Bayer CropScience

Document Title

Amendment of Summary of the toxicological studies

Thiacloprid OD 240 (240 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

Date

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Bayer CropScience

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Version history

Date	Data points containing amendments or additions[1] and brief description	Document identifier and version number
2014-10-06	Original submission	M-497906-01-1
2014-10-06	Sanitized version of original submission	M-497906-01-2
2016-10-20	Update of document to include data and information to demonstrate negligible exposure	M-497906-02-1
2016-10-20	Sanitized version of updated document to include data and information to demonstrate negligible exposure	M-497906-02-2

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

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

INTRODUCTION

This document summarises the information related to the toxicological studies and exposure (operators, workers and bystanders) for the plant protection product Thiacloprid OD240 (Specification 102000021774) which contains the active substance thiacloprid. Thiacloprid OD240 has already been evaluated as the representative formulation during the Annex I inclusion of thiacloprid.
A full risk assessment according to the Uniform principles is provided which demonstrates that the product is safe for operators, workers and bystanders.

Thiacloprid was included into Annex I of Directive 91/414/EEC in 2004 (Directive 2004/99/EC).

Where appropriate this document refers to the conclusions of the EU review of the active substances. This will be where the active substance data are relied upon in the risk assessment of the formulation.

For the implementation of the uniform principles of Annex VI, the conclusions of the review report on thiacloprid, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 29 June 2004 shall be taken into account.

The Review Report (SANCO/4347/2000 – Final) for thiacloprid is considered to provide the relevant scientific information for the review of the product.

In the Annex I Inclusion Directive for thiacloprid there are no specific provisions under Part B which need to be considered related to toxicology of operator/worker/bystander exposure.

CP 7.1 Acute toxicity

The toxicological studies for acute oral, dermal and inhalation toxicity, skin and eye irritation, as well as for skin sensitisation were performed in 2002 with the formulation thiacloprid OD 240 (240 g/L) (in the following described as thiacloprid OD 240), Batch No. 07690/0086(0082).
At the time the studies were performed the formulation was described by Article No. 0005683696 and Development No. 3000266399, which are corresponding to Specification No. 102000007918.

The specification of the product has not changed significantly since then and therefore all the studies are considered to be still valid for this submission.

Thiacloprid OD 240 contains the active substance thiacloprid (240 g/L) according to the specifications 102000007918 and 102000021774 (current specification).

Full details of the formulation specification can be found in the confidential part of this submission.

In the study reports the formulation was named: YRC 2894 240 OD.

The table below summarises the results of the acute toxicological studies conducted with the formulated product thiacloprid OD 240:

Type of study	Results	Report / document No
Acute oral rat	LD_{50}: > 500, < 2000 mg/kg bw	[redacted], F. (2002) CP 7.1.1/01 Report AT00042 [M-064983-01-1]
Acute dermal rat	LD_{50}: > 4000 mg/kg bw	[redacted], F. (2002) CP 7.1.2/01 Report AT00072 [M-066910-01-1]
Acute inhalation rat	LC_{50}: > 846 mg/m³ (maximum technically attainable concentration)	[redacted], J. (2002) CP 7.1.3/01 Report AT00065 [M-066768-01-1]
Skin irritation rabbit	Irritating	[redacted], J. (2002) CP 7.1.4/01 Report AR00006 [M-057895-01-1]
Eye irritation rabbit	Irritating	[redacted], J. (2002) CP 7.1.5/01 Report AR00005 [M-057879-01-1]
Skin sensitisation guinea pig (Maximization test)	Not sensitising	[redacted], H. W. (2003) CP 7.1.6/01 Report AT00233 [M-075780-01-1]

Thiacloprid OD 240 (240 g/L) is of moderate acute toxicity after oral administration and non-toxic after dermal and inhalative exposure to rats. The product is irritating to the skin and eyes of rabbits, but shows no skin sensitising potential in the Maximization test on guinea pigs.
According to the decision of ECHA RAC of March 2015 the active substance thiacloprid is classified, among others, with STOT-SE 3; H336 (may cause drowsiness or dizziness), Carc. 2, H351 (suspected

of causing cancer) and Repro. 1B; H360FD (may damage fertility and the unborn child). As the formulation thiacloprid OD 240 contains 240 g/L of the active ingredient the classification as STOT-SE 3; H336, Carc. 2; H351 and Repro. 1B; H360FD also has to be applied to the formulation.

