented	Fluopicolide	0.0806
	Propamocarb	0.1094
	Cumulative risk Resident-Child (HI)[2]	**0.1900**
Workers, with Workwear For details please refer to 7.2.3. Only the worst-case scenario is presented	Fluopicolide	0.3437
	Propamocarb	0.5488
	Cumulative risk Workers (HI)[2]	**0.8925**

[1] The higher exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI =Hazard Index
[3] HQ = Hazard Quotient

For lettuce uses the Hazard Index is < 1. Therefore, the combined exposure to all active substances in FLC+PCH SC 687.5 is not expected to present a risk for operators, workers, bystanders, and residents. No further refinement of the assessment is required.

Table 7.2.3-10: Long-term risk assessment from combined exposure to fluopicolide and propamocarb on cucumbers

Scenario	Active Substance	Estimated exposure / AOEL (RV/NAS) (HQ)[3]
Crop: Cucumbers (Indoor) *Application rate: 0.1 kg/ha fluopicolide / 1 kg/ha propamocarb* ***Applied by manual-knapsack sprayer***		
Operators, with gloves and coveralls during mixing and loading and application. For details please refer to 7.2.1. Only the worst-case scenario is presented	Fluopicolide	0.10
	Propamocarb	0.156
	Cumulative risk Operators (HI)[2]	**0.256**
Resident – Adult[1] For details please refer to 7.2.2. Only the worst case scenario is presented	Fluopicolide	N/A
	Propamocarb	N/A
	Cumulative risk Resident-Adult (HI)[2]	N/A
Resident – Child[1] For details please refer to 7.2.2. Only the worst-case scenario is presented	Fluopicolide	N/A
	Propamocarb	N/A
	Cumulative risk Resident-Child (HI)[2]	N/A
Workers, with workwear and protective gloves *F*or details please refer to 7.2.3. Only the worst-case scenario is presented	Fluopicolide	0.1651
	Propamocarb	0.2461
	Cumulative risk Workers (HI)[2]	**0.4112**

[1] The higher exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI =Hazard Index
[3] HQ = Hazard Quotient

For lettuce uses the Hazard Index is < 1. Therefore, the combined exposure to all active substances in FLC+PCH SC 687.5 is not expected to present a risk for operators, workers, bystanders, and residents. No further refinement of the assessment is required.

Overall conclusion on combined exposure

Exposure estimates predict acceptable risk for operators, residents, and workers for all intended uses of FLC+PCH SC 687.5 from combined long-term exposure to fluopicolide and propamocarb. Propamocarb and fluopicolide are not acutely toxic therefore a combined acute exposure risk assessment is not needed.

CP 7.3 Dermal adsorption

Fluopicolide

A summary of the dermal absorption rates for fluopicolide in the fluopicolide + propamocarb hydrochloride SC 687.5 (62.5+625 g/L) (also named FLC+PCH SC 687.5) formulation is presented in the following table.

Table 7.3-1: Dermal absorption rates for fluopicolide in FLC+PCH SC 687.5

	fluopicolide
	Value (% of dose applied)
Concentrate	0.26%
Dilution (dilution factor)	5.1% @ 0.25 g/L

Justification for proposed values – Fluopicolide

The proposed dermal absorption rates for fluopicolide are based on an *in vitro* human skin dermal absorption study using the FLC+PCH SC 687.5 formulation. The study results are summarized in the following table. A summary of the study considering the human skin absorption is described in detail below. The absorption through rat skin is not described in this summary because it will not be used for non-dietary human exposure assessment.

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

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Justification provided on representativity of study formulation for current product	Reference
In vitro (rat/human)	Human: 0.26%	Human: 5.1% (1 in 250)	FLC+PCH SC 687.5	Not required.	M-222382-01-1 [redacted] 2003.

Data Point:	KCP 7.3/01
Report Author:	[redacted]
Report Year:	2003
Report Title:	(14C-EXP1120A - Comparative in vitro dermal penetration study using human and rat skin
Report No:	C037214
Document No:	M-222382-01-1
Guideline(s) followed in study:	EU Directive 91/414/EEC Annex III, Section 7.3; OECD 417, 428 (draft) (2002)
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR (2005)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Material and methods:

Rat:	
Species, strain:	Rat, Sprague-Dawley CD
Source:	Charles River (UK) Ltd, Margate, Kent, UK.
Sex:	Male.
Number:	6
Anatomical site:	Dorsal
Skin Preparation:	Each rat (identified by tail mark) was killed by cervical dislocation or overdose of carbon dioxide. After sacrifice, the rat was shaved with electric clippers and the skin removed. Connective tissue, blood and any residual fat were removed from the dermis using absorbent tissue. The resulting full thickness skin membrane was then wiped briefly with 70% ethanol/water to remove residual fat and blood, wiped dry and re-hydrated with distilled water ready for dermatoming. A mini dermatome was used to cut slices of skin which contained epidermis and some dermis
Human skin:	Source: International Institute for the Advancement of Medicine, USA Number and sex: 2 donors, female. Anatomical region: Back. Thickness: approximately 300 µm.
Test Material:	
Non-radiolabelled:	Batch: PAN02/02. Purity = 99.3% w/w.
Radiolabelled:	[phenyl-U-^{14}C]-fluopicolide Batch: SEL 1200. Specific activity: 5.50 MBq/mg. Radiopurity of the formulation: 99.8%.
Formulation:	The formulation used in this experiment was the Fluopicolide + propamocarb hydrochloride 687.5 formulation (EXP11120A, specification N° 10200001106/4) containing fluopicolide at a concentration of 62.5 g/L. It was used at two nominal concentrations of fluopicolide: neat, 62.5 g/L and 0.25 g/L. The same formulations were used concurrently in the *in vivo* dermal study BAG/369.
Test system:	The Scott-Dick flow-through diffusion cell (Lockley, Roper, Howes and Williams, 1997) was constructed from stainless steel and permitted the contents of the receptor chamber to be continuously stirred. The skin membranes were maintained at approximately 32°C using a water-heated manifold. The flowrate of 1.5 mL/hr allowed approximately 6 receptor chamber content changes per hour. The receptor fluid used was physiological saline, supplemented 5% w/v with bovine serum albumin, adjusted to pH 7.4. Skin samples were cut from the dermatomed slice and placed onto the receptor chamber of the flow-through diffusion cell. The donor chamber was then fixed in place providing an exposure area of 0.64 cm^2 skin and the assembled diffusion cell inserted in-line in the flow-through set-up. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity:

The integrity of the selected skin samples was estimated by measuring the penetration of tritiated water (^3H_2O) through each membrane prior to application of [^{14}C]-fluopicolide. An aliquot (250 µL, occluded) was applied to the surface of the skin membrane and the lower chamber perfused with distilled water at a flowrate of approximately 1.5 mL/hr and eluant collected at 30-minute intervals. After 5 hours, residual ^3H_2O on the surface of the membrane was removed, the surface washed with distilled water, and residual ^3H_2O removed by priming the upper chamber with distilled water and perfusing the lower chamber with distilled water overnight.

Tritiated water was used as an indicator for the skin membranes, as a number of the samples fulfilled the exclusion criterion of having a permeability coefficient of less than 3.0 x 10"3 cm/hr. On examination of the fluopicolide absorption data from skin membranes with Kp values greater than 3.0 x 10~3 cm/hr, it was considered that if the total absorption and absorption profiles were similar to those of membranes with Kp values of less than 3.0 x 10"3 cm/hr, in the same group, the data from these cells would be acceptable.

Two human cells (cells 4 and 7) from the high dose, Group 1 and one cell (cell7) from the human low dose group, Group 3 as the Kp values were greater than 3.0 x 10^{-3} cm/hr.

Cells 12 and 13 from the rat high dose group (group 2) were excluded because of poor recoveries of radioactivity.

Treatment:

Prior to dosing, the flow-rate was checked (approximately 1.5 mL/hr) by weighing the receptor fluid passed over a measured period of time and adjusted accordingly. Samples of receptor fluid were taken and analysed for background radioactivity (residual tritiated water). All cells used had acceptably low radioactivity levels (< 50 dpm) in the receptor fluid prior to dosing.

The dose preparation was applied to the skin membrane with a calibrated positive displacement pipette at the rate of approximately 10 µL/cm^2 exposed skin area (6.4 µL dose, un-occluded). The actual amount of [^{14}C]-Fluopicolide applied was determined using quality control (QC) checks taken before, during and after dosing each dose group.

Sampling:

The receptor fluid passing through the receptor chamber was collected into plastic scintillation vials held in a fraction collector. The fraction collector was moved on after dose application for each group was complete. Samples were then collected hourly for the duration of the experiment (24 hours).

At 8 hours after application, the skin was swabbed with 1 % v/v Tween 80 in aqueous sodium chloride solution (0.9 g/L) until no further radioactivity was removed (confirmed with a Geiger-Müller mini-monitor).

At the end of the study, the skin membranes were tape stripped using 3M Scotch "Magic" tape. The initial two tape strips (1 and 2) were collected separately into glass vials and represented residual surface (non-absorbed) dose. Subsequent tape strips containing the stratum corneum were pooled in batches of three and analysed separately (6 to 12 strips for human skin). The remaining skin was retained separately.

The receptor fluid remaining in the cell and outlet tubing at the end of the experiment was retained and analysed for mass balance purposes only. The diffusion cell components were also retained, washed and the washings analysed for mass balance purposes.

Radioassay: The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC)

Findings:
Fluopicolide was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

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

The study results are presented in the following table.

Table 7.3-3: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopicolide in a SC 687.5 formulation at the rates of 62.5 g/L to human skin samples (All cells).

Dose Level: 62.5 g/L	**Distribution of radioactivity (% dose applied)**					**Group Human HD N°= 5 K N°= 1.2**	
Donor N°	H1	H1	H1	H2	H2		
Sex	Female	Female	Female	Female	Female		
Cell N°	1	2	3	5	6	MEAN	SD
Skin wash 8h	99.95	82.55	92.32	95.32	89.96	92.02	6.48
Total swabs	**99.95**	**82.55**	**92.32**	**95.32**	**89.96**	**92.02**	**6.48**
Total SC 1 +SC 2	**0.07**	**0.32**	**2.18**	**0.21**	**1.15**	**0.79**	**0.89**
Donor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL NON-ABSORBED	**100.02**	**82.87**	**94.50**	**95.53**	**91.11**	**92.81**	**6.40**
Total skin	**0.017**	**0.010**	**1.823**	**0.043**	**0.050**	**0.33**	**0.73**
SC3-5	0.076	0.098	0.108	0.086	0.085	0.09	0.01
SC6-8	n.d.	n.d.	0.059	n.d.	0.036	0.02	0.03
SC9-11	0.061	n.d.	0.088	0.036	n.d.	0.04	0.04
SC12-15	0.048	n.d.	n.d.	n.d.	n.d.	0.01	0.02
TOTAL SC 3+ [a]	**0.185**	**0.098**	**0.255**	**0.122**	**0.121**	**0.16**	**0.06**
TOTAL DOSE SITE	**0.191**	**0.108**	**0.264**	**0.134**	**0.133**	**0.17**	**0.06**
Receptor fluid (0 - 24h)	**0.006**	**0.015**	**0.007**	**0.016**	**0.017**	**0.01**	**0.01**
%Ratio receptor 12h/24h	n.a.	n.a.	n.a.	n.a.	n.a.	**n.a.**	**n.a.**
Residual receptor fluid	n.d.	n.d.	0.000	n.d.	0.001	**0.00**	**0.00**
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	**0.006**	**0.015**	**0.007**	**0.016**	**0.018**	**0.01**	**0.01**

Dose Level: **62.5 g/L**	**Distribution of radioactivity (% dose applied)**					**Group Human HD N= 5 K N° = 1.2**	
POTENTIAL (dose site+ receptor)	**0.20**	**0.12**	**0.27**	**0.15**	**0.15**	**0.18**	**0.06**
POTENTIAL (skin+ receptor)	0.01	0.03	0.02	0.03	0.03	0.02	0.01
TOTAL RECOVERY	**100.02**	**82.99**	**94.77**	**95.67**	**91.26**	**92.9**	**6.4**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	No (include SC values)
Recovery <95%?	Correction needed #
Total % Potentially Absorbable adjusted according to EFSA (2017)	**Mean (%dose site +%receptor) + (SD*1.2) = 0.25%**

Normalisation was applied to all values as no specific sample type appeared to be responsible for the lower than 95% recovery from any of the “absorbed” fractions. Most probably due to losses during the skin swabbing procedures or an over-estimate of the amount applied.

