Bayer CropScience

Document Title

Summary of the toxicological studies
Deltamethrin EW 15 (15 g/L)

Data Requirements

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

According to the guidance document, SANCO/10181/2013, for preparing dossiers for the approval of a chemical active substance

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Date

2015-12-02

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number
2014-06-03	CP 7.2.2.1 Estimation of bystander and resident exposure CP 7.2.3.1 Estimation of worker exposure Updates were provided following RMS (UK CRD) request (COP 2014/00717: RENEWAL OF APPROVAL OF DELTAMETHRIN)	M-473163-02-1
2015-12-02	CP 7.3 updated by adding the position paper M-533594-01-1 to confirm the evaluation according to the latest EFSA (2012) guidance.	M-473163-03-1

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

Additions to the document after the Completeness Check are highlighted in yellow. Content not necessary anymore is crossed out.

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

This document is an updated version of the previous document (M-473163-01-1). The update was requested by RMS (UK CRD) during the Completeness Check step of the Annex I Renewal (AIR) dossier.

The updated sections are sections CP7.2.2.1 and CP 7.2.3.1.

CP 7.1 Acute toxicity

All relevant data concerning the toxicological properties of the active substance deltamethrin are compiled in the following documents:

- Annex II, section 3, point 5 of either the original EU dossier (1995)
- it's the Addendum of the original EU dossier (2001)
- The baseline dossier submitted for the AIR submission
-

Within this section of the dossier, only those data concerning the formulated product Decis EW15 have been included.

Throughout the development of the formulation, the recipe has been slightly modified in order to improve its smell (addition of fresh fragrance) and its toxicological profile (removal of parabens). The formulation Decis EW15 (specification: **102000025993-01**) for which the AIR dossier is presented is derived from the following recipes:

Decis EW15 (15 g ai/L)		
Code (UVP, Specification)		
UVP80269285	Specification: **102000025993-01**	Fresh fragrance containing recipe Parabens free recipe Recipe similar to 102000013165-05 except that for some co-formulants (antifoam and emulsifier), equivalent co-formulants were added
UVP05759284	Specification: 102000013165-05	Fresh fragrance containing recipe Parabens free recipe
UVP05759284	Specification: 102000013165-04	Fresh fragrance containing recipe Parabens containing recipe
UVP05946743	Specification: none	Without fresh fragrance Parabens containing recipe

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As explained in the confidential part (Document J), studies performed with Decis EW15 (UVP05946743 (AE F032640 00 EW01 B1)) are used to support Decis EW15 (UVP05759284, Specification: 102000013165). The toxicological data package generated can be also used to support the current recipe specification: 102000025993-01, UVP80269285.

The following tests were performed with the formulated product Decis EW15 (UVP05946743 = (AE F032640 00 EW01 B1):

- LD_{50} oral, rat
- LD_{50} dermal, rat

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- Skin irritation, rabbit
- Eye irritation, rabbit
- Skin sensitization (Buehler 9 inductions/ applications)

The following test was performed with the formulation Decis EW15 (102000013165 = UVP05759284 = AB0375031):
- Sensitisation of the skin (the local lymph node assay).

Separate testing for inhalation toxicity was not conducted, because it was not triggered according to the criteria of Directive 94/79/EEC due to the physical-chemical properties of this formulated product and its intended uses in the field.

Results of all studies show low acute toxicity as demonstrated in the table below.

Type of study	Species	Sex	Result	Reference
Acute oral toxicity	Rat	Male and Female	LD_{50} > 2000 mg/kg bw	[redacted], 2000 M-197188-01-1
Acute dermal toxicity	Rat	Male and Female	LD_{50} > 2000 mg/kg bw	[redacted], 2000 M-198291-01-1
Skin irritation	Rabbit	Male	Not irritant	[redacted], 2000 M-198293-01-1
Eye irritation	Rabbit	Male	Not irritant	[redacted], 2000 M-197189-01-1
Skin sensitization (Mod. Buehler test 9 ind.)	Guinea pig	Male and Female	Not sensitising	[redacted], 2000 M-195603-01-1
Skin sensitization (LLNA test)	Mouse	Male and Female	Not sensitising	[redacted] 2005 M-248033-03-1

Classification/labelling according to current rating systems is triggered as follows:

- EU Directive 1999/45/EC: None
- Regulation (EC) No 1272/2008 (CLP): None
- GHS (rev.4) 2011: None

CP 7.1.1 Oral toxicity

Report: **KCP7.1.1/01, [redacted], 2000**
Title: Rat acute oral toxicity: Deltamethrin 15 g/l, oil in water emulsion – code AE F032640 00 EW01 B1
Document No: M-197188-01-1
Guidelines: EEC Directive 92/69, Method B1, 31/07/1992.
OECD guidelines 401 for Testing of Chemicals, 24/02/1987.
EPA Pesticide Assessment Guidelines, Subd. F, 81-1, 11/1984.
GLP: Yes

Material and Methods:

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The test article was Deltamethrin 15 g/L, oil in water emulsion – code AE F032640 00 EW01 B1 (batch No. TA124/99SG) is a white liquid formulation containing Deltamethrin (theoretical concentration: 15.0 g/L, measured concentration: 15.1 g/L).

A group of Sprague-Dawley rats (5 males/5 females) received the formulation once by gavage at a dose of 2000 mg/kg. The rats were kept under observation for 14 days. Mortality, clinical signs and body weights were recorded. At the end of the observation period, the surviving animals were sacrificed and autopsied.

Findings:

	Dose (mg/kg)	**Number of animals**	**Number of death**	**Onset of death after (days)**	**Number of animals with clinical signs**
Males	2000	5	1	2	5
Females	2000	5	0	/	5

- Mortality: 1 male died on day 2.
- Clinical signs:
Reduction of spontaneous activity, coat bristling, dyspnoea (laboured breathing) and trembling were observed on the day following the day of treatment. By day 2, all symptoms had completely disappeared.
- Body weights: The body weight gains of the animals were not influenced by the treatment.
- Necropsy:

Autopsy revealed no abnormalities of any kind in the animals died during the course of the study or in those killed at the end of the observation period.

Conclusion:
The oral LD_{50} of the formulation was found to be higher than 2000 mg/kg b.w. in Sprague-Dawley rats.

The study result triggers the following classification/labelling:
- EU Directive 1999/45/EC: none
- Regulation (EC) No 1272/2008 (CLP): none
- GHS (rev. 4) 2011: unclassified

CP 7.1.2 Dermal toxicity

Report: **KCP 7.1.2/01, [redacted], 2000**
Title: AE F032640 00 EW01 B1: Single dose toxicity study by the cutaneous route in the rat (limit test).
Document No: M-198291-01-1
Guidelines: EEC Directive 92/69, Method B3, 31/07/1992.
OECD guidelines 402 for Testing of Chemicals, 24/02/1987.
GLP Yes

Material and Methods:
The test article was Deltamethrin 15 g/L, oil in water emulsion – code AE F032640 00 EW01 B1 (batch No. TA124/99SG) is a white liquid formulation containing deltamethrin (theoretical concentration: 15.0 g/L, measured concentration: 15.1 g/L).

Testing was started with a preliminary study. Neat test product was applied once at doses of 1010 and 2009 mg/kg to the skin of the Sprague-Dawley rats (2 animals / sex / group). The product was kept in contact with the skin under a semi-occlusive bandage for 24 consecutive hours over approximately 10% of the body surface.

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The main study was then conducted at a dose of 2009 mg/kg, administered under the same conditions to a group of 10 rats (5 animals / sex). Mortality and abnormal clinical signs were recorded 15 minutes after the application, then at 1, 2 and 4 hours, and thereafter once daily over the 14 days of the study. Skin examinations were carried out from the 2nd to the 14th day after treatment. All animals were weighed immediately after application of the product (day 1), then on days 8 and 15. The animals were autopsied after the final observation (day 15).

Findings:

	Dose (mg/kg)	Number of animals	Number of deaths	Onset of death after (days)	Clinical signs
Males	2 009	5	0	/	0
Females	2 009	5	0	/	0

- Mortality: No deaths occurred during the study.
- Body weights: The body weight gain was normal.
- Clinical signs: No abnormal clinical signs were observed during the study. No dermal lesions (erythema or oedema) were observed at the site where the product had been applied.
- Effects on organs: No abnormalities were noted at necropsy.

Conclusion:
The dermal LD_{50} of the formulation was greater than 2009 mg/kg b.w. for male and female Sprague-Dawley rats.

The study result triggers the following classification/labelling:
- EU Directive 1999/45/EC: none
- Regulation (EC) No 1272/2008 (CLP): none
- GHS (rev. 4) 2011: unclassified

CP 7.1.3 Inhalation toxicity

Since Decis EW15 is commercialized in the form of an emulsion oil in water formulation, no acute inhalation study is required. When this type of formulation is applied on fields no contamination by inhalation is expected due to the physico-chemical properties of the formulated product and its indicated uses.

Testing is not triggered according to Directive 94/79/EEC because this formulation

- is not a gas or liquefied gas,
- is not a smoke generating formulation or fumigant,
- is not to be used with fogging equipment,
- is not a vapour releasing preparation,
- is not an aerosol,
- is not a powder, is dust-free, and hence does not contain a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis),
- is not to be applied from aircraft and
- does not contain active substance with a vapour pressure > 1 x 10^{-2} Pa

The active ingredient deltamethrin is toxic by inhalation but its concentration is below 25%. Moreover, none of the inerts are labelled toxic by inhalation. As a consequence, by calculation this formulation is not classified for inhalation. Therefore no risk by inhalation is anticipated and these are additional arguments not to perform an animal test and consequently comply with animal welfare.

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CP 7.1.4 Skin irritation

Report:	**KCP 7.1.4/01, [redacted], 2000b**
Title:	AE F032640 00 EW01 B1: Primary cutaneous irritation and corrosivity test in the rabbit – 3 rabbits
Document No:	M-198293-01-1
Guidelines:	EEC Directive 92/69, Method B4, 31/07/1992. OECD guidelines 404 for Testing of Chemicals, 17/07/1992.
GLP	Yes

Material and Methods

The test article was Deltamethrin 15 g/L, oil in water emulsion – code AE F032640 00 EW01 B1 (batch No. TA124/99SG) is a white liquid formulation containing deltamethrin (theoretical concentration: 15.0 g/L, measured concentration: 15.1 g/L).