According the study results the following classification/labelling is triggered:

~~EU directive 1999/45/EC (as amended):Xn (harmful)~~
~~R22 (Harmful if swallowed)~~
~~R38 (Irritating to skin)~~
~~R36 (Irritating to the eyes)~~
~~R40 (limited evidence of a carcinogenic effect; based on the classification of the active ingredient)~~

Regulation (EC) No 1272/2008 (CLP):
Acute Tox. 4; H302: Harmful if swallowed
Skin Irrit. 2; H315: Causes skin irritation
Eye Irrit. 2; H319: Causes serious eye irritation
~~Carcinogenicity Cat 2; H351 (suspected of causing cancer; based on the classification of the active ingredient)~~
STOT-SE 3; H336 (may cause drowsiness and dizziness; based on the classification of the active ingredient)
Carc. 2; H351 (suspected of causing cancer; based on the classification of the active ingredient)
Repro. 1B; H360FD (may damage fertility and the unborn child; based on the classification of the active ingredient)

CP 7.1.1 Oral toxicity

Report:	[redacted]ü; [redacted]; 2002; M-064983-01-1
Title:	YRC 2894 240 OD (c.n.: Thiacloprid) - Study for acute oral toxicity in rats
Report No.:	AT00042
Document No.:	M-064983-01-1
Guidelines:	**OECD 423; Directive 67/548/EEC, Annex IV B, Part B, B.1 tris; US-EPA 712-C-98-190, OPPTS 870.1100; The test substance is a commercial product known to be stable and homogenous in both undiluted and in ready-to-us dilution with water. Therefore, analytical determinations of stability and homogeneity of the aqueous formulations were not performed.**
GLP/GEP:	**yes**

I. Material and methods

A. Materials

1. Test material:	YRC 2894 240 OD
Article/Development no.:	00-05683696 / 30-00266399
Description:	white dispersion
Lot/Batch no.:	07690/0086(0082)
Content:	243.95 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2002-10-09
2. Vehicle:	demineralized water
3. Test animals:	
Species:	rat
Strain:	Wistar rat, HsdCpb:WU
Age:	approx. 8 – 10 weeks
Weight at dosing:	215 – 270 g (males); 156 – 194 g (females)
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard diet "[redacted], Switzerland), *ad libitum*
Water:	tap water, *ad libitum*
Housing:	conventionally group caged in polycarbonate cages; bedding: low-dust wood granulate type BK 8/15 (Ssniff, Spezialdiaeten GmbH, Soest, Germany)

B. Study design and methods

1. Animal assignment and treatment:	
Dose:	200 – 500 mg/kg bw (males) 200 – 500 - 2000 mg/kg bw (females)
Application route:	oral (gavage)
Application volume:	10 mL/kg bw
Fasting time:	before administration: approx. 17 hours ± 1 hour after administration: approx. 2 hours

Group size: 3 rats/sex/group

Post-treatment observation period: 14 days

Observations: mortality, clinical signs, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.1-1: Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Duration of signs	Time of death	Mortality (%)
Male rats						
200	0	0	3	-	-	0
500	0	3	3	1h – 2d	-	0
Female rats						
200	0	1	3	1h – 2h	-	0
500	0	3	3	1h – 2d	-	0
2000	3	3	3	45' – 2d	2h – 2d	100
LD_{50}: > 500 < 2000 mg/kg bw						

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

´: minutes h: hours d: days

B. Clinical observations

After administration of 200 mg/kg bw one female displayed decreased motility and reactivity, laboured breathing and narrowed palpebral fissures between 1 and 2 h after dosing.

At 500 mg/kg bw constipation, decreased motility and reactivity, laboured breathing and narrowed palpebral fissures were observed in male and female animals. Additionally, one female showed piloerection.

A dose of 2000 mg/kg bwled to mortality in all treated animals between 2 h after dosing and day 2. Clinical signs were decreased motility and reactivity, laboured breathing, narrowed palpebral fissures and convulsions. One female lay in abdominal position and another female showed spasmodic state and temporary tremor.

The observed signs started 45 minutes after dosing and lasted up to day 2.

C. Body weight

There were no toxicological effects on body weight or body weight gain.

D. Necropsy

No gross pathological changes were observed at the end of the post-treatment observation period in the animals of the 200 and 500 mg/kg bw groups .

In the 2000 mg/kg bw animals whicht died during the observation period dark-red discolouration of the liver and general autolysis were noted.