SD: standard deviation

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

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

The mean recovery of the cells is below 95% therefore the data were normalized for all cells except cell 1.

Table 7.3-4: Distribution of radioactivity at 24 hours after dose application of [14C]- fluopicolide in a SC 687.5 formulation at the rates of 62.5 g/L to human skin samples (All cells), Normalized

Dose Level: **62.5 g/L**	**Distribution of radioactivity (% dose applied)**					**Group Human HD N= 5 K N° = 1.2**	
Donor N°	H1	H1	H1	H2	H2		
Sex	Female	Female	Female	Female	Female		
Cell N°	1	2	3	5	6	MEAN	SD
Skin wash 8h	99.95	99.47	97.41	99.63	98.58	99.01	1.03
Total swabs	**99.95**	**99.47**	**97.41**	**99.63**	**98.58**	**99.01**	**1.03**
Total SC 1 + SC 2	**0.07**	**0.39**	**2.30**	**0.22**	**1.26**	**0.85**	**0.94**
Donor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL NON-ABSORBED	**100.02**	**99.86**	**99.72**	**99.85**	**99.84**	**99.86**	**0.11**
Total skin	**0.006**	**0.012**	**0.009**	**0.013**	**0.013**	**0.01**	**0.00**
SC3-5	0.076	0.118	0.114	0.090	0.093	0.10	0.02
SC6-8	n.d.	n.d.	0.062	n.d.	0.039	0.02	0.03
SC9-11	0.061	n.d.	0.093	0.038	n.d.	0.04	0.04
SC12-15	0.048	n.d.	n.d.	n.d.	n.d.	0.01	0.02

Dose Level: 62.5 g/L	**Distribution of radioactivity (% dose applied)**					**Group Human HD N= 5 K N° = 1.2**	
TOTAL SC 3+ [a]	**0.185**	**0.118**	**0.269**	**0.128**	**0.133**	**0.17**	**0.06**
TOTAL DOSE SITE	**0.19**	**0.13**	**0.28**	**0.14**	**0.15**	**0.18**	**0.06**
Receptor fluid (0 - 24h)	0.006	0.018	0.007	0.017	0.019	**0.01**	**0.01**
%Ratio receptor 12h/24h	n.a.	n.a.	n.a.	n.a.	n.a.	**n.a.**	**n.a.**
Residual receptor fluid	n.d.	n.d.	0.000	n.d.	0.001	**0.00**	**0.00**
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	**0.01**	**0.02**	**0.01**	**0.02**	**0.02**	**0.01**	**0.01**
POTENTIAL (dose site+ receptor)	**0.197**	**0.148**	**0.286**	**0.157**	**0.165**	**0.19**	**0.06**
POTENTIAL (skin+ receptor)	0.01	0.03	0.02	0.03	0.03	0.02	0.01
TOTAL RECOVERY	**100.02**	**100.00**	**100.00**	**100.00**	**100.00**	**100.01**	**0.01**
Evaluation according to EFSA Guidance							
Absorption >75% within half of study duration?						No. (include SC values)	
Recovery <95%?						Not applicable – data normalised	
Total % Potentially Absorbable adjusted according to EFSA (2017)						**Mean (%dose site +%receptor) + (SD*1.2) = 0.26%**	

SD: standard deviation

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

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

Table 7.3-5: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopicolide in a SC 687.5 formulation at the rates of 0.25 g/L to human skin samples (Reported cells).

Dose Level: 0.25 g/L	**Distribution of radioactivity (% dose applied)**						**Group Human HD N= 6 K N° = 1**	
Donor N°	H1	H1	H1	H1	H2	H2		
Sex	Female	Female	Female	Female	Female	Female		
Cell N°	1	2	3	4	5	6	MEAN	SD
Skin wash 8h	80.74	80.91	93.37	86.92	82.49	90.19	85.77	5.26
Total swabs	**80.74**	**80.91**	**93.37**	**86.92**	**82.49**	**90.19**	**85.77**	**5.26**
Total SC 1+ SC 2	**1.33**	**4.96**	**4.15**	**5.11**	**4.81**	**1.84**	**3.70**	**1.68**
Donor chamber	0.966	1.847	2.588	1.233	0.746	0.506	1.31	0.78
TOTAL NON-ABSORBED	**83.03**	**87.72**	**100.11**	**93.26**	**88.05**	**92.54**	**90.78**	**5.88**
Total skin	**0.22**	**0.40**	**0.59**	**0.47**	**0.65**	**0.29**	**0.44**	**0.17**

Dose Level: 0.25 g/L	**Distribution of radioactivity (% dose applied)**						**Group Human HD N= 6 K N° = 1**	
SC3-5	1.151	0.985	0.843	1.734	2.395	0.904	1.34	0.61
SC6-8	0.259	0.230	0.235	0.413	1.003	0.695	0.47	0.31
SC9-11	0.155	0.266	0.332	0.135	0.288	0.349	0.25	0.09
SC12-15	n.s.	0.117	n.d.	n.s.	0.142	0.142	0.07	0.07
TOTAL SC 3+ [a]	**1.57**	**1.60**	**1.41**	**2.28**	**3.83**	**2.09**	**2.13**	**0.90**
TOTAL DOSE SITE	**1.78**	**2.00**	**2.00**	**2.75**	**4.48**	**2.38**	**2.56**	**1.00**
Receptor fluid (0 - 24h)	0.621	0.899	1.818	0.903	1.160	0.616	**1.00**	**0.45**
%Ratio receptor 12h/24h	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	**n.a.**	**n.a.**
Residual receptor fluid	0.009	0.021	0.039	0.012	0.008	0.005	0.02	0.01
Receptor chamber	n.d.	0.201	n.d.	n.d.	0.187	n.d.	0.06	0.10
TOTAL DIRECT	**0.63**	**1.12**	**1.86**	**0.92**	**1.36**	**0.62**	**1.08**	**0.47**
POTENTIAL (dose site+ receptor)	**2.41**	**3.12**	**3.86**	**3.67**	**5.83**	**3.00**	**3.65**	**1.19**
POTENTIAL (skin+ receptor)	0.85	1.52	2.45	1.39	2.00	0.91	1.52	0.62
TOTAL RECOVERY	**85.45**	**90.83**	**104.00**	**96.93**	**93.97**	**95.54**	**94.45**	**6.2**
Evaluation according to EFSA Guidance								
Absorption >75% within half of study duration?						No. (include SC values)		
Recovery <95%?						Correction needed [#]		
Total % Potentially Absorbable adjusted according to EFSA (2017)						**Mean (%dose site +%receptor) + (SD*1) = 4.8%**		

[#] Normalisation was applied to all values as no specific sample type appeared to be responsible for the lower than 95% recovery from any of the “absorbed” fractions. Most probably due to losses during the skin swabbing procedures or an over-estimate of the amount applied.

SD: standard deviation

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

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

The mean recovery of cells is below 95% therefore the data were normalized for all cells except cell 3.

Table 7.3-6: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- fluopicolide in a SC 687.5 formulation at the rates of 0.25 g/L to human skin samples (All cells), Normalized

Dose Level: 0.25 g/L	**Distribution of radioactivity (% dose applied)**						**Group Human HD N= 6 K N° = 1**	
Donor N°	H1	H1	H1	H1	H2	H2		
Sex	Female	Female	Female	Female	Female	Female		
Cell N°	1	2	3	4	5	6	MEAN	SD
Skin wash 8h	94.49	89.08	93.37	89.67	87.87	94.40	91.48	2.94
Total swabs	**94.49**	**89.08**	**93.37**	**89.67**	**87.87**	**94.40**	**91.48**	**2.94**
Total SC 1 + SC 2	**1.55**	**5.46**	**4.15**	**5.27**	**5.12**	**1.93**	**3.91**	**1.75**
Donor chamber	1.13	2.03	2.59	1.27	0.79	0.53	1.39	0.78
TOTAL NON-ABSORBED	**97.17**	**96.57**	100.11	**96.22**	**93.79**	**96.86**	**96.79**	**2.03**

Dose Level: 0.25 g/L	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Total skin	**0.25**	**0.44**	**0.59**	**0.48**	**0.69**	**0.30**	**0.46**	**0.17**
SC3-5	1.35	1.08	0.84	1.79	2.55	0.93	1.43	0.65
SC6-8	0.30	0.25	0.24	0.43	1.07	0.73	0.50	0.33
SC9-11	0.18	0.29	0.33	0.14	0.31	0.37	0.27	0.09
SC12-15	n.s.	0.13	n.d.	n.s.	0.15	0.15	0.07	0.08
TOTAL SC 3+ [a]	**1.83**	**1.76**	**1.41**	**2.35**	**4.08**	**2.19**	**2.27**	**0.95**
TOTAL DOSE SITE	**2.08**	**2.20**	**2.00**	**2.84**	**4.77**	**2.49**	**2.73**	**1.04**
Receptor fluid (0 - 24h)	0.727	0.990	1.82	0.932	1.24	0.645	1.06	0.43
%Ratio receptor 12h/24h	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	**n.a.**	**n.a.**
Residual receptor fluid	0.01	0.02	0.04	0.01	0.01	0.02	0.02	0.01
Receptor chamber	n.d.	0.22	n.d.	n.d.	0.20	n.d.	0.07	0.11
TOTAL DIRECT	**0.74**	**1.23**	**1.86**	**0.94**	**1.44**	**0.65**	**1.14**	**0.46**
POTENTIAL (dose site+ receptor)	**2.82**	**3.43**	**3.86**	**3.78**	**6.21**	**3.14**	**3.87**	**1.21**
POTENTIAL (skin+ receptor)	0.99	1.67	2.45	1.43	2.15	0.92	1.60	0.61
TOTAL RECOVERY	**106.00**	**100.00**	**104.00**	**100.00**	**100.00**	**100.00**	**100.66**	**1.62**
Evaluation according to EFSA Guidance								
Absorption >75% within half of study duration? (include SC values)							No.	
Recovery <95%?							Not applicable – data normalised correction needed	
Total % Potentially Absorbable adjusted according to EFSA (2017)							**Mean (%dose site +%receptor) + (SD*1) = 5.1%**	

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
SD: standard deviation
n.d.: below limit of detection; n.s.: no sample; n.a: not applicable
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-fluopicolide in the fluopicolide SC 687.5 formulation was investigated at two nominal concentrations corresponding to the neat product (62.5 g /L) and a representative spray dilution of 0.25 g/L.

Concentrate (62.5 g/L)

The mean percentage of fluopicolide in the FLC+PCH SC 687.5 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 0.26%.

Low Dose level (Spray dilution at 0.25 g/L)

The mean percentage of fluopicolide in the FLC+PCH SC 687.5 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 5.1%.

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for fluopicolide in the FLC+PCH SC 687.5 formulation:

	Human Skin
Concentrate (62.5 g/L)	0.26%
Low dose (0.25 g/L)	5.1%

Assessment and conclusion by applicant:
An acceptable study yielding valid conclusions

Propamocarb

A summary of the dermal absorption rates for propamocarb in the fluopicolide + propamocarb-HCl SC 687.5 (FLC+PCH SC 687.5) formulation is presented in the following table.

Table 7.3-7: Dermal absorption rates for propamocarb in FLC+PCH SC 687.5

	Propamocarb
	Value (% of dose applied)
Concentrate	2.0%
Dilution (dilution factor)	2.9% @ 5 g/L 8.6% @ 0.3 g/L

Justification for proposed values – Propamocarb

The proposed dermal absorption rates for propamocarb are based on an *in vitro* human skin dermal absorption study using the FLC+PCH SC 687.5 formulation. The study results are summarized in the following table. A full summary of the study is described in detail below.

Table 7.3-8: Summary of the results of submitted dermal absorption studies for Propamocarb

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Justification provided on representativity of study formulation for current product	Reference
In vitro (Human)	2.0%	2.9% (1 in 125) 8.6% (1 in 2083)	FLC+PCH SC 687.5	Not required	[redacted] 2015; M-516805-01-1

Data Point:	KCP 7.3/02
Report Author:	[redacted]
Report Year:	2003
Report Title:	In vivo dermal absorption in the male rat Code: (14C)-EXP11120A
Report No:	C037215
Document No:	M-222384-01-1
Guideline(s) followed in study:	OECD Guideline of Testing of Chemicals, Toxicokinetics, 417, Adopted April 1984 using the latest draft of the OECD Test Guideline 427 and the respective OECD Guidance Documents for the conduct of in vivo skin absorption studies (April 2002).
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR (2005)
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

This study is an *in vivo* dermal absorption study in rats. This study is no longer relevant as an *in vitro* study through human skin is available, which provides the best estimate of dermal absorption. Therefore, this study has not been considered further for this renewal.