Three male New Zealand albino rabbits with shaved intact skin received 0.5 mL of the test article under a semi-occlusive bandage. After an exposure period of 4 hours the bandage was removed and all traces of product removed from the skin.

The skin was examined for erythema and oedema in accordance with a numerical scale at 1, 24 (day 1), 48 and 72 hours after removal of the bandage. However, in view of the lesions observed at 72 hours and in order to establish possible reversibility, the observations were continued from day 4 to day 7. Mortality checks were carried out twice per day. The animals were weighed on the day of treatment. Mean values were calculated on the basis of the evaluation of skin lesions carried out for each rabbit examined at 24, 48 and 72 hours.

Findings:

Table 7.1.4-1 Summary of irritant effects (Score)

Results hours after removal of the dressing (semi-occlusive, 4h)									
Rabbit no.	Parameter	24 h	48 h	72 h	Day 4	Day 5	Day 6	Day 7	Mean score 24h + 48h + 72h (Response)
68625	Erythema	1	1	0	0	0	0	0	0.67 (-)
	Oedema	0	0	0	0	0	0	0	0.00 (-)
68626	Erythema	2	2	1	1	1	0	0	1.67 (-)
	Oedema	1	0	0	0	0	0	0	0.33 (-)
68627	Erythema	2	2	2	2	2	1	0	2.00 (+)
	Oedema	2	2	1	1	0	0	0	1.67 (-)

(-) non-irritant according to E.C. criteria
(+) irritant according to E.C. criteria

- Mortality: no mortality occurred during the study.

- Clinical signs:

The lesions observed at 72 hours proved to be completely reversible at the examination on the last day of the observation period (day 7). Under the conditions of the study, application of the product caused moderate skin irritation in the rabbit, but only 1 out of 3 rabbits showing positive criteria, then product should not be classified as irritant.

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Conclusion:
The test substance was considered as non-irritant when administered by dermal route in rabbits.

The study result triggers the following classification/labelling:
- EU Directive 1999/45/EC: none
- Regulation (EC) No 1272/2008 (CLP): none
- GHS (rev. 4) 2011: unclassified

CP 7.1.5 Eye irritation

Report:	**KCP 7.1.5/01, [redacted], 2000**
Title:	Deltamethrin 15 g/l, oil in water emulsion – code AE F032640 00 EW01 B1. Rabbit eye irritancy.
Document No:	M-197189-01-1
Guidelines:	EEC Directive 92/69, Method B5, 31/07/1992. OECD guidelines 405 for Testing of Chemicals, 24/02/1987.
GLP	Yes

Material and Methods:
The test article was Deltamethrin 15 g/L oil in water emulsion – code AE F032640 00 EW01 B1 (batch No. TA124/99SG) is a white liquid formulation containing deltamethrin (theoretical concentration: 15.0 g/L, measured concentration: 15.1 g/L).

A single dose of 0.1 mL was applied to the conjunctival sac of the left eye of a male New Zealand albino rabbit. The right eye served as control. The eyes were not rinsed after application.
Since application of the preparation did not show any severe irritating properties in the first rabbit, the product was administered in the same way to two other male rabbits. The eyes were examined at 1, 24, 48 and 72 hours after application, then once daily until the eye reactions had proved reversible. The degree of irritation of the cornea, iris and conjunctivae were scored for each animal according to the OECD criteria (Draize).

Findings:

Table 7.1.5-1 Summary of Irritant Effects (Score)

		Rabbit number	24 hours	48 hours	72 hours	120 hours	Mean 24 + 48 + 72 hours
CONJUNC-TIVA	**Chemosis**	Male 566	1	1	1	0	1.0 (-)
		Male 579	1	1	0	-	0.7 (-)
		Male 580	2	1	0	-	1.0 (-)
	Redness	Male 566	2	1	0	0	1.0 (-)
		Male 579	1	1	0	-	0.7 (-)
		Male 580	1	0	0	-	0.3 (-)
	Discharge	Male 566	0	0	0	0	0
		Male 579	0	0	0	-	0
		Male 580	0	0	0	-	0
IRIS	**Inflammation**	Male 566	0	0	0	0	0
		Male 579	0	0	0	-	0
		Male 580	0	0	0	-	0

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		Rabbit number	24 hours	48 hours	72 hours	120 hours	Mean 24 + 48 + 72 hours
CORNEA	Degree of opacity	Male 566	0	0	0	0	0
		Male 579	0	0	0	0	0
		Male 580	0	0	0	0	0
	Area	Male 566	0	0	0	0	0
		Male 579	0	0	0	0	0
		Male 580	0	0	0	0	0

Only very slight or slight conjunctival reactions (very slight to slight chemosis and very slight to slight conjunctival reddening) were observed in all animals, starting from day 1 and continuing till day 3 or 4. No other eye reaction was observed during the study. Under the conditions of the study, application of the product caused slight but reversible eye irritation in the rabbit.

Conclusion:
The test substance was considered as non-irritant when administered by ocular route in rabbits.

The study result triggers the following classification/labelling:
- EU Directive 1999/45/EC: none
- Regulation (EC) No 1272/2008 (CLP): none
- GHS (rev. 4) 2011: unclassified

CP 7.1.6 Skin sensitization

Report: **KCP 7.1.6/01, [redacted], 2000**
Title: AE F032640 00 EW01 B1 - Sensitizing potential in the guinea-pig – Modified Buehler Test (9 induction applications).
Document No: M-195603-01-1
Guidelines: Adapted from Guidelines O.E.C.D. n° 406 (1992), E.E.C. 92/69 - Annex V – method B6 (1992), modified by the use of 9 topical applications during induction.
GLP Yes

Material and Methods
The potential of the test article AE F032640 00 EW01 B1 (batch TA124/99SG: white liquid containing deltamethrin: theoretical: 15 g/L, real: 1.48 % w/w) to induce delayed contact hypersensitivity following cutaneous application was evaluated in the albino Hartley guinea-pig.

Forty animals of both sexes were allocated to one control group of 10 animals (induction: vehicle - challenge: test article), one treated group of 20 animals (induction and challenge: test article) and one positive control group of 10 animals (induction: DNCB - challenge: DNCB + propylene glycol alone).

Examinations for morbidity/mortality were performed twice daily, at the beginning and at the end of the working day. The animals were weighed on day 1 (1st administration) and day 30.

During induction, the nine 6 hour topical occlusive applications were performed as follows:
In the treated group, 0.5 mL of the test article as supplied (minimally irritant concentration) was applied per animal.

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In the control group, the applications were carried out under the same conditions as in the treated group, water for injection replacing the test article.

In the positive control group, the applications were carried out under the same conditions as in the treated group, DNCB in a 0.5 % (w/v) solution in 1,2 propylene glycol replacing the test article. The rest period was 10 days without treatment.

During the challenge, the topical occlusive application for 6 hours was performed in the treated and control groups with the test article in a 50 % (v/v) solution in water for injection and at the dose level of 0.5 mL per animal (Maximum Non-Irritant Concentration: M.N.I.C.). In the positive control group this application was carried out with 0.5 ml of DNCB in a 0.5 % (w/v) solution in 1,2-propylene glycol. 1,2- propylene glycol was also applied during challenge.

The cutaneous macroscopic examinations were performed according to the Draize scale to the challenge application sites, 24 and 48 hours after removal of the occlusive dressing.

Findings
The results were as follow:

Table 7.1.6-1: Acute sensitisation in the guinea-pig

	Number of animals with positive response	
	24 hours	48 hours
Treated group (10 males and 10 females)	0/20	0/20
Control group (negative: 5 males and 5 females)	0/10	0/10
Positive control group (5 males and 5 females) (0.5 % DNCB in 1,2 propylene glycol)	10/10	10/10

-No mortality was observed during the study.
-Body weight changes in the treated animals were not influenced by treatment when compared with controls.
-The repeated applications of the test article and the positive control article[1] provoked signs of irritation during induction in the treated and positive control groups.
-After the challenge, the macroscopic examinations did not reveal any lesion of delayed hypersensitivity in the 20 guinea-pigs of the treated group.
- No cutaneous abnormality was noted in the 10 guinea-pigs of the control group. Positive reactions were noted in the 10 animals of the positive control group.

Conclusion
Under our experimental conditions and according to the modified method established by Buehler, a challenge application with the test article at a concentration of 50 % (V/V) did not provoke any reaction of cutaneous sensitization.

The study result triggers the following classification/labelling:
- EU Directive 1999/45/EC: none
- Regulation (EC) No 1272/2008 (CLP): none
- GHS (rev. 4) 2011: unclassified

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[1] Taking into account the cutaneous irritation observed after some applications of the positive control article during induction, the application site was changed and a total of two sites were used in the positive control group.

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Report:	**KCP 7.1.6/02, [redacted] 2005**
Title:	DECIS EW 15 (Development no. 30-00375031) -Evaluation of potential dermal sensitization in the local lymph node assay
Document No:	M-248033-03-1
Guidelines:	O.E.C.D. Guideline 429 (2002)
GLP	Yes

Material and Methods

The dermal contact sensitization potential of Decis EW 15 (Development no. 30-00375031), an agrochemical formulation containing the active ingredients Deltamethrin at 15 g/L (measured 14.79 g/L) (batch N°: 08398/0045) was tested using the murine Local Lymph Node Assay.

Twenty-four female CBA/J mice were allocated to 6 groups of four animals each:
- four groups received the test substance at a concentration of 2.5, 5, 10 or 25% in vehicle,
- one positive control group received 0.25% p-Benzoquinone in 1% DECIS EW 15 (Development no. 30-00375031) and 99% Pluronic acid at 1% in water. The positive control was spiked in the formulation to ensure that under the conditions of this assay, the study demonstrated appropriate sensitivity with the positive control.
- one control group received the vehicle, 1% Pluronic acid in water.

The test substance, positive control or the vehicle were applied on external surfaces of each ear (50 µL/ animal) for three consecutive days (Days 0, 1 and 2) at the appropriate concentrations. On Day 5, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated thymidine and the obtained values were used to calculate proliferation indices.