III. Conclusion

Thiacloprid OD 240 is moderately toxic after acute oral administration.

The study result triggers the following classification/labelling:
~~- EU directive 1999/45/EC (as amended): Xn; R22 (Harmful if swallowed)~~
- Regulation (EC) No 1272/2008 (CLP): Acute Tox. 4; H302 (Harmful if swallowed)

CP 7.1.2 Dermal toxicity

Report:	[redacted]g; [redacted]; 2002; M-066910-01-1
Title:	YRC 2894 240 OD (c.n.: Thiacloprid) - Study for acute dermal toxicity in rats
Report No.:	AT00072
Document No.:	M-066910-01-1
Guidelines:	**OECD 402; Directive 67/548/EEC, Annex V, Part B.3.; US-EPA 712-C-98-192, OPPTS 870.1200; none**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material: YRC 2894 240 OD

Article/Development no.:	00-05683696 / 30-00266399
Description:	white dispersion
Lot/Batch no.:	07690/0086(0082)
Content:	243.95 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2002-10-09

2. Vehicle: none

3. Test animals:

Species:	rat
Strain:	Wistar rat, HsdCpb:WU
Age:	males: approx. 9 weeks, females: approx. 12 weeks
Weight at dosing:	males: 231 – 247 g, females: 208 – 218 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	Standard diet "[redacted], Switzerland), *ad libitum*
Water:	tap water, *ad libitum*
Housing:	individually in polycarbonate cages; bedding: low-dust wood granulate type BK 8/15 (Ssniff, Spezialdiaeten GmbH, Soest, Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	Dose (mg/kg bw)	Surface area (cm^2)	Range (mg/cm^2)
	males 4000	15.75	58.7 – 62.7
	females 4000	15.75	59.4 – 62.3
Application route:	dermal, semi-occlusive dressing		
Exposure:	24 hours		
Group size:	5 rats/sex/group		
Post-treatment observation period:	at least 14 days		
Observations:	mortality, clinical signs, skin effects, body weights, gross necropsy		

II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*			Occurrence of signs	Time of death	Mortality [%]
Male rats						
4000	0	5#	5	2d – 6d	-	0
Female rats						
4000	0	4#	4	2d – 7d	-	0
LD_{50}: > 4000 mg/kg bw						

* 1st number = number of dead animals, 2nd number = number of animals with signs, 3rd number = number of animals in the group

d: day

#: animals showed local skin findings only

B. Clinical observations

A dermal dose of 4000 mg/kg body weight was tolerated by male and female rats without clinical signs and without mortalities.

Locally, a partial reddening of the treatment area was observed in all males (day 2 to 4) and four females (day 2 to 6). Additionally, a partial formation of scale of the treatment area was observed in three males (day 3 to 6) and three females (day 5 to 7).

C. Body weight

There were no toxicological effects on body weight or body weight development.

D. Necropsy

The necropsies performed at the end of the post-treatment observation period revealed no treatment-related findings.

III. Conclusion

Thiacloprid OC 240 is non-toxic after acute dermal administration.

The study result triggers the following classification/labelling:

~~- EU directive 1999/45/EC (as amended): none~~
- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.3 Inhalation toxicity

Report:	[redacted], [redacted]; 2002; M-066768-01-1
Title:	YRC 2894 240 OD (Common-name: Thiacloprid) - Study on acute inhalation toxicity in rats according to OECD no. 403
Report No.:	AT00065
Document No.:	M-066768-01-1
Guidelines:	**OECD 403; Directive 92/69/EEC, Method B.2; US-EPA 712C-98-193, OPPTS 870.1300; none**
GLP/GEP:	**yes**

I. Materials and methods

A. Materials

1. Test material:

Article/Development no.:	00-05683696 / 00-00266399
Description:	white suspension
Lot/Batch no.:	07690/0086(0082)
Content:	243.95 g/L
Stability of test compound:	guaranteed for study duration; expiry date: 2002-10-09