Data Point:	KCP 7.3/04
Report Author:	[redacted]
Report Year:	2015
Report Title:	FLC + PCH SC 687.5 [14C]-propamocarb HCl - In vitro dermal absorption study using human skin
Report No:	SA 14050
Document No:	M-516805-01-1
Guideline(s) followed in study:	OECD 428 (2004); OECD Assessment No 28, (2004); EFSA Panel on Plant Protection Products and their Residues (PPR), : Guidance on Dermal Absorption (2012)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously submitted
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Material and methods:

Human skin: Source: Biopredic, Rennes & Xenometrics, Hegenheim, France.
Number and sex: minimum of 4 donors per dose level, female.
Anatomical region: Abdomen.
Thickness: 365 to 491 µm.

Test Material:

Non-radiolabelled: Batch: EK1C000430.
Purity = 70.4% (w/w).

Radiolabelled: [1-^{14}C]-propamocarb
Batch: KML 9864.
Specific activity: 3.75 MBq/mg.
Radiopurity of the formulation: > 98.5%.

Formulation: The formulation used in this experiment was the fluopicolide + propamocarb HCl SC 687.5 formulation (specification N° 102000013376) containing fluopicolide (62.5 g/L) and propamocarb (625 g/L). It was used at three nominal concentrations of propamocarb: neat, 625 g/L with 2 spray dilutions of 2 g/L and 0.3 g/L.

Test system: A flow-through diffusion cell system (Franz's cell modified, Gallas, France) was used to study the absorption of the test substance (exposure area of 1 cm^2 skin). A diffusion cell consisted of a donor chamber and a receptor chamber between which the skin was positioned. The receptor fluid was Eagle's medium supplemented with 5% bovine serum albumin and gentamycin (50 mg/L) at a pH of *ca* 7.4. The receptor chamber was warmed by a constant circulation of warm water which maintained the receptor fluid at 32 ± 2°C (close to the normal skin temperature). The receptor fluid was pumped through the receptor chamber at a rate of 1.5 mL/h and stirred continuously whilst in the receptor chamber by means of a magnetic bar.

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300® System, Courage & Khazaka) was placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Skin samples with a TEWL of

greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

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

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

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

Findings:

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

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

The study results are presented in the following Table.

Table 7.3-9: Distribution of radioactivity at 24 hours after dose application of [^{14}C]-propamocarb in a SC 687.5 formulation at the rates of 625 g/L to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Donor N°	X2014/1-6	X2014/3-7	X2014/1-1	X2014/2-1	X2014/1-20	608-01-0414-III-1		
Sex	Female	Female	Female	Female	Female	Female		
Cell N°	H01	H02	H03	H04	H05	H06	MEAN	SD
Skin wash 8h	78.47	93.40	96.26	93.70	92.58	96.25	**91.78**	**6.69**
Skin wash 24h	0.0041	0.0441	0.0033	0.1090	0.2875	0.0775	0.09	0.11
Surrounding swabs 24 h	0.0014	0.0055	0.0026	0.0045	0.0897	0.0039	0.02	0.04
Total swabs	**78.48**	**93.45**	**96.27**	**93.82**	**92.96**	**96.33**	**91.88**	**6.72**
SC 1	0.0023	0.0166	0.0016	0.0994	1.1055	0.0296	0.21	0.44
SC 2	0.0013	0.0092	0.0063	0.0221	0.0960	0.0337	0.03	0.04
Total SC 1 + SC 2	**0.0036**	**0.0258**	**0.0079**	**0.1215**	**1.2015**	**0.0633**	**0.24**	**0.47**
Donor chamber	n.d.	0.0441	0.0213	0.0877	1.3134	0.0828	0.31	0.56
TOTAL NON-ABSORBED	**78.48**	**93.52**	**96.29**	**94.02**	**95.47**	**96.48**	**92.38**	**6.91**
Skin	0.0027	0.1214	0.0049	0.1541	0.8022	0.4014	0.25	0.31
Surrounding skin	0.0012	0.0191	0.0034	0.0021	0.3942	0.0092	0.07	0.16
Total skin	**0.0039**	**0.1405**	**0.0083**	**0.1562**	**1.1964**	**0.4106**	**0.32**	**0.45**
SC3	0.0096	0.0068	0.0021	0.1056	0.1603	0.0140	0.05	0.07
SC4	0.0012	0.0050	0.0011	0.0156	0.1278	0.0515	0.03	0.05
SC5	n.s.	0.0064	n.s.	0.0098	n.s.	0.0184	0.01	0.01
SC6	n.s.	0.0122	n.s.	n.s.	n.s.	n.s.	0.00	0.00
SC7	n.s.	0.0069	n.s.	n.s.	n.s.	n.s.	0.00	0.00
SC8	n.s.	0.0310	n.s.	n.s.	n.s.	n.s.	0.01	0.01
TOTAL SC3+	**0.0108**	**0.0683**	**0.0032**	**0.1310**	**0.2881**	**0.0839**	**0.10**	**0.10**
TOTAL DOSE SITE	**0.0147**	**0.2088**	**0.0115**	**0.2872**	**1.4845**	**0.4945**	**0.42**	**0.55**
Receptor fluid (0 - 12h)	0.0270	0.0643	0.0310	0.0375	0.0552	0.0445	0.043	0.014
Receptor fluid (0 - 24h)	0.0453	0.2440	0.0540	0.0692	0.1967	0.1105	0.120	0.082
%Ratio receptor 12h/24h	60	26	57	54	28	40	**44**	**15**
Residual Rec Fluid	0.0115	0.5108	0.0104	0.0441	0.4323	0.0974	0.18	0.23
Receptor chamber	0.1560	0.0000	0.0000	0.1809	0.2455	0.1434	0.12	0.10
TOTAL DIRECT	**0.2128**	**0.7548**	**0.0644**	**0.2942**	**0.8745**	**0.3513**	**0.43**	**0.32**
POTENTIAL (dose site+ receptor)	**0.2275**	**0.9636**	**0.0759**	**0.5814**	**2.3590**	**0.8458**	**0.84**	**0.82**
POTENTIAL (skin+ receptor)	0.2167	0.8953	0.0727	0.4504	2.0709	0.7619	0.74	0.72
TOTAL RECOVERY	**78.71**	**94.48**	**96.37**	**94.61**	**97.83**	**97.32**	**93.2**	**7.2**
Evaluation according to EFSA Guidance								
Absorption >75% within half of study duration?					No. (include SC values except SC1 &2)			
Recovery <95%?					Yes (due to H01) correction needed			
Total % Potentially Absorbable adjusted according to EFSA (2017)					**Provided in the next table**			

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

SD: standard deviation

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

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

The cell H01 showed very low recovery outside of the acceptable range indicated in the OECD 428 guideline and is therefore considered to be an outlier and was excluded in the study report, therefore the updated results are presented in the table below.

Table 7.3-10: Distribution of radioactivity at 24 hours after dose application of [^{14}C]-propamocarb in a SC 687.5 formulation at the rates of 625 g/L to human skin samples (Reported cells).

	Distribution of radioactivity (% dose applied)						
Donor N°	X2014/3-7	X2014/1-1	X2014/2-1	X2014/1-20	608-01-0414-III-1	Group Human HD N=5 K N°=1.2	
Sex	Female	Female	Female	Female	Female		
Cell N°	H02	H03	H04	H05	H06	MEAN	SD
Skin wash 8h	93.40	96.26	93.70	92.58	96.25	**94.44**	**1.71**
Skin wash 24h	0.0441	0.0035	0.1090	0.2875	0.0775	0.10	0.11
Surrounding swabs 24 h	0.0055	0.0026	0.0045	0.0897	0.0039	0.02	0.04
Total swabs	**93.45**	**96.27**	**93.81**	**92.96**	**96.33**	**94.56**	**1.61**
SC 1	0.0166	0.0016	0.0994	1.1055	0.0296	**94.56**	**1.61**
SC 2	0.0092	0.0063	0.0221	0.0960	0.0337	0.25	0.48
Total SC 1 + SC 2	**0.0258**	**0.0079**	**0.1215**	**1.2015**	**0.0633**	0.03	0.04
Donor chamber	0.0441	0.0213	0.0877	1.3434	0.0828	**0.28**	**0.51**
TOTAL NON-ABSORBED	**93.52**	**96.29**	**94.02**	**95.47**	**96.48**	**94.88**	**1.36**
Skin	0.1214	0.0049	0.1541	0.8022	0.4014	0.30	0.32
Surrounding skin	0.0191	0.0034	0.0021	0.3942	0.0092	0.09	0.17
Total skin	**0.1405**	**0.0083**	**0.1562**	**1.1964**	**0.4106**	**0.38**	**0.48**
SC3	0.0068	0.0021	0.1056	0.1603	0.0140	0.058	0.071
SC4	0.0050	0.0011	0.0156	0.1278	0.0515	0.040	0.053
SC5	0.0064	n.s.	0.0098	n.s.	0.0184	0.007	0.008
SC6	0.0122	n.s.	n.s.	n.s.	n.s.	0.002	0.005
SC7	0.0069	n.s.	n.s.	n.s.	n.s.	0.001	0.003
SC8	0.0310	n.s.	n.s.	n.s.	n.s.	0.006	0.014
TOTAL SC 3+ [a]	**0.0683**	**0.0032**	**0.1310**	**0.2881**	**0.0839**	**0.11**	**0.11**
TOTAL DOSE SITE	**0.2088**	**0.0115**	**0.2872**	**1.4845**	**0.4945**	**0.50**	**0.58**
Receptor Fluid (0 - 12h)	0.0643	0.0310	0.0375	0.0552	0.0445	0.047	0.013
Receptor fluid (0 - 24h)	0.2440	0.0540	0.0692	0.1967	0.1105	**0.135**	**0.082**
%Ratio receptor 12h/24h	26	57	54	28	40	**41**	**14**
Residual Rec Fluid	0.5108	0.0104	0.0441	0.4323	0.0974	0.22	0.23
Receptor chamber	0.0000	0.0000	0.1809	0.2455	0.1434	0.11	0.11
TOTAL DIRECT	**0.75**	**0.06**	**0.29**	**0.87**	**0.35**	**0.47**	**0.34**

	Distribution of radioactivity (% dose applied)					Group Human HD N= 5 K N° = 1.2	
Donor N°	X2014/3-7	X2014/1-1	X2014/2-1	X2014/1-20	608-01-0414-III-1		
Sex	Female	Female	Female	Female	Female		
POTENTIAL (dose site+ receptor)	**0.9636**	**0.0759**	**0.5814**	**2.3590**	**0.8458**	**0.97**	**0.85**
POTENTIAL (skin+ receptor)	0.8953	0.0727	0.4504	2.0709	0.7619	0.85	0.75
TOTAL RECOVERY	**94.48**	**96.37**	**94.61**	**97.83**	**97.32**	**96.12**	**1.53**
Evaluation according to EFSA Guidance							
Absorption >75% within half of study duration?					No (exclude SC values except SC1 & 2)		
Recovery >95%?					No correction needed		
Total % Potentially Absorbable adjusted according to EFSA (2017)					**Mean (%dose site +%receptor) + (SD*1.2) = 2.0%**		

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

SD: standard deviation

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

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

Table 7.3-11: Distribution of radioactivity at 24 hours after dose application of [^{14}C]- propamocarb in a SC 687.5 formulation at the rates of 5 g/L to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	X2014/4-10	X2014/2-3	X2014/5-12	TRA2001 B559	B2014/2	X2014/6-1		
Cell N°	H07	H08	H09	H010	H11	H12	MEAN	SD
Skin wash 8h	85.84	88.53	81.99	88.50	93.62	89.00	87.92	3.84
Skin wash 24h	0.23	0.14	0.04	0.33	0.03	0.00	0.13	0.13
Surrounding swabs 24 h	0.0180	0.0288	0.0045	0.0073	0.0022	0.0083	0.01	0.01
Total swabs	**86.12**	**88.69**	**82.03**	**88.84**	**93.65**	**89.01**	**88.06**	**3.83**
SC1	0.363	0.056	0.018	0.119	0.005	0.012	0.10	0.14
SC2	0.028	0.033	0.022	0.115	0.011	0.003	0.03	0.04
Total SC1+SC2	**0.38**	**0.09**	**0.04**	**0.23**	**0.02**	**0.02**	**0.13**	**0.15**
Donor chamber	0.168	0.614	0.068	0.152	0.096	0.543	0.27	0.24
TOTAL NON-ABSORBED	**86.67**	**89.40**	**82.14**	**89.22**	**93.76**	**89.57**	**88.46**	**3.85**
Skin	0.96	0.09	0.21	1.20	0.02	0.16	0.44	0.51
Surrounding skin	0.175	0.283	0.042	0.028	0.007	0.386	0.15	0.16
Total skin	**1.14**	**0.37**	**0.25**	**1.22**	**0.03**	**0.54**	**0.59**	**0.49**
SC3	0.028	0.050	0.033	0.091	0.009	0.002	0.035	0.032
SC4	0.025	0.043	0.035	0.120	0.008	0.011	0.040	0.041
SC5	n.s.	0.061	0.032	0.127	0.020	n.s.	0.040	0.048
SC6	n.s.	0.033	0.031	0.102	0.025	n.s.	0.032	0.037
SC7	n.s.	0.484	n.s.	0.108	0.022	n.s.	0.102	0.191