Findings

Table 7.1.6-2: Acute sensitisation in the mouse (cell count index)

Group Number	Test Group Name	Mean DPM	Stimulation Index Values
1	control 1% Aqueous Pluronic Acid	506.0	
2	DECIS EW 15 (Development no. 30-00375031) 2.5% 1% Aqueous Pluronic Acid	971.0	1.9
3	DECIS EW 15 (Development no. 30-00375031) 5% 1% Aqueous Pluronic Acid	779.0	1.5
4	DECIS EW 15 (Development no. 30-00375031) 10% 1% Aqueous Pluronic Acid	1247.0	2.5
5	DECIS EW 15 (Development no.30-00375031) 25% 1% Aqueous Pluronic Acid	1282.0	2.5
6	p-Benzoquinone 0.25% in 1% DECIS EW 15 (Development no.30-00375031) and 99% Aqueous Pluronic Acid at 1%	4054.0	8.0

- No mortality and no clinical signs were observed during the study.
- No cutaneous reactions were observed in the vehicle, reference control or treated groups.
- The proliferation index values of the test substance were 1.9, 1.5, 2.5 and 2.5 at treatment concentrations of 2.5, 5, 10 and 25% respectively.

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- The proliferation index value of the positive control was 8 at treatment concentration of 0.25% of p-Benzoquinone in 1% DECIS EW 15 (Development no.30-00375031) and 99% Pluronic acid at 1% in water.

Conclusion
Decis EW 15 was found to be non-sensitizing formulation in the Local Lymph Node Assay.

The study result triggers the following classification/labelling:

- EU Directive 1999/45/EC:	none
- Regulation (EC) No 1272/2008 (CLP):	none
- GHS (rev. 4) 2011:	unclassified

CP 7.1.7 Supplementary studies on the plant protection product

None.

CP 7.1.8 Supplementary studies for combinations of plant protection products

As tank mixture of Decis EW15 is not recommended on the label, such supplementary studies are deemed unnecessary.

CP 7.2 Data on exposure

CP 7.2.1 Operator exposure

Decis EW15 is an emulsion oil in water (EW), considered as an Emulsion Concentrate (EC) formulation for calculations, containing 15 g/L of deltamethrin. It is used as a foliar insecticide.

The representative uses supported in the present AIR dossier are as follows:
Wheat: 2 x 6.25 g ai/ha
Sugarbeet: 1 x 7.5 g ai/ha
Cauliflower: 2 x 7.5 g ai/ha

It is assumed as a worse case that the formulation is packaged in 0.25 L containers. In practice, larger volumes will be commercialized for the larger treatment areas (1 and 3L), but 0.25L was taken into account here to represent the worst case. This is not always realistic, especially when preparing large volumes**.**

Applications of Decis EW15 will be achieved *via* field crop sprayers. Water will be the diluent/carrier in all situations. Usage information pertinent to the operator exposure is summarised in the following table.

The following section covers the representative uses to be covered in the AIR dossier:

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Table 7.2.1-1: Summary of representative use patterns

Crop	Application technique	Maximum dose rate		Spray volume (L/ha)	No of appl.	Interval between appl. (days)	PHI (days)
		(L/ha product)	(g a.s/ha) Deltamethrin				
Wheat	FCS	0.42	6.25	100 to 600	2	14	30
Sugarbeet		0.5	7.5*	100* to 600	1	-	30
Cauliflower		0.5	7.5	200 to 1000	2	14	7

FCS = Field Crop Sprayer. Appl. = application.
PHI = Pre Harvest Interval.
* = worst case used for calculations = highest dose rate and lower spray volume

Consideration on acceptable operator exposure level (AOEL)
Considering the proposed use pattern of Decis EW15 it is appropriate to compare predicted exposures to an AOEL derived from sub-chronic dosing studies. An Acceptable Operator Exposure Level (AOEL) of 0.0075 mg/kg bw/day is established for deltamethrin from a 1-year Dog study based on neurological signs (lowest NOAEL: 1 mg/kg bw/day) adjusted for 75% oral absorption and a safety factor of 100.

Dermal Absorption
In compliance with the recent EFSA guidance document on dermal absorption[2] the in vitro data from the human skin samples was used to provide the dermal absorption values used in this risk assessment.
The human *in vitro* dermal absorption values that can be used for exposure assessments are:

- 2% for the neat formulation (15 g/L)
- 12% for the intermediate dose (0.05 g/L)
- 14% for the low dose (0.005 g/L).

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

- Uniform Principles for Safeguarding the Health of applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992. ("German model").

- Revised UK-POEM Model, as available on
  http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/UK_POEM1.xls

  [Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992. ("UK model")]

It should be noted that "no PPE" in the German Model considers a lightly dressed operator, wearing a short sleeved T-Shirt, shorts and shoes. Such an unprotected operator should never handle plant protection products

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

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as this clothing is not in accordance with good occupational practice. Therefore, a coverall or alternatively, work trousers, a work jacket and sturdy footwear should be regarded as basic working clothing for operators handling plant protection products. This scenario is in line with the UK POEM, if "no PPE" is considered (i.e. an operator wearing typical (long sleeved) working clothing). Both models allow estimates for protected operators wearing additional PPE, if necessary.

A comparison of the corresponding exposure estimate with the proposed AOEL (in terms of percentage of the AOEL) is presented in Table 7.2.1-2. Detailed assumptions and considerations as well as exposure calculations are presented in chapter CP 7.2.1.1.

Table 7.2.1-2: Comparison of estimated systemic operator exposure to deltamethrin [mg/kg bw/day] with the proposed AOEL

Application type	Crop	PPE	Total systemic exposure deltamethrin [mg/kg bw/day]	% of AOEL [0.075 mg/kg bw/day]
Field crop sprayer	Low field crops	**Field uses, German model (70 kg operator)**		
		No PPE [1)]	0.00072	**9.6**
		With PPE [2)]	0.00062	**8.2**
		Field uses, UK POEM (60 kg operator)		
		No PPE [1)]	0.0123	**165**
		With PPE [3)]	0.0017	**23**

1) Short trousers and a short sleeved shirt
2) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear and protective gloves during mixing/loading
3) One layer of typical work wear (e.g. trousers and a long sleeved shirt) as well as sturdy foot wear and protective gloves during mixing/loading and application.

Both models estimates predict that the formulation Decis EW15 can be used safely with field crop sprayers when gloves are worn during mixing loading and application. As a good practice when handling pesticides, wearing gloves during spraying would reduce the exposure.

The detailed calculations are presented in the Tables 7.2.1.1-1 & 2.

Summary of estimates

The **German model** estimates predict that Decis EW15 can be used safely on wheat, sugar beet and cauliflower with field crop sprayers and even if protective gloves are not worn during mixing loading.

The **UK POEM** estimates predict that Decis EW15 can be used safely on wheat, sugar beet and cauliflower with field crop sprayers if protective gloves are not worn during mixing loading and application.

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CP 7.2.1.1 Estimation of operator exposure

a) Estimation according to the German model

Exposure is calculated for field application technique with the maximum dose rate. Lower dose rates will be covered by this calculation and separate evaluations are not made. The following assumptions are made:

Field crop sprayer

Treated area:	20 ha/day
Max. dose rate:	0.5 L/ha Decis EW15 corresponding to 0.0075 kg/ha deltamethrin

Dermal absorption: 14% for diluted product and 2% for concentrate product.

Operator body weight: 70 kg

Taking into account these parameters the exposure is estimated as follows:

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Table 7.2.1.1-1 Calculation of operator exposure to deltamethrin using field crop sprayers (German model, without and with PPE)

Operator exposure estimate: German model. Tractor-mounted/trailed boom sprayer: hydraulic nozzles

Product:	Decis EW15				
Active substance:	Deltamethrin		a.s. concentration:	15	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha]:	0.5			Hands:	Gloves
Work rate [ha/day]:	20		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	None
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	2.0	(concentrate)		Body:	None
	14.0	(dilution)			

Calculation of route exposure:

Route	Specific exposure [mg/kg a.s.]	a.s. handled [kg/day]	Estimated exposure [mg/kg bw/day] No PPE	Reduction factor	with PPE	
I_M =	0.0006	0.15	0.000001	1.0	0.000001	I = Inhalation
$D_{M(H)}$ =	2.4	0.15	0.0051	0.01	0.000054	D = Dermal
I_A =	0.001	0.15	0.000002	1.0	0.000002	M = Mix/Loading
$D_{A(C)}$ =	0.06	0.15	0.0001	1.0	0.000129	A = Application
$D_{A(H)}$ =	0.38	0.15	0.0008	1.0	0.000814	H = Hands
$D_{A(B)}$ =	1.6	0.15	0.0034	1.0	0.003429	C = Head
						B = Body

Absorbed dose:

Route		Absorption [%]	No PPE: Estimated route exposure [mg/kg bw/day]	No PPE: Systemic exposure [mg/kg bw/day]	With PPE: Estimated route exposure [mg/kg bw/day]	With PPE: Systemic exposure [mg/kg bw/day]
Dermal:	Mix/Loading	2.0	0.005143	0.000103	0.000051	0.000001
	Application	14.0	0.004371	0.000612	0.004371	0.000612
Inhalation:	Mix/Loading	100	0.000001	0.000001	0.000001	0.000001
	Application	100	0.000002	0.000002	0.000002	0.000002
		Total =		**0.000718**		**0.000616**

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b) Estimation according to the UK-POEM

For comparison with the above German model estimates, the UK POEM is also used to estimate the exposure. Using the UK-POEM, the highest exposure for each application type is calculated if the maximum dose rates and the minimum spray volumes are used. Lower dose rates and higher spray volume will be covered by this calculation and separate evaluations are not made.

Taking into account the more realistic parameters, the following assumptions are made:

Treated area: 50 ha/6 hours per day
Volume applied: 100 L/ha as a worst case
Container size: 0.25L as a worst case
Max. dose rate: 0.0075 kg as/ha deltamethrin

Exposure estimates based on UK-POEM and proportions of the systemic AOEL accounted for by the estimates are summarised in the following table. Detailed calculations are presented in the table 7.2.1.1-2.