2. Vehicle: none

3. Test animals:

Species:	rat
Strain:	Wistar rat, HsdCpb:WU
Age:	approx. 8 weeks
Weight at dosing:	males: 173 – 196 g , females: 155 – 176 g
Source:	[redacted], Germany
Acclimatisation period:	at least 5 days
Diet:	standard fixed-formula diet, [redacted] 3883 = NAFAG 9441 pellets maintenance diet for rats and mice ([redacted], Switzerland), *ad libitum*
Water:	tap water, *ad libitum*
Housing:	individually in conventional Makrolon® type II cages; bedding: type BK 8/15 low-dust wood granulate (Ssniff, Spezialdiäten GmbH, Soest, Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0 – 846 mg/m³ air (maximum technically attainable concentration), liquid aerosol
Application route:	inhalation (nose-only)
Exposure:	4 hours
Group size:	5 rats/sex/group
Post-treatment observation period:	2 weeks
Observations:	mortality, clinical signs, body weights, body temperature, reflex measurements, gross necropsy

2. Generation of the test atmosphere / chamber description

Table 7.1.3-1 Generation and characterization of chamber atmosphere

	Group 1	Group 2
Target concentration (mg/m³)	Control (air)	5000
Actual concentration (mg/m³)	-	846#
Temperature (mean, °C)	22.1	21.0
Relative humidity (mean, %)	< 5.4	< 6.6
MMAD (µm)	-	1.79
GSD	-	1.94
Aerosol mass < 3 µm (%)	-	78.3
Mass recovered (mg/m³)	-	748.7

MMAD = Mass Median Aerodynamic Diameter, GSD = Geometric Standard Deviation;

Actual concentration: conversion to test substance: filter mass x 100/95.6

#: maximum technically attainable concentration

- : not applicable.

II. Results and discussion

A. Mortality

Table 7.1.3-2 Doses, mortality / animals treated

Actual concentration (mg/m³)	Toxicological result*			Occurrence of signs	Time of death	Mortality (%)	Rectal temperature (°C)	
Male rats								
0	0	0	5	-	-	0	37.7	
846	0	5	5	0d – 3d	-	0	33.1	**
Female rats								
0	0	0	5	-	-	0	38.5	
846	0	2	5	0d – 1d	-	0	36.4	**
LC_{50}: > 846 mg/m³ air (maximum technically attainable concentration)								

* 1st number = number of dead animals, 2nd number = number of animals with signs after cessation of exposure, 3rd number = number of animals exposed

d: day

**:$p < 0.01$

B. Clinical observations

0 mg/m³ air: All rats tolerated the exposure without specific signs.

The male rats of the 846 mg/m^3 dose group displayed piloerection, bradypnea, laboured breathing pattern, nasal discharge (serous), reddened nostrils, red encrustations of the nostrils, reduced motility and high-legged gait. The 846 mg/m^3 females showed piloerection, bradypnea, nasal discharge (serous), reddened nostrils and red encrustations of the nostrils.

A battery of reflex measurements was made on the first post-exposure day. None of rats exposed to the test substance experienced abnormal reflexes.

Statistical comparisons of the rectal temperature between control and exposure groups revealed a significant decrease of body temperatures. All rats appeared normal on the fourth postexposure day.

C. Body weight

There was a mild and transient decrease in body weight in males of the 846 mg/m^3 air group, which is considered to be of no toxicological relevance.

D. Necropsy

In rats exposed to the test substance macroscopic findings were unremarkable.

III. Conclusion

Thiacloprid OD 240 (liquid aerosol) proved to have essentially no acute inhalation toxicity to rats.

The study result triggers the following classification/labelling:

~~- EU directive 1999/45/EC (as amended): none~~

- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.4 Skin irritation

Report: [redacted]*; [redacted]; 2002; M-057895-01-1
Title: Acute skin irritation test (patch test) of YRC 2894 240 OD in rabbits
Report No.: AR00006
Document No.: M-057895-01-1
Guidelines: **EC guideline B.4., OECD 404; none**
GLP/GEP: **yes**

I. Materials and methods

A. Materials

1. Test material: YRC 2894 240 OD
Development no.: 30-00266399
Description: white dispersion
Lot/Batch no: 07690/0086(0082)
Content: 243.95 g/L
Stability of test compound: guaranteed for study duration; expiry date: 2002-10-09