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 4	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	X2014/4-10	X2014/2-3	X2014/5-12	TRA2001 B559	B2014/2	X2014/6-1		
SC8	n.s.	n.s.	n.s.	0.104	0.020	n.s.	0.021	0.042
SC9	n.s.	n.s.	n.s.	0.067	0.018	n.s.	0.014	0.027
SC10	n.s.	n.s.	n.s.	0.051	0.021	n.s.	0.012	0.021
SC11	n.s.	n.s.	n.s.	0.087	0.018	n.s.	0.017	0.035
SC12	n.s.	n.s.	n.s.	0.055	0.016	n.s.	0.012	0.022
SC13	n.s.	n.s.	n.s.	n.s.	0.076	n.s.	0.013	0.000
Total SC3+	**0.05**	**0.67**	**0.13**	**0.91**	**0.25**	**0.01**	**0.34**	**0.37**
TOTAL DOSE SITE	**1.19**	**1.04**	**0.38**	**2.14**	**0.28**	**0.55**	**0.93**	**0.69**
Receptor fluid (0 - 12h)	0.051	0.158	3.473	0.310	0.330	0.624	0.83	1.31
Receptor fluid (0 - 24h)	0.058	0.235	4.007	0.317	0.463	0.808	1.02	1.48
%Ratio receptor 12h/24h	89	56	87	60	72	77	**73**	**14**
Residual Rec Fluid	0.057	0.029	0.029	0.041	0.024	0.025	0.034	0.013
Receptor chamber	0.219	0.466	0.162	0.148	0.166	0.639	0.300	0.205
TOTAL DIRECT	**0.33**	**0.78**	**4.20**	**0.71**	**0.65**	**1.47**	**1.36**	**1.44**
POTENTIAL (dose site+ receptor)	**1.52**	**1.82**	**4.58**	**2.84**	**0.93**	**2.03**	**2.29**	**1.28**
POTENTIAL (skin+ receptor)	1.47	1.15	4.45	1.93	0.68	2.01	1.95	1.32
TOTAL RECOVERY	**88.2**	**91.2**	**86.7**	**92.1**	**94.7**	**91.6**	**90.7**	**2.9**
Evaluation according to EFSA Guidance (2017)								
Absorption >75% within half of study duration? No (include SC values except SC1 & 2)								
Mean Recovery <95%? Correction needed #								
Total % Potentially Absorbable adjusted according to EFSA (2017) Mean (%dose site +%receptor) + (SD*1) = **3.6%**								

Normalisation was applied to all values as no specific sample type appeared to be responsible for the lower than 95% recovery from any of the "absorbed" fractions. Most probably due to losses during the skin swabbing procedures or an over-estimate of the amount applied.

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

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

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

In the study report both Cells H07 and H09 were excluded from the reported cells due to "low recoveries". However, looking at the cumulative absorption profile of all the cells it shows that cell H09 can be considered as outlier compared to other cells as shown in the graphs below.

Figure 7.3-1: Cumulative Absorption Profile after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the nominal rate of 5 g/L to human skin (All cells)

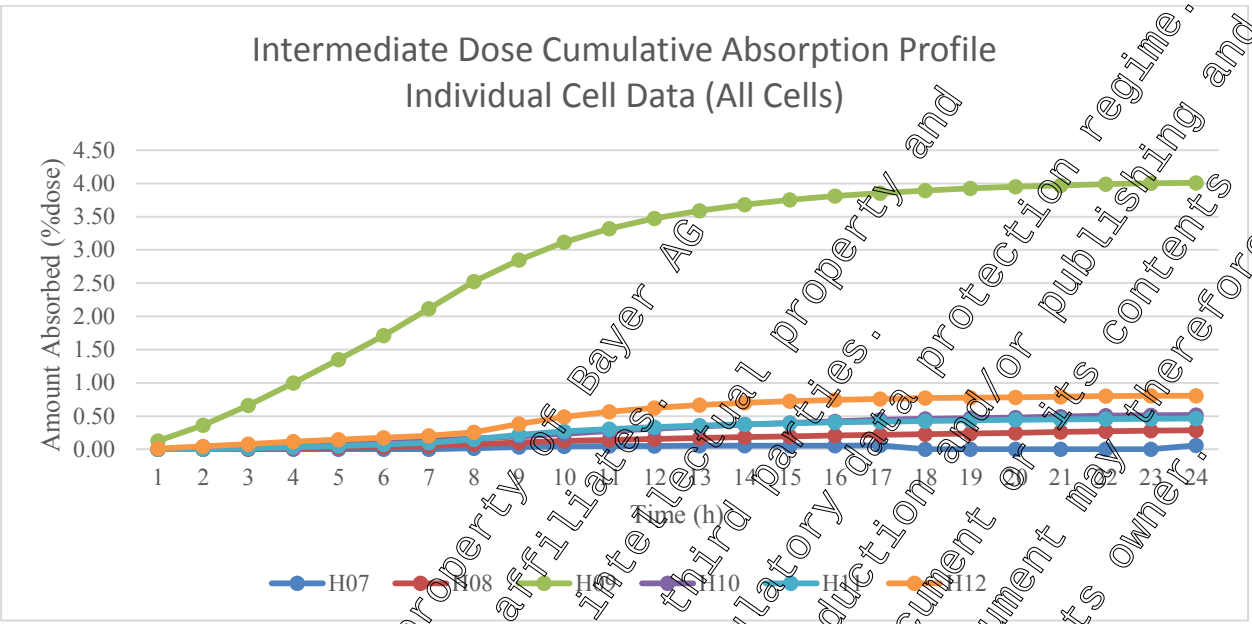
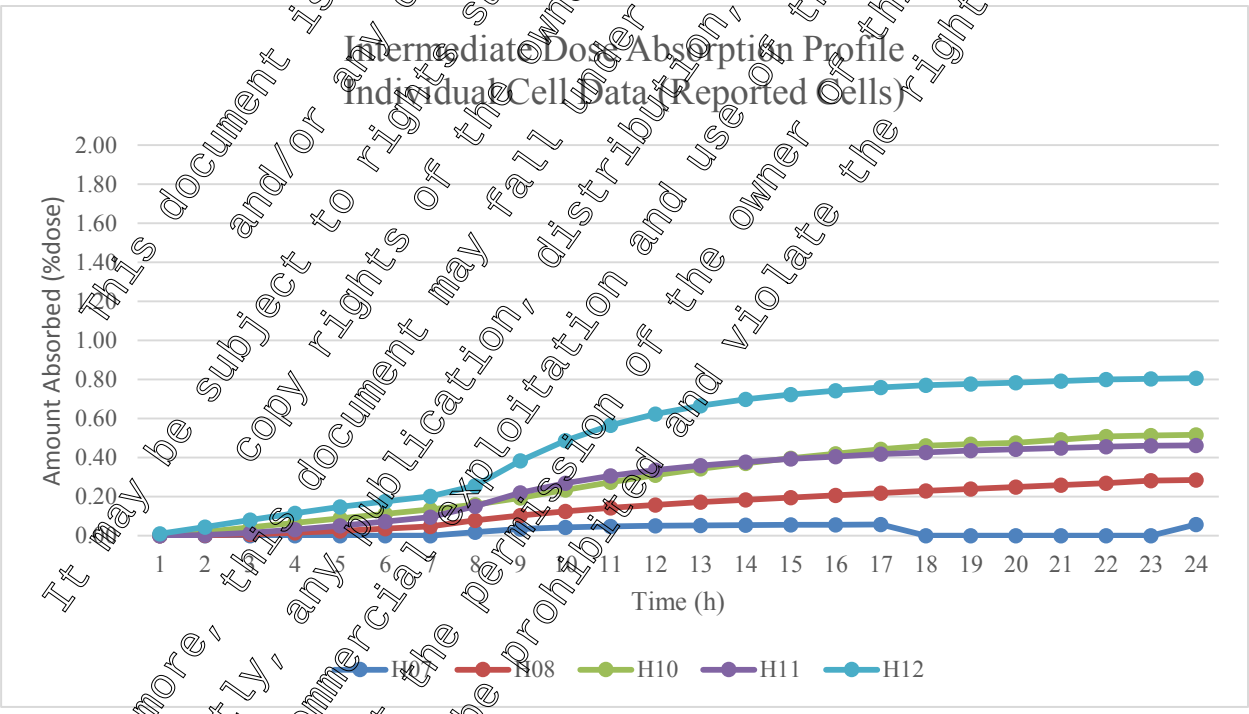


Figure 7.3-2: Cumulative Absorption Profile after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the nominal rate of 5 g/L to human skin (Reported cells)



Considering recovery all cells showed low recoveries (<95%) the results are presented normalized in the following table.

Table 7.3-12: Distribution of radioactivity at 24 hours after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the rate of 5 g/L to human skin samples (reported cells) normalized.

	Distribution of radioactivity (% dose applied)					Group Human DD N= 5 K N° = 1.2	
Donor N°	X2014/4-10	X2014/2-3	TRA200 1B559	B2014/2	X2014/6-1		
Sex	Female	Female	Female	Female	Female		
Cell N°	H07	H08	H10	H11	H12	MEAN	SD
Skin wash 8h	97.37	97.05	96.13	98.86	97.17	97.31	0.99
Skin wash 24h	0.26	0.15	0.36	0.03	0.00	0.16	0.15
Surrounding swabs 24 h	0.020	0.032	0.008	0.002	0.009	0.01	0.01
Total swabs	**97.65**	**97.23**	**96.49**	**98.90**	**97.18**	**97.49**	**0.89**
SC 1	0.41	0.08	0.13	0.01	0.01	0.12	0.17
SC 2	0.02	0.04	0.12	0.01	0.00	0.04	0.05
Total SC 1 + SC 2	**0.44**	**0.10**	**0.25**	**0.02**	**0.02**	**0.17**	**0.18**
Donor chamber	0.19	0.67	0.16	0.10	0.59	0.34	0.27
TOTAL NON-ABSORBED	**98.27**	**98.01**	**96.91**	**99.01**	**97.79**	**98.00**	**0.76**
Skin	1.09	0.10	1.30	0.02	0.17	0.54	0.61
Surrounding skin	0.20	0.31	0.03	0.01	0.42	0.19	0.18
Total skin	**1.29**	**0.41**	**1.33**	**0.03**	**0.59**	**0.73**	**0.57**
SC3	0.032	0.055	0.099	0.010	0.002	0.04	0.04
SC4	0.028	0.044	0.131	0.008	0.012	0.05	0.05
SC5	n.s.	0.067	0.138	0.022	n.s.	0.05	0.06
SC6	n.s.	0.036	0.111	0.027	n.s.	0.03	0.05
SC7	n.s.	0.330	0.118	0.024	n.s.	0.13	0.23
SC8	n.s.	n.s.	0.113	0.022	n.s.	0.03	0.05
SC9	n.s.	n.s.	0.073	0.018	n.s.	0.02	0.03
SC10	n.s.	n.s.	0.055	0.022	n.s.	0.02	0.02
SC11	n.s.	n.s.	0.094	0.018	n.s.	0.02	0.04
SC12	n.s.	n.s.	0.060	0.017	n.s.	0.02	0.03
SC13	n.s.	n.s.	n.s.	0.080	n.s.	0.02	0.04
TOTAL SC 3+ [a]	**0.060**	**0.734**	**0.991**	**0.268**	**0.014**	**0.41**	**0.43**
TOTAL DOSE SITE	**1.35**	**1.14**	**2.32**	**0.30**	**0.60**	**1.14**	**0.78**
Receptor fluid (0 - 12h)	0.058	0.174	0.337	0.355	0.681	0.32	0.24
Receptor fluid (0 - 24h)	0.065	0.312	0.562	0.489	0.882	0.46	0.30
%Ratio receptor 12h/24h	89	56	60	73	77	**70**	**9**
Residual Rec Fluid	0.07	0.03	0.04	0.02	0.03	0.04	0.02
Receptor chamber	0.25	0.51	0.16	0.18	0.70	0.36	0.24
TOTAL DIRECT	**0.38**	**0.85**	**0.77**	**0.69**	**1.61**	**0.86**	**0.46**
POTENTIAL (dose site+ receptor)	**1.73**	**1.99**	**3.09**	**0.99**	**2.21**	**2.00**	**0.76**
POTENTIAL (skin+ receptor)	1.67	1.26	2.10	0.72	2.20	1.59	0.61