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Table 7.2.1.1-2 Calculation of operator exposure to deltamethrin using field crop sprayers (UKPOEM, without and with PPE)

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Decis EW 15**	Active substance	**Deltamethrin**
Formulation type	organic solvent-based	a.s. concentration	**15** mg/ml
Dermal absorption from product	**2** %	Dermal absorption from spray	**14** %
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**0.5** l/ha	Work rate/day	**50** ha
Application volume	**100** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	0.25	litres
Hand contamination/operation	0.01	ml
Application dose	0.5	litres product/ha
Work rate	50	ha/day
Number of operations	100	/day
Hand contamination	1	ml/day
Protective clothing	None	Gloves
Transmission to skin	100 %	10 %
Dermal exposure to formulation	1.000 ml/day	0.1 ml/day

DERMAL EXPOSURE DURING SPRAY APPLICATION

Application technique	Tractor-mounted/trailed boom sprayer/hydraulic nozzles					
Application volume	100 spray/ha					
Volume of surface contamination	10 ml/h					
Distribution	Hands	Trunk	Legs			
	65 %	10 %	25 %			
Clothing	None	Permeable	Permeable	Gloves	Permeable	Permeable
Penetration	100 %	5 %	15 %	10	5	15 %
Dermal exposure	6.5	0.05	0.375 ml/h	0.65	0.05	0.375 ml/h
Duration of exposure	6 h			6 h		
Total dermal exposure to spray	41.550 ml/day			6.450 ml/day		

ABSORBED DERMAL DOSE

	Mix/load	Application	Mix/load	Application
Dermal exposure	1.000	41.550 ml/day	0.100	6.450 ml/day
Concen. of a.s. product or spray	15	0.075 mg/ml	15	0.075 mg/ml
Dermal exposure to a.s.	15.000	3.116 mg/day	1.500	0.484 mg/day
Percent absorbed	2	14 %	2	14 %
Absorbed dose	0.300	0.436 mg/day	0.030	0.068 mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h
Duration of exposure	6	h
Concentration of a.s. in spray	0.075	mg/ml
Inhalation exposure to a.s.	0.0045	mg/day
Percent absorbed	100	%
Absorbed dose	0.0045	mg/day

PREDICTED EXPOSURE	No PPE	With PPE
Total absorbed dose	0.7408 mg/day	0.1022 mg/day
Operator body weight	60 kg	60 kg
Operator exposure	0.0123 mg/kg bw/day	0.0017 mg/kg bw/day

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CP 7.2.1.2 Measurement of operator exposure

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

CP 7.2.2 Bystander and resident exposure

There is no official model available to calculate the exposure of bystanders. Some proposals were given by the EUROPOEM Bystander Working Group but the report is still a draft and not officially published because slight changes may still be accepted following comments provided by the members of the working group. Therefore, as long as there is no official guidance on how to calculate bystander exposure an approach is presented in this document that considers both dermal exposure - derived from available drift data - and inhalation exposure – derived from the operator exposure models simulating a bystander who is exposed in a similar way as an unprotected operator spraying in the field.
Additionally, exposure to residents is assessed as well.

This approach is following a guidance of the German Federal Institute for Risk Assessment (BfR)[3] and is in line with what has been published by US EPA and CRD recently. All technical details with regard to figures and assumptions are provided in this guidance.

Exposure estimates and proportions of the systemic AOELs accounted for by the estimates are summarised in the following table. Detailed information and calculations are presented in chapter CP 7.2.2.1.

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

Substance	Person	Total systemic exposure (mg/kg bw/day)*	AOEL mg/kg bw/day	% of AOEL
Exposure of bystanders to field crop sprayer drift				
Deltamethrin	Bystander: adult	0.000005	**0.075**	**0.07**
	Bystander child	0.000004		**0.05**
Exposure of residents close to field crop sprayer drift				
Deltamethrin	Resident: adult	0.000000613	**0.075**	**0.008**
	Resident child	0.00000123		**0.016**

* Assumes a 60 kg bodyweight for an adult and 16.15 kg for a child
Deltamethrin dermal penetration of 14% for the diluted spray and 100 % absorption *via* the inhalation route.

Assessment

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

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The result of the calculations reveals that the situation with respect to bystander and resident exposure is favourable for the intended uses of Decis EW15. Bystanders and residents will not be exposed to critical levels of deltamethrin during spray application of Decis EW15 in the fields.

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.

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).
According to Martin *et al.* are presented hereafter the drift values used to run calculations for both bystanders and residents.

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Table 7.2.2.1-1: Percent drift values for different crops ([redacted] 2001, current version 27.03.2006)

Crop, Distance 10 m	Percent Drift (1 application) (90th percentile values)	Percent Drift (2 application) (82th percentile values)
Field crops	**0.29**	**0.24**
Fruit crops, early	11.81	9.61
Fruit crops, late	3.60	3.11
Grapes	1.23	1.07
Hops	5.77	4.18
Vegetables, ornamentals & small fruit: < 50 cm > 50 cm	 **0.29** 1.23	 **0.24** 1.07

For the current risk assessment the worst case with drifts for application on field crops are considered. A drift value of **0.29%** was used for bystanders (present for just one application) and **0.24%** for residents (possibly submitted to 2 applications).

Exposure calculations are performed according to the following equations:

a) **Bystander exposure**

<u>Deltamethrin</u>

Dermal exposure due to spray drift following low crop application using field crop sprayer.

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

Where:

SDE_B	= Systemic Exposure of Bystanders via the Dermal Route (mg/kg bw/day)	
AR	= Application Rate (mg/m²)	0.0075 kg a.s./ha = 0.75 mg/m².
D	= Drift (%)	0.29%.
BSA	= Exposed Body Surface Area (m²)	1 m² (adult), 0.21 m² (child).
DA	= Dermal Absorption (%)	14%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

Inhalation exposure due to spray drift.

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

Where:

SIE_B	= Systemic Exposure of Bystanders via the Inhalation Route (mg/kg bw/day).	
I_A^*	= Specific Inhalation Exposure (mg/kg a.s. handled per day) = 0.001 mg/kg a.s. (field crop sprayer).	
AR	= Application Rate (kg a.s./ha)	0.0075 kg a.s./ha.
A	= Area Treated (ha/day)	50 ha (tractor).
T	= Time [Duration] (min)	5 min.
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

Total Systemic Exposure of Bystanders.

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

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

Table 7.2.2.1-2: Calculations for bystander exposure to deltamethrin

Adults	**Children**
Bystander of Field Crop, tractor mounted/trailed	
Dermal exposure: SDE_B = (AR x D x BSA x DA) / BW (0.75 x 0.29% x 1 x 14 %) / 60 Absorbed dose: 0.000005075 mg/kg bw/day	Dermal exposure: SDE_B = (AR x D x BSA x DA) / BW (0.75 x 0.29% x 0.21 x 14 %) / 16.15 Absorbed dose: 0.000003959 mg/kg bw/day
Inhalation exposure: SIE_B = (I_A* x AR x A x T x IA) / BW (0.001 x 0.0075 x 20 x 5/360 x 100%) / 60 Absorbed dose: 0.0000000347 mg/kg bw/day	Inhalation exposure: SIE_B = (I_A* x AR x A x T x IA) / BW (0.001/1.74 x 0.0075 x 20 x 5/360 x 100%) / 16.15 Absorbed dose: 0.0000000741 mg/kg bw/day
Total systemic exposure: **$SE_B = SDE_B + SIE_B$**	**Total systemic exposure:** **$SE_B = SDE_B + SIE_B$**
Total absorbed dose: 0.00000511 mg/kg bw/day	**Total absorbed dose: 0.00000403 mg/kg bw/day**
% of AOEL: 0.0681	**% of AOEL: 0.0537**

* based on children's inhalation rate of 1.0 m^3/h for moderate activity (US EPA 2001, therefore ratio between children's and adults' inhalation rate: 1.0/1.74)

b) Residential exposure

Deltamethrin

Dermal exposure *via* deposits caused by spray drift

SDE_R = (AR x D x TTR x TC x H x DA) / BW

Where: SDE_R = Systemic Exposure of Residents via the Dermal Route (mg/kg bw/day).
AR = Application Rate (mg/cm^2) x 2 (for no. of applications >2).
Deltamethrin: 0.0075 kg a.s./ha x 2 = 0.015 mg/cm^2.

D	= Drift (%)	0.24%.
TTR	= Turf Transferable Residues (%)	5%.
TC	= Transfer Coefficient (cm^2/hour)	7300 cm^2/h (adult), 2600 cm^2/h (child).
H	= Exposure Duration (hours)	2 h.
DA	= Dermal Absorption (%)	14%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

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Inhalation exposure due to vapour drift.

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

Where:

SIE_R	= Systemic Exposure of Residents via the Inhalation Route (mg/kg bw/day).	
AC_V	= Airborne Concentration of Vapour (mg/m³): 0 mg/m³ (vapour pressure of deltamethrin = 1.24×10^{-8} Pa at 25°C = 4.2×10^{-11} Pa at 20°C and 25°C = non-volatile).	
IR	= Inhalation Rate (m³/day)	16.57 m³/day (adult), 8.31 m³/day (child).
IA	= Inhalation Absorption (%)	100%.
BW	= Body Weight (kg/person)	60 kg (adult), 16.15 kg (child).

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

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

Where:

SOE_H	= Systemic Oral Exposure via the Hand to Mouth Route (mg/kg bw/day).	
AR =	Application Rate (mg/cm²) x 2 (for no. of applications >2). Deltamethin: 0.0075 kg a.s./ha x 2 = 0.015 mg/cm²	
D	= Drift (%)	0.24%.
TTR	= Turf Transferable Residues (%)	5%.
SE	= Saliva Extraction Factor (%)	50%.
SA	= Surface Area of Hands (cm²)	20 cm².
Freq	= Frequency of Hand to Mouth (events/hour)	20 events/h.
H	= Exposure Duration (hours)	2 h.
OA	= Oral Absorption (%)	75%.
BW	= Body Weight (kg/person)	16.15 kg (child).

Children's object-to-mouth transfer

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

Where:

SOE_O	= Systemic Oral Exposure via the Object to Mouth Route (mg/kg bw/day).	
AR =	Application Rate (mg/cm²) x 2 (for no. of applications >2). Deltamethrin: 0.0075 kg a.s./ha x 2 = 0.015 mg/cm².	
D	= Drift (%)	0.24%.
DFR	= Dislodgeable Foliar Residues (%)	20%.
IgR	= Ingestion Rate for Mouthing of Grass/Day (cm²)	25 cm²/day.
OA	= Oral Absorption (%)	75%.
BW	= Body Weight (kg/person)	16.15 kg (child).

Total systemic exposure of residents is then estimated for

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

Where:

SE_R	= Systemic Exposure of Residents (mg/kg bw/day).
SDE_R	= Systemic Dermal Exposure of Residents (mg/kg bw/day).