2. Vehicle: none

3. Test animals:
Species: rabbit

Strain:	Himalayan
Age:	approx. 4.5 months
Weight at dosing:	2.2 – 2.4 kg
Source:	[redacted] Germany
Acclimatisation period:	at least 20 days
Diet:	standard diet for rabbits '[redacted] K-H V2333' ([redacted], Germany), *ad libitum* before and after the exposure period
Water:	tap water, *ad libitum* before and after the exposure period
Housing:	exposure period: singly in special restrainers which allowed free movement of the head but prevented a complete body turn; before/after exposure: individually in cage units 425 mm x 600 mm x 380 mm (Dipl. Ing. W. Ehret GmbH, Schoenwalde, Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose:	0.5 mL/patch (area: approx. 6 cm^2)
Application route:	single dermal application to the shaved, intact dorsal skin (semi-occlusive procedure)
Exposure:	4 hours
Group size:	3 male rabbits
Observations:	clinical signs, skin effects, body weight (at the beginning of the study)

II. Results and discussion

A. Findings

An erythema was noted in all animals:

- animal no. 1: erythema grade 2: 72 h - 5 days, erythema grade 1: 1 - 48 h and 6 - 7 days after patch removal;
- animal no. 2: erythema grade 2: 72 h -5 days, erythema grade 1: 24 - 48 h and 6 - 8 days after patch removal;
- animal no. 3: erythema grade 2: 72 h - 5 days, erythema grade 1: 24 - 48 hours and 6 days after patch removal.

In addition, skin induration was noted in animal no. one 72 hours after patch removal as well as in animal nos. two and three 72 hours to 5 days after patch removal; laceration of the skin was noted in all animals 4 and 5 days after patch removal; peeling of the skin was noted in animal no. one and three 6 to 9 days and in animal no. two 6 to 8 days after patch removal.

There were no systemic intolerance reactions.

Table 7.1.4-1 Summary of irritant effects (Score)

Animal	Observation (after patch removal)	24h	48h	72h	Mean scores	Response	Reversible (days)
1#	Erythema (redness) and eschar formation	1	1	2	1.33	--	8
	Oedema formation	0	0	0	0.00	--	na
2##	Erythema (redness) and eschar formation	1	1	2	1.33	--	9
	Oedema formation	0	0	0	0.00	--	na
3###	Erythema (redness) and eschar formation	1	2	2	1.33	--	7
	Oedema formation	0	0	0	0.00	--	na

Response: -- = negative for mean scores ≥1.5 (GHS)
≥2 (Directive 1999/45/EC)
≥2.3 (Regulation (EC) No 1272/2008)
(+) = mild irritant ≥1.5 - <2.3 (GHS category 3)
\+ = irritant for mean scores ≥2 (Directive 1999/45/EC)
≥2.3 (Regulation (EC) No 1272/2008 and GHS category 2)

*: in respect of the result 1 h after dressing removal na = not applicable

#: Additional findings, rabbit no. 1: skin induration (72 h after patch removal), skin laceration (4-5 days after patch removal), peeling of the skin (6-9 days after patch removal)

##: Additional findings, rabbit no. 2: skin induration (72 h – 5 days after patch removal), skin laceration (4-5 days after patch removal), peeling of the skin (6-8 days after patch removal)

###: Additional findings, rabbit no. 3: skin induration (72 h – 5 days after patch removal), skin laceration (4-5 days after patch removal), peeling of the skin (6-9 days after patch removal)

III. Conclusion

Induration, laceration and peeling of the skin observed in all three rabbits from 72 h to 8 or 9 days after patch removal are considered to be indicative for a significant inflammation of the skin. Thiacloprid OD 240 is therefore considered to be irritating to the skin, although no further trigger values for this classification are met .

The study result triggers the following classification/labelling:

~~- EU directive 1999/45/EC (as amended): Xi; R38 (Irritating to skin)~~
- Regulation (EC) No 1272/2008 (CLP): Skin Irrit. 2; H315 (Causes skin irritation)

CP 7.1.5 Eye irritation

Report: [redacted]:;[redacted]; 2002; M-057879-01-1
Title: Acute eye irritation study of YRC 2894 240 OD by instillation into the conjunctival sac of rabbits
Report No.: AR00005
Document No.: M-057879-01-1
Guidelines: **EC guideline B.5., OECD 405; none**
GLP/GEP: **yes**

I. Materials and methods

A. Materials

1. Test material: YRC 2894 240 OD

Development no.: 30-00266399
Description: white dispersion
Lot/Batch no: 07690/0086(0082)
Content: 243.95 g/L
Stability of test compound: guaranteed for study duration; expiry date: 2002-10-09

2. Vehicle: none

3. Test animals:

Species: rabbit
Strain: Himalayan
Age: approx. 4.5 months
Weight at dosing: 1.8 – 2.4 kg
Source: [redacted] Germany
Acclimatisation period: at least 20 days
Diet: standard diet for rabbits '[redacted]K-H V2333' ([redacted], Germany), *ad libitum* before and after the exposure period
Water: tap water, *ad libitum* before and after the exposure period
Housing: individually in cage units 425 mm x 600 mm x 380 mm (Dipl. Ing. W. Ehret GmbH, Schoenwalde, Germany); for 8 hours following test substance application: in special restrainers which allowed free movement of head but prevented a complete body turn, wiping of the eyes with the paws and excluded irritation of the eyes by excrements and urine.