	Distribution of radioactivity (% dose applied)					Group Human HD N= 5 K N° = 1.2	
Donor N°	X2014/4-10	X2014/2-3	TRA200 1B559	B2014/2	X2014/6-1		
Sex	Female	Female	Female	Female	Female		
TOTAL RECOVERY normalized	100.00	100.00	100.00	100.00	100.00	**100.00**	**0.00**
Evaluation according to EFSA Guidance							
Absorption >75% within half of study duration?					No (include SC values except SC1 & 2)		
Recovery <95%?					Correction applied		
Total % Potentially Absorbable adjusted according to EFSA (2017)					**Mean (%dose site +%receptor) + (SD*1.2) = 2.9%**		

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

SD: standard deviation

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

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

Table 7.3-13: Distribution of radioactivity at 24 hours after dose application of [^{14}C]-propamocarb in a SC 687.5 formulation at the rates of 0.3 g/L to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	608-01-0414-III-1	X2014/2-4	X2014/5-25	X2014/1-21	603-01-0414-V-1	598-01-0314-IV-1		
Cell N°	H13	H14	H15	H16	H17	H18	MEAN	SD
Skin wash 8h	78.07	78.45	85.53	85.01	81.79	85.45	82.38	3.48
Skin wash 24h	1.84	0.40	0.33	0.26	0.29	0.79	0.65	0.61
Surrounding swabs 24 h	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.00
Total swabs	**79.93**	**78.87**	**85.88**	**85.28**	**82.11**	**86.27**	**83.06**	**3.21**
SC1	0.10	0.09	0.04	0.06	0.09	0.13	0.09	0.03
SC2	0.10	0.07	0.03	0.05	0.09	0.11	0.08	0.03
Total SC1 + SC2	**0.20**	**0.15**	**0.07**	**0.11**	**0.18**	**0.24**	**0.16**	**0.06**
Donor chamber	0.45	0.39	0.69	0.46	0.39	0.45	0.47	0.11
TOTAL NON-ABSORBED	**80.58**	**79.41**	**86.64**	**85.86**	**82.68**	**86.96**	**83.69**	**3.26**
Skin	1.14	1.03	0.29	0.07	0.48	0.81	0.64	0.43
Surrounding skin	0.06	0.06	0.03	0.03	0.14	0.09	0.07	0.04
Total skin	**1.20**	**1.09**	**0.32**	**0.10**	**0.62**	**0.90**	**0.70**	**0.44**
SC3	0.125	0.165	0.028	0.043	0.150	0.207	0.12	0.07
SC4	0.089	0.156	0.050	0.056	0.183	0.282	0.14	0.09
SC5	0.113	0.195	0.035	0.040	0.212	0.209	0.13	0.08
SC6	0.139	0.189	0.051	0.058	0.112	0.215	0.13	0.07
SC7	0.174	0.384	0.078	0.049	0.182	0.148	0.17	0.12
SC8	0.177	0.174	0.032	0.030	0.177	0.100	0.12	0.07
SC9	0.146	0.189	0.060	0.041	0.139	0.137	0.12	0.06
SC10	0.168	0.199	0.042	0.043	0.105	0.107	0.11	0.06
SC11	0.132	0.152	0.039	0.812	0.087	n.s.	0.20	0.00

	Distribution of radioactivity (% dose applied)						Group Human HD N= 6 K N° = 1	
Sex	Female	Female	Female	Female	Female	Female		
Donor N°	608-01-0414-III-1	X2014/2-4	X2014/5-25	X2014/1-21	603-01-0414-V-1	598-01-0314-IV-1		
SC12	0.088	0.072	0.037	n.s.	0.074	n.s.	0.05	0.00
SC13	1.952	0.087	0.037	n.s.	0.070	n.s.	0.36	0.00
SC14	n.s.	0.128	0.040	n.s.	0.070	n.s.	0.04	0.05
SC15	n.s.	0.065	n.s.	n.s.	0.059	n.s.	0.02	0.03
Total SC3+	**3.30**	**2.15**	**0.53**	**1.17**	**1.62**	**1.40**	**1.70**	**0.95**
TOTAL DOSE SITE	**4.50**	**3.24**	**0.85**	**1.27**	**2.24**	**2.30**	**2.40**	**1.33**
Receptor fluid (0 - 12h)	10.29	0.25	2.2	1.66	3.43	3.98	3.64	3.52
Receptor fluid (0 - 24h)	14.99	0.55	2.92	2.32	4.76	5.55	5.18	5.13
%Ratio receptor 12h/24h	69	45	76	72	100	72	**72**	**67**
Residual Rec Fluid	0.509700	0.281400	0.494700	0.221100	0.357300	0.332800	0.32	0.11
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	**15.50**	**0.83**	**3.11**	**2.54**	**5.12**	**5.89**	**5.50**	**5.23**
POTENTIAL (dose site+ receptor)	**20.00**	**4.07**	**3.96**	**3.81**	**7.36**	**8.19**	**7.90**	**6.22**
POTENTIAL (skin+ receptor)	16.70	1.92	3.43	2.64	5.74	6.79	6.20	5.47
TOTAL RECOVERY	**100.6**	**83.5**	**90.6**	**89.7**	**90.0**	**95.2**	**91.59**	**5.77**
Evaluation according to EFSA Guidance (2017)								
Absorption <75% within half of study duration?					No (include SC values except SC1 &2)			
Mean Recovery <95%?					Correction needed#			
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%dose site +%receptor) + (SD*1) = **14%**			

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

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

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

Normalisation was applied to all values as no specific sample type appeared to be responsible for the lower than 95% recovery from any of the "absorbed" fractions, most probably due to losses during the skin swabbing procedures or an over-estimate of the amount applied.

In the study report both Cells H13 and H14 were excluded from the reported cells due to "high recovery" and "low recovery" respectively. However, looking at the cumulative absorption profile of all the cells it shows that cell H13 can be considered as outlier compared to other cells as shown in the graphs below whereas H14 has a comparable profile. Recoveries were quite low for all other cells and when normalized the data of the cell H14 are comparable to the other cells. In conclusion only the cell H13 has been excluded from the results.

Figure 7.3-3: Cumulative Absorption Profile after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the nominal rate of 0.3 g/L to human skin (All cells)

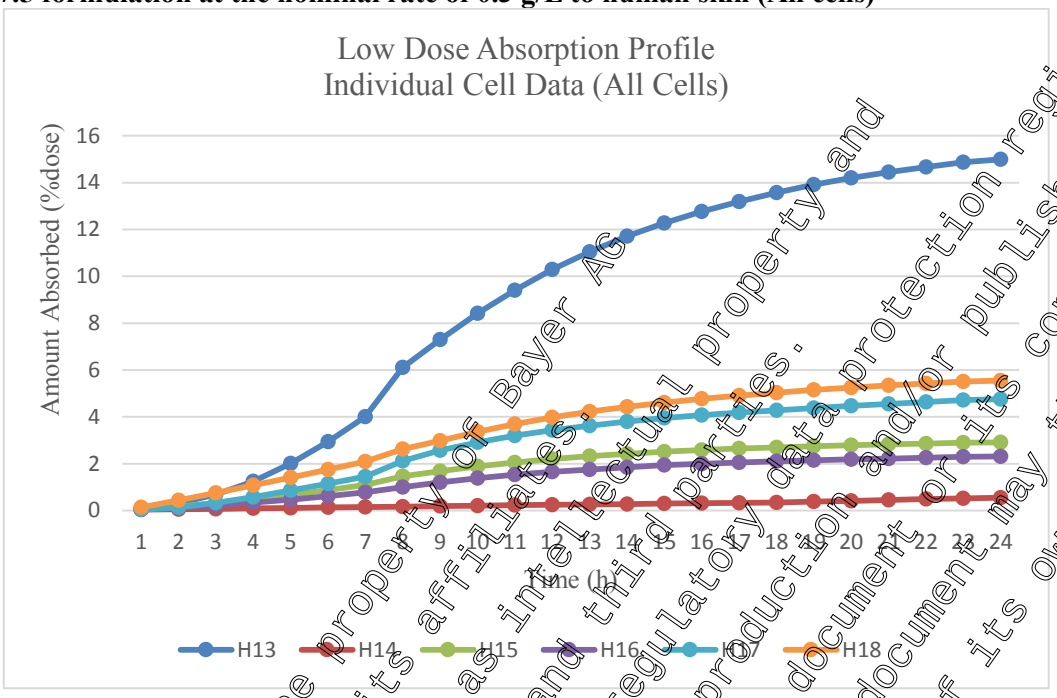
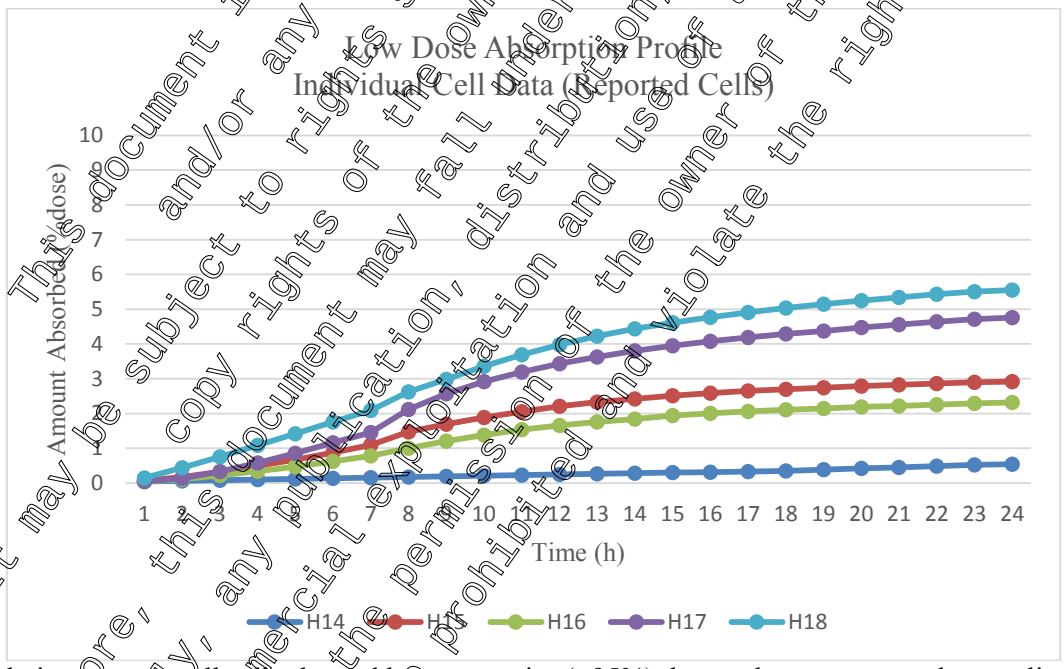


Figure 7.3-4: Cumulative Absorption Profile after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the nominal rate of 0.3 g/L to human skin (Reported cells)



Considering recovery all cells showed low recoveries (<95%) the results are presented normalized in the following table.

Table 7.3-14: Distribution of radioactivity at 24 hours after dose application of [^{14}C]-propamocarb in an SC 687.5 formulation at the rate of 0.3 g/L to human skin samples (reported cells) normalized.