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

Table 7.2.2.1-3: Calculations for resident exposure to deltamethrin

Adults	Children
Resident: Exposure after application with Field Crop, tractor mounted/trailed	
Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ $(0.00015 \times 0.24\% \times 5\% \times 7300 \times 2 \times 14\%) / 60$ Absorbed dose: 0.0000006132 mg/kg bw/d	Dermal exposure: $SDE_R = (AR \times D \times TTR \times TC \times H \times DA) / BW$ $(0.00015 \times 0.24\% \times 5\% \times 2600 \times 2 \times 14\%) / 16.15$ Absorbed dose: 0.0000008114 mg/kg bw/d
Inhalation exposure: $SIE_R = (AC_V \times IR \times IA) / 1000 \times BW$ $(0 \times 16.57 \times 100\%) / 60$ Absorbed dose: 0.0 mg/kg bw/d	Inhalation exposure: $SIE_R = (AC_V \times IR \times IA) / BW$ $(0 \times 8.31 \times 100\%) / 16.15$ Absorbed dose: 0.0 mg/kg bw/d
	Oral exposure (hand-to-mouth transfer): $SOE_H = (AR \times D \times TTR \times SE \times SA \times Freq \times H \times OA) / BW$ $(0.00015 \times 0.24\% \times 5\% \times 50\% \times 20 \times 20 \times 2 \times 75\%) / 16.15$ Absorbed dose 0.0000003344 mg/kg bw/d
	Oral exposure (object-to-mouth transfer): $SOE_O = (AR \times D \times DFR \times IgR \times OA) / BW$ $(0.00015 \times 0.24\% \times 20\% \times 25 \times 75\%) / 16.15$ Absorbed dose 0.0000000836 mg/kg bw/d
Total systemic exposure:	**Total systemic exposure:**
$SE_R = SDE_R + SIE_R$	**$SE_R = SDE_R + SIE_R + SOE_H + SOE_O$**
Total absorbed dose: 0.0000006613 mg/kg bw/d	**Total absorbed dose: 0.00000123 mg/kg bw/d**
% of AOEL: 0.0082	**% of AOEL: 0.0164**

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At the request of RMS (UK CRD), assessments of bystander exposure to vapour, spray drift & fallout (children's model) was conducted in accordance with the UK guidance:

The exposure of bystanders and residents (considered to be wearing light ordinary clothing) was calculated for the field crop spraying scenario. A summary table of the exposure estimates for bystanders and residents and proportions of the systemic AOEL's accounted for by the estimates are provided in Table 7.2.2.1-4. Detailed information and calculations are presented below.

Table 7.2.2.1-4: Predicted systemic exposure of bystanders and residents as a proportion of the AOEL – according to UK PSD and US-EPA recommendations

Compound	Systemic Exposure (mg/kg bw/day)	AOEL (mg/kg/day)	%AOEL
Deltamethrin		0.0075	
Bystander	0.000013		**0.17**
Residential			
Adult vapour exposure	0.0002533		**3.38**
Children's vapour exposure	0.0005533		7.38
Children's dermal exposure	0.000007		0.10
Children's Hand-to-Mouth exposure	0.000002		0.03
Children's object-to -mouth exposure	0.000001		0.007
Children's Total Exposure	0.000563		**7.51**

Conclusion
It is concluded that bystanders and residents will not be exposed to critical levels of deltamethrin during spray application of the formulated product with field crop sprayers.

Bystanders are persons:

- who are located within or directly adjacent to the area where pesticide application or treatment is in process or has taken place,
- whose presence is quite incidental and unrelated to work involving pesticides but whose position may put them at risk of exposure,
- who take no action to avoid or control exposure and
- that do not wear protective clothing and perhaps only little ordinary clothing.

Residents are persons:

- who live, work or attend school or any other institution adjacent to an area that has been treated with a plant protection product,
- whose presence is quite incidental and unrelated to work involving plant protection products but whose position may put them at risk of potential exposure,
- who take no action to avoid or control exposure,
- for whom it is assumed that no protective clothing is worn and perhaps little ordinary clothing and
- who might be in the location for 24 hours a day.

The exposure to young children playing in an adjacent lawn/playing field is taken as the expected worst case example for residential exposure.

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Assessment of exposure is performed for the following three scenarios:

- Exposure from spray drift at the time of application
- Exposure from inhalation of pesticide which volatilises from the crop or soil surface after the application has been made
- Exposure of a small child playing on a lawn including
  - Children's dermal exposure.
  - Children's hand-to-mouth exposure.
  - Children's object-to-mouth exposure.

1. Exposure from spray drift at the time of application

Bystander exposure assessment for applications using tractor mounted/trailed field crop sprayers:

An estimate of bystander exposure during application to cereals is presented by this evaluation, based on a study conducted by Lloyd and Bell[4] (1983) which reports direct measurements of simulated bystander exposure from applications with field crop sprayers. The average potential dermal exposure for a bystander, positioned 8 metres downwind from the sprayer and the average amount of spray passing through the breathing zone were 0.1 and 0.006 mL spray/person, respectively.

Using these data total systemic exposure can be estimated as follows:

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[4] Lloyd G.A. & Bell G.J., Hydraulic nozzles: comparative spray drift study, MAFF 1983.

a) Deltamethrin:

BYSTANDER EXPOSURE	Active Substance: Deltamethrin
SE = (PDE x SC x %abs + PIE x SC x 100%)/BW	
PDE (potential dermal exposure) =	0.1 mL/spray
PIE (potential inhalation exposure) =	0.006 mL/spray
SC (concentration of active in spray) =	0.0375 g/L
%abs (percentage dermal absorption) =	14 %
BW (body weight) =	60 kg
SE (systemic exposure) =	**0.000013** mg/kg bw/day

Assuming an application of 0.0075 kg deltamethrin in 200 litres of water, no protection from clothing and 100% inhalation, retention and absorption of PIE, the estimated bystander exposure is 0.000013 mg/kg bw/day. This is equivalent to 0.17% of the AOEL (0.0075 mg/kg bw/day).

2. Exposure from inhalation of a pesticide which volatilises from the crop or soil surface after the application has been made

Exposure to vapour post application is not likely to be significant given the low vapour pressures of the active substances (vapour pressure $< 1 \times 10^{-5}$ hPa for deltamethrin corresponding to non-volatile substances) and is not likely to present a concern.

This conclusion is supported by studies conducted in Germany, where lindane (vapour pressure = 5.6×10^{-3} Pa at 25 °C), parathion (1.3×10^{-3} Pa at 25 °C) and pirimicarb (4×10^{-3} Pa at 25 °C) were applied in field trials to provide measurements of residues in air adjacent to treated crops (Pjz`äyJ a/ ä: 2003). Each active substance was applied at the same rate and in the same water volume. Applications were achieved using field crop sprayers fitted with 12 metre booms. Monitoring of residues in air over 21 hours, 10 metres downwind of treated barley plots, provided 21 hour time weighted air concentrations of 0.29 and 0.58 µg/m^3 (lindane), 0.07 and 0.12 µg/m^3 (parathion) and <0.02 and 0.04µg/m^3 (pirimicarb). The meteorological conditions during the trial included wind speeds of up to 23.4 km/h and temperatures up to 28°C. The study authors report wind speeds in the second trial (Trial B) were significantly higher (2X to 3X) than in the first trial (Trial A) and this is expected to have contributed to the variability of these results. It is noted that the higher 21 hour TWA value for each active substance was determined from Trial B.

In view of the small size of this data set (2 trials for each of the three active substances) a precautionary approach is to use a value of 1 µg/m^3 to predict bystander exposure from vapour after application of the spray. Based on these measurements and assuming:

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- a body weight of 60 kg for an adult (based on the 50th percentile value for females aged 16 to 24 years in 1995-7 Health Surveys for England),

- a body weight of 15 kg for a small child (based on the average value for male and female children aged 2 and 3 years in 1995-7 Health Surveys for England),

- a respired volume of 15.2 m^3/day (based on mean values for the long term inhalation rate for adult males aged 19 to >65 years published in the United States Environmental Protection Agency (US EPA) Exposure Factors Handbook) and

- a respired volume of 8.3 m^3/day (based on mean values for the long term inhalation rate for children aged 3 to 5 years published in the US EPA Exposure Factors Handbook).

The potential exposure to vapour is estimated to be 0.000253 mg/kg bw/day for an adult and 0.000553 mg/kg bw/day for a child. These exposures are equivalent to 3.38% and 7.38% of the systemic AOEL of deltamethrin, for adult and child, respectively.

3. Exposure of a small child playing on a lawn

Drift fallout from applications may be deposited in gardens adjacent to treated areas, and individuals in such locations may be exposed through contact with such deposits. It is possible to estimate such exposures using spray drift fallout values and the approach used by the United States Environmental Protection Agency to estimate residential exposure from contact with treated lawns. The following exposure assessment considers the scenario of a small child playing on a lawn.

a. Children's dermal exposure

Allowing for an untreated headland of 1 m, the level of fallout from spray drift at the boundary with a neighbouring area is predicted to be equivalent to 2.77% of the applied dose[5]. This level of fallout deposit is predicted to decline to 0.57% at a distance of 5 m from the boundary. By integration, the average level of fallout over the whole area from the boundary to a point 3 m outside is estimated to be about 1% of the applied dose (90th percentile).

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[5] Rautmann, D.; Streloke, M.; Winkler, R. (2001): New basic drift values in the authorisation procedure for plant protection products. In: Forster, R.; Streloke, M.; Workdshop on Risk Assessment and Risk Mitigation Measures in the context of the Authorization of Plant Protection Products (WORMM). Mitt. Biol. Bundesanst. Land-Forstwirtsch. Berlin-Dahlem, Heft 381.

Active Substance: Deltamethrin

CHILDRENS DERMAL EXPOSURE

Systemic exposure via the dermal route were calculated using the cited drift fallout values and the following equation:

SE(d) = (AR X DF X TTR X TC X H X DA)/BW

AR (Application rate)	=	0.015 kg ai/ha
		0.15 µg ai/cm^2
DF (drift fallout value)	=	1 %
TTR (Turf transferable residue)	=	5 %
TC (Transfer Coefficient)	=	5200 cm^2/h
H (Duration of exposure)	=	2 hrs/day
DA (dermal absorption)	=	14 %
BW (Body weight)	=	15 kg
SE(d) (Systemic exposure via the dermal route)	=	**0.0073 µg/kg bw/day**

CHILDRENS HAND TO MOUTH EXPOSURE

Hand-to-mouth exposures were calculated using turf transferable residue levels using the following equation:

SE(h) = (AR X DF X TTR X (SE/100) X SA X freq X H)/BW

AR (Application rate)	=	0.015 kg ai/ha
		0.15 µg ai/cm^2
DF (drift fallout value)	=	1 %
TTR (Turf transferable residue)	=	5 %
SE (Saliva extraction factor)	=	50 %
SA (Surface area of the hands in mouth contact)	=	20 cm^2/h
Freq (Frequency of events)	=	20 events/hour
H (Duration of exposure)	=	2 hrs/day
BW (Body weight)	=	15 kg
SE(h) (Systemic exposure via the hand to mouth route)	=	**0.0020 µg/kg bw/day**

CHILDRENS OBJECT TO MOUTH

Object to mouth exposures were calculated using turf transferable residue levels using the following equation:

SE(o) = (AR X DF X TTR X IgR)/BW

AR (Application rate)	=	0.015 kg ai/ha
		0.15 µg ai/cm^2
DF (drift fallout value)	=	1 %
TTR (Turf transferable residue)	=	20 %
IgR (ingestion rate for mouthing of 25 cm^2 grass/day)	=	25 cm^2
BW (Body weight)	=	15 kg
SE(o) (systemic exposure via mouthing activity)	=	**0.0005 µg/kg bw/day**

TOTAL EXPOSURE	=	**0.0098 µg/kg bw/day**
(sum of dermal, hand-to-mouth and object-to-mouth)	=	**0.00001 mg/kg bw/day**

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Children's total exposure:

On the basis of the above estimates, the total systemic exposure to deltamethrin for a child playing on a lawn contaminated by spray drift during the application of the formulated product represents 7.51% of the systemic AOEL.

CP 7.2.2.2 Measurement of bystander and resident exposure

Since the risk assessment carried out indicated that the health-based limit values (AOEL) for the active substances deltamethrin will not be exceeded under practical conditions of use, a study to provide a measure of bystander and resident exposure to the formulated product Decis EW15 under field conditions was not necessary and therefore was not carried out.

CP 7.2.3 Worker exposure

Summary
The formulation Decis EW15 is an insecticide that is applied to various crops. In fields, work activities are tasks like harvesting or scouting which are done by farmers usually throughout the growing season. Re-entry exposure is therefore evaluated and compared with the AOEL of deltamethrin.

CP 7.2.3.1 Estimation of worker exposure

The greatest potential for worker exposure following re-entry will be contamination *via* the skin. Risk of inhalation exposure during re-entry is generally confined to a brief period after application, while the product is drying, which will be rapid under outdoor conditions and would generally be avoided according to good agricultural practices. Exposure to workers entering treated areas are predicted using an exposure model proposed by Hoernicke *et al*,[6] (1998) and Krebs *et al*. [7](2001). The following assumptions are made:

- Re-entry exposure is predominantly *via* the dermal route (contact with the foliage)
- Residues on the foliage depend on:
    - i) application rate
    - ii) extent of remaining residues from previous applications
    - iii) the Leaf Area Index (LAI) [total size of foliage compared to surface area]
- Transfer of residues from foliage to the clothes or skin of workers depends mainly on the intensity of contact with the foliage.
- Activities with a similar pattern can be grouped and a generic Transfer Coefficient (TC) applied
- Dislodgeable Foliar Residue (DFR) is calculated using a default value of 3 µg as/cm² per kg as/ha for one application. This figure is based Brouwer *et al*.[8] (2001). For multiple application, the RMS (CRD) considers that no decline occurs.

[6] Hoernicke, E., Nolting, H.G.; Westphal, D.: Label instructions for the protection of workers re-entering crop growing areas after application of plant protection products; Nachrichtenbl. Deut. Pflanzenschutzd. 50 (10), (1998), 267 - 269 (document no. M-107544-01-1)

[7] Krebs, B., Maasfeld, W., Schrader, J., Wolf, R., Hoernicke, E., Nolting, H-G., Backhaus, G.F. and Westphal, D. (2001) Uniform principles for safeguarding the health of workers re-entering crop growing areas after application of plant-protection products, Worker exposure to agrochemicals, Ed. R.C. Honeycutt and E.W. Day, chapter 8, 107- 117, CRC Press (2001), (document no.: M-209388-01-1)

[8] Brouwer ,D.H.; de Haan, M.; van Hemmen, J.J.: (2001); Modeling re-entry exposure estimates: techniques and application rates; Worker exposure to agrochemicals, Ed. R.C. Honeycutt and E.W. Day, chapter 9, 119- 138, CRC Press (2001), (document no.: M-128767-01-1)

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- Workers re-enter the treated culture shortly after the spray has dried on plant surfaces, nevertheless it is now recommended to use the higher dermal absorption values amongst neat and diluted values.

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

D = DFR x TC x WR x AR x P.
Where:

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

Maximum work rates considered are 2 hours for scouting cereals and 8 hours for hand harvesting vegetables.

DFR values:

In a first approach, an estimated worst case for DFR of 3 µg as/cm² per kg as/ha was considered (per application). According to RMS (CRD) request, two applications were considered in this risk assessment resulting in an estimated worst case DFR of 6 µg as/cm² per kg as/ha.

In a third approach (refined one), the notifier used available data from residue trials on vegetables which indicate mean DT_{50} values between 2.7 days (lettuce) and 5.1 days (tomato). The summaries of these trials and the calculations are provided in documents M-192201-01-1 and M-292624-01-1. The DT_{50} value of 5.1 days was used in the following calculations for a conservative estimate.

Report: **KCP 7.2.3.1/01, [redacted]; [redacted], 1999**
Title: Estimation of half-life of residues on leafy crops Deltamethrin
Document No: M-192201-01-1
Guidelines:
GLP No

Based on 39 supervised residue trials in lettuce (28) and spinach (11) the dissipation half-life of deltamethrin on leafy crops was calculated via 1st order kinetics. The individual half-lives of 2.7 days in lettuce and 2.9 days in spinach indicated a very high similarity in the dissipation behaviour of deltamethrin in both vegetables. Therefore, the dissipation half-life for the category "leafy crops" can be estimated to be about 2.8 days. It appears reasonable to assume, that this dissipation half-life is also applicable for young growing cereal shoots. The calculated initial residue levels were 0.17 mg/kg for lettuce and 0.54 mg/kg for spinach respectively.

Report: **KCP 7.2.3.1/02[redacted], 2007**
Title: Calculation of the dissipation half-life of residues of deltamethrin on tomato and cucumber
Document No: M-292624-01-1
Guidelines:
GLP No

Deltamethrin residue data from supervised field trials on tomatoes and cucumbers were taken into consideration to calculate the dissipation half-life of deltamethrin residues on these crops. The available residue data are from field and greenhouse trials, with one to four applications of deltamethrin at intervals of one to two weeks. The

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total application rates range from 38 to 91 g ha-1 in cucumber and from 18 to 90 g a.s. ha-1 in tomato. The rate of the last application, which is most relevant in this context, ranges from 13 to 38 g ha-1 in cucumber and from 10 to 30 g a.s. ha-1 in tomato. Samples were taken between the day of the last treatment and up to eight days after the last treatment (DALT 0 to 3 in cucumber, DALT 0 to 8 in tomato). Only residues data for fruit samples were considered here. Only those trials were included in the half-life calculations that provide residue data above the limit of quantification (0.01 or 0.02 mg kg-1) for DALT 0 and at least one other sampling date. This left nine data sets for cucumber and 26 data sets for tomato. All data reported as "< LOQ" were set to the LOQ of 0.01 or 0.02 mg kg-1 for the calculations. Because of the different use patterns in the residue trials, the initial residue (at DALT 0) differ significantly, ranging from 0.01 to 0.1 mg kg-1. Therefore, in each data set all residue values were normalised to the residue at DALT 0 (set to 100 %).

The mean residue for each sampling date were calculated (separately for cucumber and tomato), which gave dissipation curves over three days (cucumber) or eight days (tomato) of deltamethrin residues on these crops. The calculated DT50 values of deltamethrin residues are:

- 4.2 days for cucumber
- 5.1 days for tomato

The results for cucumber and tomato are in good agreement and show a rapid decline

<u>Transfer Coefficient values:</u>

Hoernicke *et al* (1998) propose that a transfer coefficient (TC) of 30,000 (cm²/person/h) be used for the transfer of residues from foliage to the clothes or skin of a worker in initial estimates of exposure. This value is considered to represent a worst case for worker exposure, being derived from tasks requiring intensive contact with foliage and representing an unprotected worker.

As no specific TCs are available in Europe to assess re-entry activities performed in cereals a conservative value of 2500 cm²/person/h has been used in this risk assessment. This value was obtained from the Europoem II data for vegetables which are believed to be the most reasonable surrogate from the available data for scouting activities in cereal crops.
Nevertheless, a value of 5000 cm²/person/h was requested by RMS (CRD).to calculate the worker exposure during scouting.

Predicted exposures are compared with the AOEL of deltamethrin. Systemic exposure values assume the a dermal absorption value of 14%. A body weight of 60 kg is assumed for the re-entry worker. Exposure estimates based on proportions of the systemic AOEL accounted for by the estimates are summarised in the following table. Detailed calculations are presented on the following pages.

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Table 7.2.3.1-1: Summary of predicted worker exposures arising from the use of Decis EW 15 and comparison with the AOEL

Crop	Systemic exposure* (mg/kg bw/day)	AOEL (mg/kg bw/day)	% of AOEL
Cereals DFR: 3 µg/cm²	**0.000263**	0.0075	**3.5**
Cereals DFR: 6µg/cm²	0.00105		**14**
Vegetables DFR: 3µg/cm²	0.001050		**14**
Vegetables DFR: 6µg/cm²	0.0021		**28**
Vegetables DFR: 0.05 µg/cm²	0.000018		**0.24**

*14% dermal absorption, 60 kg worker

Assessment

The exposure of workers entering treated areas is well within acceptable levels following application of Decis EW15.