	Distribution of radioactivity (% dose applied)					Group Human HD N= 5 K N° = 1.2	
Sex	Female	Female	Female	Female	Female		
Donor N°	X2014/2-4	X2014/5-25	X2014/1-21	603-01-0414-V-1	598-01-0314-IV-1		
Cell N°	H14	H15	H16	H17	H18	MEAN	SD
Skin wash 8h	93.98	94.40	94.81	90.84	89.80	92.76	2.28
Skin wash 24h	0.48	0.36	0.28	0.32	0.84	0.46	0.22
Surrounding swabs 24 h	0.02	0.03	0.02	0.02	0.02	0.02	0.00
Total swabs	**94.48**	**94.78**	**95.11**	**91.19**	**90.66**	**93.24**	**2.14**
SC1	0.10	0.04	0.07	0.10	0.14	0.09	0.04
SC2	0.08	0.04	0.06	0.10	0.12	0.08	0.03
Total SC1 + SC2	**0.18**	**0.08**	**0.12**	**0.20**	**0.26**	**0.17**	**0.07**
Donor chamber	0.47	0.76	0.52	0.44	0.47	0.53	0.13
TOTAL NON-ABSORBED	**95.12**	**95.65**	**95.75**	**91.83**	**91.39**	**93.94**	**2.15**
Skin	1.24	0.22	0.08	0.53	0.85	0.60	0.45
Surrounding skin	0.07	0.03	0.03	0.16	0.10	0.08	0.05
Total skin	**1.31**	**0.35**	**0.11**	**0.69**	**0.95**	**0.68**	**0.47**
SC3	0.198	0.031	0.048	0.167	0.217	0.13	0.09
SC4	0.186	0.055	0.063	0.204	0.296	0.16	0.10
SC5	0.234	0.039	0.045	0.235	0.220	0.15	0.10
SC6	0.226	0.056	0.065	0.124	0.226	0.14	0.08
SC7	0.460	0.086	0.055	0.202	0.156	0.19	0.16
SC8	0.208	0.035	0.034	0.197	0.105	0.12	0.08
SC9	0.226	0.067	0.046	0.155	0.144	0.13	0.07
SC10	0.228	0.046	0.048	0.117	0.112	0.11	0.08
SC11	0.181	0.043	0.905	0.096	n.s.	0.25	0.38
SC12	0.086	0.040	n.s.	0.082	n.s.	0.04	0.04
SC13	0.105	0.041	n.s.	0.077	n.s.	0.04	0.05
SC14	0.153	0.045	n.s.	0.077	n.s.	0.05	0.06
SC15	0.071	n.s.	n.s.	0.066	n.s.	0.03	0.04
Total SC3+	**2.58**	**0.53**	**1.17**	**1.62**	**1.40**	**1.55**	**0.73**
TOTAL DOSE SITE	**3.89**	**0.85**	**1.27**	**2.24**	**2.30**	**2.23**	**1.14**
Receptor fluid (0 - 12h)	0.29	2.44	1.85	3.81	4.18	2.52	1.57
Receptor fluid (0 - 24h)	0.65	3.22	2.58	5.28	5.84	3.52	2.10
%Ratio receptor 12h/24h	45	76	72	72	72	**67**	**12**
Residual Rec Fluid	0.34	0.21	0.25	0.40	0.35	0.31	0.08
Receptor chamber	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.a.
TOTAL DIRECT	0.99	3.44	2.83	5.68	6.19	**3.83**	**2.13**
POTENTIAL (dose site+ receptor)	4.88	4.37	4.25	8.17	8.61	**6.06**	**2.15**

	Distribution of radioactivity (% dose applied)					Group Human HD N= 5 K N° = 1.2	
Sex	Female	Female	Female	Female	Female		
Donor N°	X2014/2-4	X2014/5-25	X2014/1-21	603-01-0414-V-1	598-01-0314-IV-1		
POTENTIAL (skin+ receptor)	2.30	3.79	2.94	6.37	7.13	4.51	2.14
TOTAL RECOVERY	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**0.00**
Evaluation according to EFSA Guidance (2017)							
Absorption >75% within half of study duration?					No (include SC values)		
Mean Recovery <95%?					Correction needed		
Total % Potentially Absorbable adjusted according to EFSA (2017)					Mean (%dose site +%receptor) + (SD*1.2) = **8.6%**		
SD: standard deviation; N: number of skin cells used for calculation							
n.d.: not detected (below the limit of detection); n.a. : not applicable							
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.							

Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-propamocarb in the propamocarb SC 687.5 formulation was investigated at three nominal concentrations corresponding to the neat product (625 g /L) and to two representative spray dilutions of 5 g/L and 0.3 g/L.

Concentrate

The mean percentage of propamocarb in the FLC+PCH SC 687.5 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 2.0%.

Intermediate Dose level (Spray dilution at 5 g/L)

The mean percentage of propamocarb in the FLC+PCH SC 687.5 formulation that was considered to be potentially absorbable for the spray dilution at 5 g/L applying the EFSA guidance (2017) to the study data was 2.9%.

Low Dose level (Spray dilution at 0.3 g/L)

The mean percentage of propamocarb in the FLC+PCH SC 687.5 formulation that was considered to be potentially absorbable for the spray dilution at 0.3 g/L applying the EFSA guidance (2017) to the study data was 8.6%.

Therefore, the following dermal absorption values can be proposed for use in the non-dietary risk assessments for propamocarb in the FLC+PCH SC 687.5 formulation:

- 2.0% for the neat formulation (625 g/L)
- 2.9% for the intermediate dose (5 g/L)
- 8.6% for the low dose (0.3 g/L).

Data Point:	KCP 7.3/03
Report Author:	[redacted]
Report Year:	1994
Report Title:	Dermal penetration in the rat propamocarb HCL
Report No:	A85147
Document No:	M-157340-01-1
Guideline(s) followed in study:	--
Deviations from current test guideline:	none
Previous evaluation:	yes, evaluated and accepted DAR 2005 for Propamocarb RAR June 2017
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

This study is an *in vivo* dermal absorption study in rats. This study is no longer relevant as an *in vitro* study through human skin is available which provides the best estimate of dermal absorption. Therefore, this study has not been considered further for this renewal.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information – data provided separately (Document JCP).

Appendix 1 Critical GAPs for this assessment

Table of supported uses for this renewal.

The critical GAPs for the non-consumer exposure assessment are highlighted in grey.

Crop and/ or situation	Country	F G or I	Pests or Group of pests controlled	Formulation		Application				Application rate per treatment			PHI	Remarks:
				Type	Conc. of a.s.	Method / kind	Timing / Growth stage of crop & season	Number min - max	Interval between applications min	g a.s./hL min - max	Water L/ha min - max	g a.s./ha min - max	Days	
(a)		(b)	(c)	(d-f)	(i)	(f-h)	(j)	(k)					(l)	(m)
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 4	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 2 years
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 4	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 3 years
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 3	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 3	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 2 years
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 3	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 3 years
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 2	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 2	7	FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 2 years
Potato	EU	F	*Phytophthora infestans* (PHYTIN)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 2		FLC: 10 - 100 PCH: 100 - 1000	100 - 1000	FLC: 100 PCH: 1000	7	1 in 3 years
Lettuce	EU	F	*Bremia lactucae* (BREMLA)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 41 - 49	1 – 2	7	FLC: 10 – 50 PCH: 100 – 500	200 - 1000	FLC: 100 PCH: 1000	7	
Lettuce	EU	F	*Bremia lactucae* (BREMLA)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 13 - 49	1 – 1	n.a.	FLC: 10 – 50 PCH: 100 – 500	200 - 1000	FLC: 100 PCH: 1000	7	
Cucumber	EU	G	*Pseudoperonospora cubensis* (PSPECU)	SC	FLC: 62.5 g/L PCH: 625 g/L	Spraying / foliar	BBCH 21 - 89	1 – 3	7	FLC: 10 - 100	1000 - 1250	FLC: 100 PCH: 1000	1	High tech greenhouse, soil-based

FLC: Fluopicolide
PCH: Propamocarb-hydrochloride
n.a.: not applicable

Appendix 2 Spreadsheets for exposure calculations

Appendix 2.1 Operator exposure - Potatoes - 4 applications per crop*

No PPE work wear - arms, body and legs covered during mixing/loading and during application.

*** This scenario also applies to the following:**

3 applications a crop, 7 days between applications & 2 applications a crop, 7 days between applications

Fluopicolide

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	0.1 kg a.s./ha	*i_AppRate*	
Assumed area treated	50 ha/day	*d_AreaTreated*	
Amount of active substance applied	5 kg a.s./day	*i_AmountAS*	
Dermal absorption of the product	0.26%	*i_AbsorpProduct*	
Dermal absorption of in-use dilution	13.00%	*i_AbsorpInuse*	
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	16767	62370	AOEM	
	Body	11058	114920	AOEM	
	Head	259	1423	AOEM	
	Protected hands (gloves)	98	990	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	99	731	AOEM	
	Protected head (hood and face shield)	4	81	AOEM	
	Inhalation	6	38	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		Reference	Comment
		75th centile	95th centile		
Application	Hands	742	7440	AOEM	
	Body	415	2134	AOEM	
	Head	20	59	AOEM	
	Protected hands (gloves)	102	4021	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	78	AOEM	
	Inhalation	2	7	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	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)	0.2341771	0.1532575	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0039030	0.0025543	
% of RVNAS	5.58%	3.65%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	1.7557051	1.1844524	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0292618	0.0197409	
% of RVAAS	#DIV/0!	#DIV/0!	

Propamocarb

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	1 kg a.s./ha	*i_AppRate*
Assumed area treated	50 ha/day	*d_AreaTreated*
Amount of active substance applied	50 kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	2.00%	*i_AbsorpProduct*
Dermal absorption of in-use dilution	8.60%	*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	

Outdoor/Soluble concentrates, emulsifiable concentrate, etc./Downward spraying/Vehicle-mounted/not relevant

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	98691	374323	AOEM	
	Body	55794	224425	AOEM	
	Head	2594	14228	AOEM	
	Protected hands (gloves)	439	9903	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	762	7313	AOEM	
	Protected head (hood and face shield)	42	886	AOEM	
	Inhalation	12	32	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			

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	7416	40226	AOEM	
	Body	4187	21376	AOEM	
	Head	196	591	AOEM	
	Protected hands (gloves)	355	5[illegible]	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	142	279	AOEM	
	Inhalation		28	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	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)	4.1739499	2.7245814
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0695342	0.0454097
% of RVNAS	23.98%	15.66%
Acute		
Total systemic exposure from mixing, loading and application (mg a.s./day)	17.6672087	11.5106467
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.2944535	0.1918441
% of RVAAS	#DIV/0!	#DIV/0!

Appendix 2.2

Operator exposure - Lettuce – Manual-Knapsack - 2 applications per crop*

No PPE work wear - arms, body and legs covered during mixing/loading and during application.
*** This scenario also applies to the following:**
1 application a crop

Fluopicolide

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	0.1 kg a.s./ha	*i_AppRate*
Assumed area treated	1 ha/day	*d_AreaTreated*
Amount of active substance applied	0.1 kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	0.26%	*i_AbsorpProduct*
Dermal absorption of in-use dilution	13.00%	*i_Absorpnuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Manual-Knapsack	
Season	not relevant	

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	9495	25482	AOEM	
	Body	803	2787	AOEM	
	Head	5	11	AOEM	
	Protected hands (gloves)	18	164	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	21	102	AOEM	
	Protected head (hood and face shield)	5	11	AOEM	
	Inhalation	15	26	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		Reference	Comment
		75th centile	95th centile		
Application	Hands	1544	4213	AOEM	
	Body	88868	137497	AOEM	
	Head	12	93	AOEM	
	Protected hands (gloves)	5	22	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	4504	62630	AOEM	
	Inhalation	26	48	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		No	Vehicle mounted downward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE	
Longer term			
Total systemic exposure from mixing, loading and application (mg a.s./day)	11.8329078	1.4354350	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.1972151	0.0239239	
% of RVNAS	281.74%	34.18%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	18.4951780	8.8191896	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.3082530	0.1469865	
% of RVAAS	#DIV/0!	#DIV/0!	

Propamocarb

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Assumed area treated	1	ha/day	*d_AreaTreated*
Amount of active substance applied	1	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	2.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	8.60%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Manual-Knapsack		
Season	not relevant		

Outdoor;Soluble concentrates, emulsifiable concentrate, etc.;Downward spraying;Manual-Knapsack

Mixing and loading

Exposure values	µg exposure/day mixed and loaded		Reference	Comment
	75th centile	95th centile		
Hands	9495	25482	AOEM	
Body	803	2787	AOEM	
Head	5	11	AOEM	
Protected hands (gloves)	18	164	AOEM	
Protected body (workwear or protective garment and sturdy footwear)	29	101	AOEM	
Protected head (hood and face shield)	5	11	AOEM	
Inhalation	7	26	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	

Application

Exposure values	µg exposure/day applied		Reference	Comment
	75th centile	95th centile		
Hands	2744	8213	AOEM	
Body	88868	237007	AOEM	
Head	12	85	AOEM	
Protected hands (gloves)	5	27	AOEM	
Protected body (workwear or protective garment and sturdy footwear)	8903	32630	AOEM	
Inhalation	26	26	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	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)	8.0335240	1.1409740	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.1338921	0.0190162	
% of RVAAS	46.17%	6.56%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	12.7698300	6.3197280	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.2128305	0.1053288	
% of RVAAS	#DIV/0!	#DIV/0!	