Detailed calculations of worker exposure during re-entry:

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Re-entry exposure to deltamethrin in cereals:

a) Considering a DFR of 3 µg as/cm² and a TC of 2500 cm²/pers/h

Product Name Decis EW15
Active substance Deltamethrin

D	=	DFR	x	TC	x	WR	X	AR	x	P	
		µg/cm²		cm²/pers/h		hrs/day		kg/ha			
		3	x	2500	x	2	x	0.0075	x	1	

= 112.5 µg a.s./pers/day
= 0.1125 mg a.s./pers/day
= 0.00188 mg a.s./kg bw/day (60 kg person)

and under consideration of 14.00% dermal absorption (for a dried foliar residue)

S = 0.00188 x 0.1400
= 0.00026 mg a.s./kg bw/day

b) Considering a DFR of 6 µg as/cm² and a TC of 5000 cm²/pers/h

Product Name Deltamethrin EW 15
Active substance Deltamethrin

D	=	DFR	x	TC	x	WR	X	AR	x	P	
		µg/cm²		cm²/pers/h		hrs/day		kg/ha			
		6	x	5000	x	2	x	0.0075	x	1	

= 450 µg a.s./pers/day
= 0.45 mg a.s./pers/day
= 0.0075 mg a.s./kg bw/day (60 kg person)

and under consideration of 14.00% dermal absorption (for a dried foliar residue)

S = 0.0075 x 0.1400
= 0.00105 mg a.s./kg bw/day

Re-entry exposure to deltamethrin in vegetables:

a) Considering a DFR of 3 µg as/cm²

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Product Name Decis EW15
Active substance Deltamethrin

D	=	DFR	x	TC	x	WR	X	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
		3	x	2500	x	8	x	0.0075	x	1

= 450 µg a.s./pers/day
= 0.45 mg a.s./pers/day
= 0.0075 mg a.s./kg bw/day (60 kg person)

and under consideration of 14.00% dermal absorption (for a dried foliar residue)

S = 0.0075 x 0.1400
= 0.00105 mg a.s./kg bw/day

b) Considering a DFR of 6 µg as/cm²

Product Name Deltamethrin EW 15
Active substance Deltamethrin

D	=	DFR	x	TC	x	WR	X	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
		6	x	2500	x	8	x	0.0075	x	1

= 900 µg a.s./pers/day
= 0.9 mg a.s./pers/day
= 0.015 mg a.s./kg bw/day (60 kg person)

and under consideration of 14.00% dermal absorption (for a dried foliar residue)

S = 0.015 x 0.1400
= 0.0021 mg a.s./kg bw/day

c) Considering the DT_{50} value of 5.1 days, the DFR value following repeated application may be calculated using the following formula:

$$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$$

Where:

DFR_0	= Initial DFR (default of 3 µg/cm²).
AR^1 to AR^n	= Application rate from the first to the n^{th} application.
d^1 to d^n	= Number of DT_{50} periods after 1^{st} to n^{th} application.

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No. of DT_{50} periods: $d^1 = (Int\ 1 + Int\ 2 + PHI)/DT_{50} = (14 + 0)/5.1 = 2.75.$
$d^2 = (Int\ 2 + PHI)/DT_{50} = 0/5.1 = 0$
$d^3 = PHI/DT_{50} = 0/5.1 = 0.$

$DFR_{n\ appl.} = ((DFR_0 \times AR^1) \times 0.5^{d1}) + ((DFR_0 \times AR^2) \times 0.5^{d2}) + \ldots + ((DFR_0 \times AR^n) \times 0.5^{dn})$
$= ((3 \times 0.0075) \times 0.5^{2.75}) + ((3 \times 0.00075) \times 0.5^{0}) + ((3 \times 0.0075) \times 0.5^{2})$
$= 0.048356\ \mu g\ as/cm^2$

		DFR	x	TC	x	WR	x	AR	x	P
		µg/cm²		cm²/pers/h		hrs/day		kg/ha		
D	=	0.05	x	2500	x	8	x	0.0075	x	1
D	=	7.5 µg a.s./pers/day								
	=	0.0075 mg a.s./pers/day								
	=	0.000125 mg/kg bw/day								
using	14.00%	dermal absorption (highest value)								
S	=	0.000125	x	0.1400						
	=	0.000018 mg/kg bw/day								

CP 7.2.3.2 Measurement of worker exposure

Not relevant.

CP 7.3 Dermal absorption

Comparative dermal absorption, in vitro using rat and human skin

Report: **KCP 7.3/01 [redacted], 2003.**
Title: [^{14}C]-Decis EW 15: *In vitro* dermal penetration study using rat skin.
Document N°: Report N°: BAC 363, BCS document N°: M-222160-01-1.
Guidelines: Section 7.3 of Annex III of the EU Directive 91/414/EEC (OECD guideline 417 and OECD Draft 428)
GLP Yes

Material and methods

Rat skin:

Species, strain: Rat, Sprague Dawley CD

Source: [redacted] (UK).

Sex: Male.

Anatomical site: Dorsal

Rat 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

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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. The full thickness skin sample was pinned out on a dermatome board (cork board with raised rubber cutting surface). A mini-dermatome was used to cut slices of skin from the dorsal region which contained epidermis and some dermis (thickness measured using a digital calliper to be approximately 300µm thick).

Test Material:

Non-radiolabelled: Batch: 97B0276B3.
Purity = 99.6%.

Radiolabelled: [benzyl-^{14}C]-deltamethrin
Batch: 10562A
Specific activity: 4.24 MBq/mg.
Radiopurity of the formulation: 98%.

Formulation: The formulation used in this experiment was the Decis EW 15 formulation that was prepared at two nominal concentrations of deltamethrin: 15 g a.s./L and 0.12 g a.s./L.

Test system: The Scott-Dick flow-through diffusion cell ([redacted] 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 flow-rate of 1.5 mL/hr allowed approximately 6 receptor chamber content changes per hour. The receptor fluid used was physiological phosphate buffered saline, supplemented with 1% Tween 80 (v/v), 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

Skin integrity: The integrity of the selected skin samples was estimated by measuring the penetration of triated water (^3H_2O) through each membrane, prior to application of [^{14}C]-Decis EW 15. An aliquot (250 µL, occluded) was applied to the surface of the skin membrane and the lower chamber perfused with distilled water at a flow-rate of approximately 1.5 mL/hr. The eluent was 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.

Ultima Gold (10 mL) was added to the receptor fluid samples and radioactivity measured by liquid scintillation counting. The absorption profile was constructed by plotting the amount of radioactivity absorbed per unit area skin (dpm/cm^2) against time (hr). The absorption rate of $^3H_20$ through the skin membrane was calculated from the gradient at steady-state (dpm/cm^2/hr). Steady-state absorption is regarded as the linear portion of the absorption profile. The permeability coefficient (Kp) for ^3H_2O (cm/hr) was men

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calculated by dividing the absorption rate by the applied concentration of radioactivity (dpm/ml).

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 Deltamethrin 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.

Group 1, data for Cells 1, 2, 3, 4, 6 and 7 were included. Cell 5 was excluded because the Kp value was much greater than 3.0 x 10^{-3} cm/hr and the total percentage absorption was much higher than for the other cells in the group.

Group 2, data for Cells 8, 9, 10, 12 and 13 were included, Cell 11 was excluded as it had burst. Cell 14 was excluded because the Kp value was much greater than 3.0 x 10^{-3} cm/hr and the total percentage absorption was higher than for the other cells in the group.

Treatment: The dose formulation 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, unoccluded). The actual amount of [^{14}C]-Decis EW15 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, at hourly intervals (high dose) or two hourly intervals (low dose) 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-Muller 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 (9 to 18 strips). 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: Radioactivity was measured by liquid scintillation counting (LSC), using either a LKB Rackbeta 1219 or a Tricarb 2300 TR liquid scintillation counter (Perkin Elmer Life Sciences). Quench correction was achieved *via* an automatic external standard ratio method. Samples were generally counted for a total of 4 minutes. The limit of detection was derived statistically from the background counts so that there was a 99% certainty that samples with a mean value greater than the limit of detection contained radioactivity from the [^{14}C]-Deltamethrin. The limit of detection throughout the study was approximately 6 dpm, which is equivalent to approximately 0.37 ng

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Deltamethrin in the high dose formulation and 0.02 ng in the low dose formulation.

Findings:
The solubility of [^{14}C]-Deltamethrin in the proposed receptor fluid, physiological phosphate buffered saline (10 mM), supplemented with 1% Tween 80, was demonstrated to be at least 4.56 µg/mL (range 4.56 to 4.77 µg/mL), after incubation for 24 hours at 32°C. The solubility of the test compound in this receptor fluid was considered to be adequate and not rate limiting to the absorption process. Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable.

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 93.3% to 104.2% of the applied dose. These study results are presented in the following table.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [14C]- Deltamethrin in an EW 15 formulation at the nominal rates of 15 g/L and 0.12 g/L to rat skin samples.
Results expressed in terms of percentage of applied radioactivity.

	High dose 15 g/L (n = 6)		Low dose 0,12 g/L, (n = 5)	
	Mean	SD	Mean	SD
Skin swabs (8h)	63.73	6.21	28.91	7.35
Surface Dose (tape-strips 1 & 2)	3.93	1.16	6.76	2.83
Donor chamber	3.19	0.44	1.51	0.30
Stratum corneum [a]	24.58	4.80	47.93	10.73
Total % non-absorbed	***95.43***	***2.93***	***85.11***	***3.66***
Skin [b]	5.79	3.40	6.28	3.27
Total % at dose site	***5.79***	***3.40***	***6.28***	***3.2.7***
Receptor fluid (0-24h)	0.64	0.27	3.69	2.12
Receptor fluid terminal	0.012	0.007	0.08	0.04
Receptor chamber	0.023	0.057	n.d.	n.a.
Total % directly absorbed [d]	***0.68***	***0.27***	***3.77***	***2.14***
Total % Potentially Absorbable [e]	***6,45***	***3.60***	***10.05***	***1.66***
TOTAL % RECOVERY	**101.9**	**1.15**	**95.16**	**4.22**

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[b]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[d]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[e]: total % directly absorbed + total % at dose site
SD: standard deviation
n.d.: not detected (below the limit of detection)
n.a. : not applicable
n: number of skin cells used for calculation

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Table 7.3-2: Mean distribution of radioactivity in the stratum corneum at 24 hours after dose application of [14C]- Deltamethrin in an EW 15 formulation at the nominal rates of 15 g/L and 0.12 g/L to rat skin samples.