Operator exposure - Lettuce – Manual-Hand-held - 2 applications per crop*

No PPE work wear - arms, body and legs covered during mixing/loading and during application.

*** This scenario also applies to the following:**

1 application a crop

Fluopicolide

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	0.1	kg a.s./ha	*i_AppRate*
Assumed area treated	4	ha/day	*d_AreaTreated*
Amount of active substance applied	0.4	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	0.26%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	13.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Manual-Hand held		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Mixing and loading	Hands	2399	8719	AOEM	
	Body	1873	5519	AOEM	
	Head	21	114	AOEM	
	Protected hands (gloves)	19	79	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	11	59	AOEM	
	Protected head (hood and face shield)	0	6	AOEM	
	Inhalation	3	28	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	1544	4213	AOEM	
	Body	88868	137003	AOEM	
	Head	12	85	AOEM	
	Protected hands (gloves)	5	22	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	8903	62636	AOEM	
	Inhalation	26	86	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	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)	11.7950999	1.3948068	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.1965850	0.0232468	
% of RVNAS	280.84%	33.21%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	18.5902080	8.7778527	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.3098368	0.1462975	
% of RVAAS	#DIV/0!	#DIV/0!	

Propamocarb

Operator exposure for FLC+PCH SC outdoor spray applications

Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Assumed area treated	4	ha/day	*d_AreaTreated*
Amount of active substance applied	4	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	2.00%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	8.60%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Manual-Hand held		
Season	not relevant		

Mixing and loading

Exposure values	µg exposure/day mixed and loaded 75th centile	95th centile	Reference	Comment
Hands	14120	52300	AOEM	
Body	9452	35443	AOEM	
Head	208	1138	AOEM	
Protected hands (gloves)	85	792	AOEM	
Protected body (workwear or protective garment and sturdy footwear)	81	688	AOEM	
Protected head (hood and face shield)	3	64	AOEM	
Inhalation	6	48	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	

Application

Exposure values	µg exposure/day applied 75th centile	95th centile	Reference	Comment
Hands	4117	15300	AOEM	
Body	236981	888352	AOEM	
Head	32	227	AOEM	
Protected hands (gloves)	13	58	AOEM	
Protected body (workwear or protective garment and sturdy footwear)	23741	153013	AOEM	
Inhalation	69	69	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	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)	21.2877647	2.7617037	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.3547961	0.0460284	
% of RVNAS	122.34%	15.87%	
Acute			
Total systemic exposure from mixing, loading and application (mg a.s./day)	35.7301052	16.5298130	
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.5955018	0.2754969	
% of RVAAS	#DIV/0!	#DIV/0!	

Appendix 2.3

Operator exposure - Cucumbers (glasshouse) - 3 applications per crop*
Dutch Glasshouse model- note that AOEL has been calculated based on 60 kg bw (not 70 kg bw stated in table) - Gloves and coveralls

Fluopicolide

OPERATOR EXPOSURE				DUTCH GREENHOUSE MODEL
form	FLC+PCH SC 687.5		Application including mixing and loading	
a.s.	Fluopicolide			
Parameter		**Value**	**Unit**	**References, comments**
MANUAL SPRAYING in greenhouses				
AR	Application rate	0.1	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
	Inhalation Exposure (without PPE)	0.1	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	1		Non-powered mask filtertype 2 (most conservative): 10, more advanced PPE see note** (Dutch model)
	Inhalation Exposure (with PPE)	0.1	mg a.s./ day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
	Dermal Exposure	20	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	10		Gloves + coverall: 10 (Dutch model)
	Dermal Exposure (with PPE)	2	mg a.s./ day	DE(PPE) = (1/PPE-factor) x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	16	%	
	AOEL	42	mg a.s./ day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	0.1000	0.1000	IE(int) = IE x (IA/100)
	Dermal	1.2000	0.3200	DE(int) = DE x (DA/100)
	Total	**1.3000**	**0.4200**	**sum**
	% AOEL			
	Inhalation	2	2	%AOEL = 100 x IE(int) / AOEL
	Dermal	76	8	%AOEL = 100 x DE(int) / AOEL
	Total	**79**	**10**	**sum**

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

** Note: Only for gasforming/gaseous preparations and soil fumigation preparations: powered full-face filtering devices with filtertype 2 (factor 20), powered full-face filtering devices with filtertype 3 (factor 40)

Propamocarb

OPERATOR EXPOSURE			DUTCH GREENHOUSE MODEL	
form	FLC+PCH SC 687.5		Application including mixing and loading	
a.s.	Propamocarb			
Parameter		**Value**	**Unit**	**References, comments**
MANUAL SPRAYING in greenhouses				
AR	Application rate	1	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./kg a.s.	For dusting see note* (Dutch model)
	Inhalation Exposure (without PPE)	**1**	mg a.s. / day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	1		Non-powered mask filtertype 2 (most conservative): 10; more advanced RPE, see note* (Dutch model)
	Inhalation Exposure (with PPE)	**1**	mg a.s. / day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s. / kg a.s.	For dusting see note* (Dutch model)
	Dermal Exposure	**200**	mg a.s. / day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	10		Gloves + coverall: 10 (Dutch model)
	Dermal Exposure (with PPE)	**20**	mg a.s. / day	DE(PPE) = (1/PPE-factor) x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	8.6	%	
	AOEL	17.4	mg a.s. / day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	1.0000	1.0000	IE(int) = IE x (IA/100)
	Dermal	17.2000	1.7200	DE(int) = DE x (DA/100)
	Total	**18.2000**	**2.7200**	**sum**
	% AOEL			
	Inhalation	6	6	%AOEL = 100 x IE(int) / AOEL
	Dermal	99	10	%AOEL = 100 x DE(int) / AOEL
	Total	**105**	**16**	**sum**

Appendix 2.4 Resident exposure – Potatoes - applications per crop*

*** This scenario is worst case so also covers the following application rates:**

3 applications a crop, 7 days between applications

2 applications a crop, 7 days between applications

Fluopicolide

Resident exposure for FLC+PCH SC			
Croptype	Root and tuber vegetables		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		d_AppEquip
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		f_FormVal
Buffer strip	2-3	m	f_Buffer
Application rate of the product	0.1	kg a.s./ha	f_AppRate
Concentration of active substance (in-use dilution for liquid applications)	2	g a.s./l	d_Concai
Dermal absorption of product	1.26%		f_AbsorpProduct
Dermal absorption of in-use dilution	33.00%		f_Absorpinuse
Oral absorption	100.00%		f_AbsorpOralRate
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	kg a.s./cm^2	d_DFR
Vapour pressure of in-use dilution	low volatile substance having a vapour pressure of <5^{-5} Pa	Pa	f_Volat
Concentration in air	0.001	mg/m^3	d_AirCon
Resident dermal spray drift exposure 75th percentile - adult	0.47	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.82	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.18	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person	
Exposure duration dermal	2	hours	d_ReExpDur
Exposure duration inhalation	2	hours	d_ReExpDurInhal
Exposure duration entry into treated crops	0.25	hours	d_ReExpDurTreatCrop
Light clothing adjustment factor	18.0%		d_ClothAF
Breathing rate adult	0.23	m^3/day/kg	d_BreathRAd
Breathing rate child (1-3 year old)	1.07	m^3/day/kg	d_BreathRCh
Drift percentage on surface (75th percentile)	5.0%		
Drift percentage on surface (mean)	1.0%		
Turf transferable residues percentage	20.0%		d_Turf
Transfer coeff. of surface deposits-adult	7300	cm^2/hour	d_ReTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	2600	cm^2/hour	d_ReTCCh
Saliva extraction percentage	50.0%		d_SalExt
Surface area of hands mouthed	20	cm^2	d_AreaHM
Frequency of hand to mouth activity	9.5	events/hour	d_ReFreqHM
Ingestion rate for mouthing of grass per day	25	cm^2	d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.00%		d_DRP
Transfer coefficient for entry into treated crops (75th percentile) - ad	7[illegible]	cm^2/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm^2/h	d_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	3980	cm^2/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1794	cm^2/h	d_TcEntryCh

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0350782	0.0107000	0.0086280	0.0699779	0.0921706
Total systemic exposure per kg body weight	0.0035078	0.0010700	0.0008628	0.0069978	0.0092171
% of RVNAS	5.01%	1.53%	1.23%	10.00%	13.17%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0502020	0.0038000	0.0169523	0.2332595	0.2360781
Total systemic exposure per kg body weight	0.0008367	0.0002300	0.0002825	0.0038877	0.0039346
% of RVNAS	1.39%	0.33%	0.40%	5.55%	5.62%

Propamocarb

Resident exposure for FLC+PCH SC

Croptype	Root and tuber vegetables		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		I_AppEquip
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		I_FormVol
Buffer strip	2-3	m	I_Buffer
Application rate of the product	1	kg a.s./ha	I_AppRate
Concentration of active substance (in-use dilution for liquid applications)	10	g a.s./l	d_ConcAS
Dermal absorption of product	2.00%		I_AbsorbProduct
Dermal absorption of in-use dilution	8.60%		I_AbsorbInuse
Oral absorption	100.00%		I_AbsorbOralInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm²	d_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5* 10-3Pa	Pa	I_Volat
Concentration in air	0.003	mg/m³	d_AirConc
Resident dermal spray drift exposure 75th percentile - adult	0.247	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.327	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.000010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.000022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.29	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.00009	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person	
Exposure duration dermal	2	hours	d_ReExpDur
Exposure duration inhalation	24	hours	d_ReExpDurInh
Exposure duration entry into treated crops	0.25	hours	d_ExpDurTreatCrop
Light clothing adjustment factor	100	%	d_ClothAd
Breathing rate adult	0.23	m³/day/kg	d_BreathRAd
Breathing rate child (1-3 year old)	1.07	m³/day/kg	d_BreathRCh
Drift percentage on surface (75th percentile)	5.60%		
Drift percentage on surface (mean)	4.10%		
Turf transferable residues percentage	5.00%		d_Turf
Transfer coeff. of surface deposits-adult	1700	cm²/hour	d_ReTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	3400	cm²/hour	d_ReTCCh
Saliva extraction percentage	50.00%		d_SalExt
Surface area of hands mouthed	20	cm²	d_AreaHM
Frequency of hand to mouth activity	9.5	events/hour	d_ReFreqHM
Ingestion rate for mouthing of grass per day	25	cm²	d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.00%		d_DRP
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm²/h	d_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	5000	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1750	cm²/h	d_TcEntryCh

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.3329004	0.0107000	0.0668841	0.4629305	0.5566532
Total systemic exposure per kg body weight	0.0232800	0.0010700	0.0065844	0.0462930	0.0556653
% of RVNAS	8.03%	0.37%	2.27%	15.96%	19.19%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.3324485	0.0138000	0.1121458	1.5431015	1.4845595
Total systemic exposure per kg body weight	0.0232407	0.0009300	0.0018691	0.0257184	0.0247427
% of RVNAS	1.91%	0.08%	0.64%	8.87%	8.53%

Appendix 2.5 Resident exposure – Lettuces – 2 applications per crop*

* This scenario is worst case so also covers 1 application a crop

Fluopicolide

Resident exposure for FLC+PCH SC			
Croptype	Leaf vegetables and fresh herbs		
Application method	Downward spraying		
Application equipment	Manual-Knapsack		i_AppEquip
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		i_Formul
Buffer strip	2-3	m	i_Buffer
Application rate of the product	0.1	kg a.s./ha	i_AppRate
Concentration of active substance (in-use dilution for liquid applications)	0.5	g a.s./l	d_ConcAS
Dermal absorption of product	0.26%		i_AbsorpProduct
Dermal absorption of in-use dilution	13.0%		i_AbsorpInuse
Oral absorption	100%		i_AbsorpOralinuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm²	d_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure < 10-3Pa	Pa	d_Volat
Concentration in air	0.001	mg/m³	d_AirConc
Resident dermal spray drift exposure 75th percentile - adult	0.0	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.0027	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.00010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.0009	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.00017	ml spray dilution/person	
Exposure duration dermal	2	hours	d_DurExpDur
Exposure duration inhalation	24	hours	d_ReExpDurInhal
Exposure duration entry into treated crops	0.25	hours	d_ExpDurEntrycrop
Light clothing adjustment factor	18.0		d_ClothFact
Breathing rate adult	1.45	m³/day/kg	d_BreathRAd
Breathing rate child (1-3 year old)	1.107	m³/day/kg	d_BreathRCh
Drift percentage on surface (75th percentile)	5.60%		
Drift percentage on surface (mean)	4.10%		
Turf transferable residues percentage	5.00%		d_Turf
Transfer coeff. of surface deposits-adult	7300	cm²/hour	d_ReTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	3500	cm²/hour	d_ReTCCh
Saliva extraction percentage	50%		d_SalExt
Surface area of hands mouthed	20	cm²	d_AreaHM
Frequency of hand to mouth activity	9.5	events/hour	d_ReFreqHM
Ingestion rate for mouthing of grass per day	25	cm	d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20%		d_DRP
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm²/h	d_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	5900	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1770	cm²/h	d_TcEntryCh

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0175381	0.0107700	0.0050057	0.0405990	0.0564148
Total systemic exposure per kg body weight	0.0017539	0.0010700	0.0005006	0.0040599	0.0056415
% of RVNAS	2.51%	1.53%	0.72%	5.80%	8.06%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0251040	0.0138600	0.0098352	0.1353300	0.1408444
Total systemic exposure per kg body weight	0.0004184	0.0002300	0.0001639	0.0022555	0.0023474
% of RVNAS	0.60%	0.33%	0.23%	3.22%	3.35%

Propamocarb

Resident exposure for FLC+PCH SC

Croptype	Leaf vegetables and fresh herbs		
Application method	Downward spraying		
Application equipment	Manual-Knapsack		i_AppEquip
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		i_FormVol
Buffer strip	2-3	m	i_Buffer
Application rate of the product	1	kg a.s./ha	i_AppRate
Concentration of active substance (in-use dilution for liquid applications)	5	g a.s./l	d_ConcAS
Dermal absorption of product	2.00%		i_AbsorpProduct
Dermal absorption of in-use dilution	8.60%		i_AbsorbInuse
Oral absorption	100.00%		i_AbsorptOralInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm²	d_DFR
Vapour pressure of in-use dilution	low volatile substances having a vapour pressure of <5* 10-3Pa	Pa	d_Volat
Concentration in air	0.001	mg/m³	d_AirConc
Resident dermal spray drift exposure 75th percentile - adult	0.0	ml spray dilution/person	
Resident dermal spray drift exposure 75th percentile - child	0.1127	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - adult	0.0010	ml spray dilution/person	
Resident inhal. spray drift exposure 75th percentile - child	0.00022	ml spray dilution/person	
Resident dermal spray drift exposure mean - adult	0.22318	ml spray dilution/person	
Resident dermal spray drift exposure mean - child	0.18	ml spray dilution/person	
Resident inhal. spray drift exposure mean - adult	0.0019	ml spray dilution/person	
Resident inhal. spray drift exposure mean - child	0.0017	ml spray dilution/person	
Exposure duration dermal	2	hours	d_ReExpDur
Exposure duration inhalation	24	hours	d_ReExpDurInh
Exposure duration entry into treated crops	0.25	hours	d_ExpDurTreatCrop
Light clothing adjustment factor	18.0%		d_ClothAF
Breathing rate adult	2.5	m³/day/kg	d_BreathAd
Breathing rate child (1-3 year old)	3.07	m³/day/kg	d_BreathCh
Drift percentage on surface (75th percentile)	3.60%		
Drift percentage on surface (mean)	4.10%		
Turf transferable residues percentage	5.0%		d_Turf
Transfer coeff. of surface deposits-adult	7300	cm²/hour	d_ReTCAd
Transfer coeff. of surface deposits-child (1-3 year old)	7300	cm²/hour	d_ReTCCh
Saliva extraction percentage	50.0%		d_SalExt
Surface area of hands mouthed	20	cm²	d_AreaHM
Frequency of hand to mouth activity	9.5	events/hour	d_ReFreqHM
Ingestion rate for mouthing of grass per day	25	cm	d_MouthGrass
Dislodgeable residues percentage transferability for object to mouth	20.0%		d_DRP
Transfer coefficient for entry into treated crops (75th percentile) - ad	7500	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (75th percentile) - ch	2250	cm²/h	d_TcEntryCh
Transfer coefficient for entry into treated crops (mean) - adult	5980	cm²/h	d_TcEntryAd
Transfer coefficient for entry into treated crops (mean) - child	1794	cm²/h	d_TcEntryCh

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.1414002	0.0107000	0.0392057	0.2685781	0.3171326
Total systemic exposure per kg body weight	0.0116400	0.0010700	0.0039201	0.0268578	0.0317133
% of RVNAS	4.01%	0.37%	1.32%	9.26%	10.94%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.1662288	0.0138000	0.0650635	0.8952602	0.8543999
Total systemic exposure per kg body weight	0.0017704	0.0002200	0.0010844	0.0149210	0.0142400
% of RVNAS	0.96%	0.08%	0.37%	5.15%	4.91%

Appendix 2.6 Worker exposure – Potatoes - 4 applications per crop*

*** This scenario is worst-case so also applies to the following:**

3 applications a crop, 7 days between applications

2 applications a crop, 7 days between applications

Fluopicolide

Worker exposure from residues on foliage for FLC+PCH SC

Crop type	Root and tuber vegetables	
Indoor or outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Worker's task	Inspection, irrigation	
Main body parts in contact with foliage	Hand and hands	
Application rate of active substance	0.1 kg a.s./ha	i_AppRate
Number of applications	4	i_AppNo
Interval between multiple applications	7 days	i_AppInt
Half-life of active substance	30 days	d_HalflifeAS
Multiple application factor	3.2	d_MAF
Dermal absorption of the product	0.26%	i_AbsorpProduct
Dermal absorption of the in-use dilution	13.00%	i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3 µg a.s./cm²	d_DFR
Working hours	2 hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	12500 cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	1400 cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.1101271	0.3483342	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0518355	0.0058056		
% of RVNAS	74.05%	8.29%		

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	3.1101271	0.0518355	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_Absorpinuse	
Dermal - Work wear - arms, body and legs covered	0.3483342	0.0058056	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse	
Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse	
Inhalation				NA for outdoor activities

Propamocarb

Worker exposure from residues on foliage for FLC+PCH SC

Crop type	Root and tuber vegetables	
Indoor or outdoor	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted	
Worker's task	Inspection, irrigation	
Main body parts in contact with foliage	Hand and hands	
Application rate of active substance	1 kg a.s./ha	i_AppRate
Number of applications	4	i_AppNo
Interval between multiple applications	7 days	i_AppInt
Half-life of active substance	30 days	d_HalflifeAS
Multiple application factor	3.2	d_MAF
Dermal absorption of the product	2.00%	i_AbsorpProduct
Dermal absorption of the in-use dilution	8.00%	i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	3 µg a.s./cm²	d_DFR
Working hours	2 hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	12500 cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	1400 cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	20.5746872	2.3043650	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	2.3429115	0.0384061		
% of RVNAS	118.25%	13.24%		

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	20.5746872	0.3429115	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_Absorpinuse	
Dermal - Work wear - arms, body and legs covered	2.3043650	0.0384061	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse	
Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse	
Inhalation				NA for outdoor activities

Appendix 2.7 Worker exposure – Lettuces - 2 application per crop*

* This scenario is worst case so also covers 1 application a crop

Fluopicolide

Worker exposure from residues on foliage for FLC+PCH SC			
Crop type	Leaf vegetables and fresh herbs		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Manual-Knapsack		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.1	kg a.s./ha	i_AppRate
Number of applications	2		i_AppNo
Interval between multiple applications	7	days	i_AppInt
Half-life of active substance	30	days	d_HalfLifeAS
Multiple application factor	1.9		d_MAF
Dermal absorption of the product	0.26%		i_AbsorpProduct
Dermal absorption of the in-use dilution	13.00%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.9	µg a.s./cm²	d_DFR
Working hours	8	hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	5800	cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	2500	cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.3489673	1.4435204	0.3348967	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0558161	0.0240587	0.0055816	
% of RVNAS	79.74%	34.37%	7.97%	

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	3.3489673	0.0558161	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	1.4435204	0.0240587	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Dermal - Working wear and gloves	0.3348967	0.0055816	d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Inhalation				Na for outdoor activities

Propamocarb

Worker exposure from residues on foliage for FLC+PCH SC			
Crop type	Leaf vegetables and fresh herbs		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Manual-Knapsack		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	i_AppRate
Number of applications	2		i_AppNo
Interval between multiple applications	7	days	i_AppInt
Half-life of active substance	30	days	d_HalflifeAs
Multiple application factor	1.9		d_MAF
Dermal absorption of the product	2.00%		i_AbsorpProduct
Dermal absorption of the in-use dilution	8.60%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm²	d_DFR
Working hours	8	hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	4800	cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	2500	cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear: arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	22.1547067	9.5494426	2.2154707	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.3692451	0.1591574	0.0369245	
% of RVNAS	127.32%	54.88%	12.73%	

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	22.1547067	0.3692451	d_DermTcUCV*d_WorkHr*i_DFR *i_MAF/1000*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	9.5494426	0.1591574	d_DermTcCV1*d_WorkHr*d_DFR *d_MAF/1000*i_AbsorpInuse	
Dermal - Working wear and gloves	2.2154707	0.0369245	d_DermTcCV2*d_WorkHr*d_DFR *d_MAF/1000*i_AbsorpInuse	
Inhalation				Na for outdoor activities

Appendix 2.8 Worker exposure – Cucumbers (glasshouse) – 3 applications per crop

Roof-fogger worker re-entry

Fluopicolide

Worker exposure from residues on foliage for FLC+PCH SC			
Crop type	Fruiting vegetables		
Indoor or outdoor	Indoor		
Application method	Worker rentry -roof fogger		
Application equipment	Manual-Knapsack		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.1	kg a.s./ha	i_AppRate
Number of applications	3		i_AppNo
Interval between multiple applications	7	days	i_AppInt
Half-life of active substance	30	days	d_HalflifeAS
Multiple application factor	2.6		d_MAF
Dermal absorption of the product	0.26%		i_AbsorpProduct
Dermal absorption of the in-use dilution	16.00%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.3	µg a.s./cm²	d_DFR
Working hours	8	hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	5800	cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	2500	cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	0.1	ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	5.7334849	2.5913297	0.6933485	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0975581	0.0441088	0.0118058	
% of RVNAS	139.39%	63.00%	16.51%	

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	5.7334849	0.0975581	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	2.4713297	0.0411888	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Dermal - Working wear and gloves	0.5733885	0.0095558	d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Inhalation	0.1200000	0.0020000	i_AppRate*d_InhalTcAut*d_WorkHr	For re-entry 16 hours after application

Propamocarb

Worker exposure from residues on foliage for FLC+PCH SC

Crop type	Fruiting vegetables		
Indoor or outdoor	Indoor		
Application method	Worker rentry -roof fogger		
Application equipment	Manual-Knapsack		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_NoApp*
Interval between multiple applications	7	days	*i_ApplInt*
Half-life of active substance	30	days	*i_Halflife*
Multiple application factor	2.6		*d_MAF*
Dermal absorption of the product	2.00%		*i_Absorpproduct*
Dermal absorption of the in-use dilution	8.60%		*i_Absorpinuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	1	µg a.s./cm²	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	8800	cm²/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm²/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm²/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	0.15	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	32.8174815	13.4833972	4.2817481	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.5336247	0.2413900	0.0713625	
% of RVNAS	184.01%	83.24%	24.61%	

2. Details

	Systemic exposure (mg a.s./day)	Systemic exposure (mg a.s./kg bw/day)	Formula	Comments
Dermal - Potential	30.8174815	0.5136247	*d_DermTcUCV*d_WorkHr*i_DFR*d_MAF/1000*i_Absorpinuse*	
Dermal - Work wear - arms, body and legs covered	13.4833972	0.2213900	*d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse*	
Dermal - Working wear and gloves	3.0817481	0.0513625	*d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_Absorpinuse*	
Inhalation	1.2000000	0.0200000	*i_AppRate*d_InhalTcAut*d_WorkHr*	For re-entry 16 hours after application