Tape-strip N°s	High Dose Group (15 g/L) % of Applied dose								
	Cell N°							Mean	SD
	1	2	3	4	6	7			
1 – 2 [a]	2.733	5.06	3.219	5.663	3.39	3.508	3.93	1.16
3 – 5	6.279	13.4	6.607	19.01	6.523	5.751	9.60	5.43
6 – 8	8.519	6.504	13.5	3.422	8.414	10.36	8.45	3.41
9 – 11	3.628	2.729	0.836	0.993	4.5	9.858	3.76	3.32
12 - 14	4.299	n.s.	n.s.	n.s.	n.s.	4.843	1.52	n.a.
15 – 17	5.017	n.s.	n.s.	n.s.	n.s.	n.s.	0.84	n.a.
18 - 20	2.475	n.s.	n.s.	n.s.	n.s.	n.s.	0.41	n.a.
Tape-strip N°s	**Low Dose Group (0.12 g/L) % of Applied dose**								
	Cell N°							Mean	SD
		8	9	10	12	13			
1 – 2 [a]		5.901	5.773	11.63	4.217	6.267	6.76	2.83
3 – 5		49.07	8.606	26.43	4.657	10.09	19.77	18.37
6 – 8		2.783	55.35	16.24	6.885	3.61	16.97	22.11
9 – 11		0.724	0.517	1.001	3.749	13.26	3.85	5.42
12 - 14		n.s.	n.s.	n.s.	10.41	11.06	4.29	n.a.
15 – 17		n.s.	n.s.	n.s.	15.23	n.s.	3.05	n.a.

[a] surface dose.
SD = standard deviation, n.s. = no sample, n.a. = not applicable.

Conclusion:

The dermal penetration of [^{14}C]-deltamethrin through rat dermatomed skin from the EW 15 formulation was investigated at two concentrations corresponding to the neat product (15 g /L) and to a representative dilution (0.12 g/L), respectively.

The distribution of radioactivity in the stratum corneum is coherent with the *in vivo* rat dermal absorption study with the majority of the radioactivity remaining in the upper layers. The mean percentage of deltamethrin in the EW 15 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining in the application site)* over a period of 24 hours for the neat formulation was 6.5%.

The mean percentage of deltamethrin in the EW 15 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining in the application site)* over a period of 24 hours for the representative spray dilution was 10.1%.

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Report:	**KCP 7.3/02, [redacted], 2009**
Title:	Deltamethrin EW 015: Comparative *in vitro* dermal absorption study using human and rat skin.
Document No:	Report N°: SA 09101, BCS document N°: M-360317-01-1.
Guidelines:	O.E.C.D. guideline for the testing of chemicals, skin absorption: *in vitro* Method 428 (April 2004), O.E.C.D. Environmental health and safety publications series on testing and assessment N°28, Guidance document for the conduct of skin absorption studies (March 2004), European Commission guidance document on dermal absorption-Sanco/222/2000 rev. 7, (March 2004).
GLP	Yes

Material and methods

Rat skin:

Species, strain: Rat, Wistar Rj: WI (IOPS HAN).

Source: [redacted] (France).

Sex: Male.

Number: 14

Anatomical site: Dorsal

Rat Skin Preparation: Each animal was killed by cervical dislocation. After sacrifice the skin was clipped and removed for use in the study. The dorsal skin was dermatomed by use of a mini-dermatome to obtain samples of ca. 400 to 550 µm in thickness.

Human skin: Source: [redacted] France.
Number and sex: 15 donors, female.
Anatomical region: Abdomen.
Thickness: 310 to 595 µm.

Test Material:

Non-radiolabelled: Batch: 97B0276B3.
Purity = 99.6%.

Radiolabelled: [benzyl-^{14}C]-deltamethrin
Batch: KATH6320.
Specific activity: 4.24 MBq/mg.
Radiopurity of the formulation: >99%.

Formulation: The formulation used in this experiment was the Deltamethrin EW 015 formulation (specification number 102000013165) which was used at three nominal concentrations: 15 g a.s./L, 0.05 g a.s./L and 0.005 g a.s./L.

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

Skin integrity: Before dose application, the integrity of the skin samples was assessed by measuring the trans-epidermal water loss (TEWL) from the stratum corneum. An evaporimeter probe (Tewameter TM300 system, Courage & Khazaka) was

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	placed securely on the top of the donor chamber and the amount of water diffusing through the skin was measured. Human and rat skin with a TEWL of greater than 15 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.
Treatment:	The dose preparation was applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm² exposed skin. The dose preparations were assayed for radioactivity content (by LSC) by using dose checks (surrogate dose) taken before, during and after the dosing process.
Sampling:	The receptor fluid passing through the receptor chamber was collected in glass vials held in a fraction collector. The fraction collector was started after dose application. Samples were then collected hourly for the duration of the experiment (24 hours). At 8 hours post-application, the skin was swabbed with freshly prepared 1% v/v Tween 80 in PBS (phosphate buffer saline) using natural sponge swabs, in order to remove and retain the non-absorbed dose, until no radioactivity was detected with a Geiger-Müller monitor. At the end of the study (24 hours after application), the treated skin and the skin adjacent to the treatment site (surrounding swabs) were swabbed. Each skin sample was tape-stripped to remove the stratum corneum. This involved the application of Monaderm adhesive tape (Monaderm, Monaco) for 5 seconds before the tape was carefully removed against the direction of hair growth. This procedure was continued until a 'shiny' appearance of the epidermis was evident, which indicated that the stratum corneum had been removed. The tape-strips were collected into scintillation vials for analysis. The skin surrounding the application site (surrounding skin) was separated from the treated skin. Both surrounding skin and tape-stripped treated skin were retained for analysis.
Radioassay:	The amounts of radioactivity in the various samples were determined by liquid scintillation counting (LSC). Samples were counted for 10 minutes or for 2 sigma % in an appropriate scintillation cocktail using a Packard 1900 TR counter with on-line computing facilities. Quenching effects were determined using an external standard and spectral quench parameter (tSIE) method. An efficiency correlation curve was prepared for each scintillation cocktail that was 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:
Deltamethrin was demonstrated to be soluble in the receptor fluid up to a concentration of 111.9 µg/mL. During the study the maximum achieved concentration was 111.4 ng/mL. The achieved concentrations were at least 1000 times lower than the determined solubility concentration, therefore the solubility in the receptor fluid was deemed to be sufficient to reduce any risk of back diffusion.

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

Good recovery data were obtained, with mean total recoveries of radioactivity in the range of 94.75% to 108.05% of the applied dose. These study results are presented in the following table.

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Table 7.3-3: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- deltamethrin in an EW 15 formulation at the rates of 15 g/L, 0.05 g/L and 0.005 g/L to human and rat skin samples.
Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)											
Dose Levels	Neat formulation: High dose (SYP13440, 15 g/L)				Dilution: Intermediate dose (SYP13442, 0.05 g/L)				Dilution: Low dose (SYP13443, 0.005 g/L)			
Species	Human (n=4)		Rat (n=6)		Human (n=5)		Rat (n=8)		Human (n=6)		Rat (n=6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT												
Skin swabs (8h)	97.49	3.49	88.75	5.17	79.05	8.44	57.74	6.14	89.66	8.82	60.76	15.23
Surface Dose (tape-strips 1 & 2)	1.25	0.71	2.16	2.58	4.20	2.81	10.66	5.04	9.29	5.37	22.02	11.73
Donor chamber	1.83	1.05	1.84	1.17	3.08	1.0	0.83	0.95	< LOQ	n.c.	< LOQ	n.c.
Total % non-absorbed	***100.6***	***2.62***	***92.75***	***3.81***	***86.33***	***8.67***	***69.23***	***3.71***	***98.95***	***9.30***	***82.78***	***15.42***
SKIN COMPARTMENT												
Skin [a]	0.41	0.41	1.41	1.84	2.71	1.46	5.18	6.22	3.99	4.60	5.50	3.50
Stratum corneum [b]	0.58	0.59	2.90	2.51	4.32	2.05	24.02	7.43	2.94	2.86	18.77	12.95
Total % at dose site	***0.99***	***0.98***	***4.31***	***3.09***	***7.02***	***2.64***	***29.220***	***4.84***	***6.93***	***7.38***	***24.27***	***14.00***
RECEPTOR COMPARTMENT												
Total % directly absorbed [c]	***0.09***	***0.15***	***0.59***	***0.36***	***1.40***	***1.82***	***2.28***	***1.72***	***< LOQ***	***n.c.***	***1.00***	***1.60***
Total % Potentially Absorbable [d]	***1.08***	***1.04***	***4.90***	***2.93***	***8.42***	***3.04***	***31.48***	***4.38***	***6.93***	***7.38***	***25.27***	***12.95***
Total % recovery	**101.6**	**2.20**	**97.64**	**2.96**	**94.75**	**9.23**	**100.7**	**1.99**	**105.9**	**2.76**	**108.1**	**3.06**

[a]: sum of radioactivity found in skin after tape-stripping procedure and in surrounding skin.
[b]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.
[c]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.
[d]: total % directly absorbed + total % at dose site
SD: standard deviation n.d.: not detected (below the limit of detection) n.a. : not applicable
n: number of skin cells used for calculation
In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program

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Conclusion:
The dermal penetration of [^{14}C]-deltamethrin through human and rat dermatomed skin from the EW 15 formulation was investigated at three concentrations corresponding to the neat product (15 g /L) and to two representative dilutions (0.05 and 0.005 g/L), respectively.

Overall, the dermal penetration of [^{14}C]-deltamethrin from the deltamethrin EW 15 formulation was very low at all concentrations used. In addition, the absorption was lower in human skin compared to rat skin at all concentrations used.

The mean percentage of deltamethrin that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.5% and 2% for the human and rat skin, respectively, yielding a factor difference of 4 between the two species for the neat product.

The mean percentage of deltamethrin that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 4.1% and 7.5% for the human and rat skin respectively, yielding a factor difference of 1.8 between the two species for the intermediate dose formulation.

The mean percentage of deltamethrin that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 4% and 6.5% for the human and rat skin respectively, yielding a factor difference of 1.6 between the two species for the low dose formulation.

Overall conclusion:
Following the 25% deviation rule of the standard deviation given in the EFSA guidance on dermal absorption (2012), the notifier used a value of 14% for spray dilution and 2% for the neat formulation.

Upon request by the RMS UK the notifier Bayer CropScience has prepared the position paper M-533594-01-1 to confirm that the above mentioned dermal absorption study has been evaluated according to the latest EFSA (2012) guidance.

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

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