B. Study design and methods

1. Animal assignment and treatment:

Dose: 0.1 mL/animal

Application route:	single instillation into the conjunctival sac of one eye
Group size:	3 male rabbits
Observations:	clinical signs, eye effects, body weight (at the beginning of the study)

II. Results and discussion

A. Findings

Corneal opacity (grade 1) was observed in all animals, lasting from 1 h to 12, 11 or 10 days after instillation of thiacloprid OD 240 in rabbit no. 1, 2 or 3, respectively. The fluorescein test performed 24 h after instillation revealed corneal staining of the whole cornea surface in all animals, the fluorescein test carried out after 7 days revealed corneal staining of 1/4 of the surface in rabbit nos. 1 and 2 as well as 1/2 of the surface in rabbit no. 3.

Irritation of the iris (grade 1) was noted from 24 h to 6, 4 or 5 days after instillation in rabbits no. 1, 2 or 3, respectively.

Conjunctival redness (grade 1) occurred in all animals 1 h after instillation, in animal no. 3 it lasted until 5 days after instillation. Rabbit no. 3 in addition displayed conjunctival chemosis (grade 1) 24 and 48 h after instillation of the test item. Furthermore, white deposits in the conjunctival sac were observed in all animals 48 and 72 hours after instillation.

There were no systemic intolerance reactions.

Table 7.1.5-1 Summary of Irritant Effects (Score)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	1	1#	1#	1.00	--/(+)	13
	Iritis	1	1	1	1.00	+	7
	Redness conjunctivae	0	0	0	0.00	--	1*
	Chemosis conjunctivae	0	0	0	0.00	--	na
2	Corneal opacity	1	1#	1#	1.00	--/(+)	12
	Iritis	1	1	1	1.00	+	5
	Redness conjunctivae	0	0	0	0.00	--	1*
	Chemosis conjunctivae	0	0	0	0.00	--	na
3	Corneal opacity	1	1#	1#	1.00	--/(+)	11
	Iritis	1	1	1	1.00	+	6
	Redness conjunctivae	1	1	1	1.00	--	6
	Chemosis conjunctivae	1	1	0	0.67	--	3

Response for mean scores:

		Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema	
--	= negative	<1	<1	<2	<2	(Regulation (EC) No. 1272/2008 and GHS)
		<1	<1	<2.5	<2	(Directive 1999/45/EC)
(+)	= mild irritant	≥1 - <3	≥1 - <2	≥2	≥2	(GHS category 2B (effects reversible within 7 days))
+	= irritant	≥1 - <3	≥1 - <2	≥2	≥2	(Regulation (EC) No. 1272/2008 (GHS category 2)
		≥2 - <3	≥1 - <2	≥2.5	≥2	(Directive 1999/45/EC)
++	= irreversible effects/ serious damage	≥3	≥1.5			(Regulation (EC) No. 1272/2008 and GHS category 1)
		≥3	≥2			(Directive 1999/45/EC)

na: not applicable, *: in respect of the result 1 h post application
#: white deposits in the conjunctival sac
24 h fluorescein test: corneal staining (all animals, whole surface)
7 days fluorescein test: corneal staining (rabbits no. 1 & 2: 1/4 of the surface, rabbit no. 3: 1/2 of the surface)

III. Conclusion

Thiacloprid OD 240 is irritating to the eyes of rabbits.

The study result triggers the following classification/labelling:

~~- EU directive 1999/45/EC (as amended): Xi, R36 (Irritating to the eyes)~~
- Regulation (EC) No 1272/2008 (CLP): Eye Irrit.2; H319: Causes serious eye irritation

CP 7.1.6 Skin sensitization

Report: [redacted],,[redacted]; 2003; M-075780-01-1
Title: YRC 2894 240 OD - Study for skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman)
Report No.: AT00233
Document No.: M-075780-01-1
Guidelines: **OECD 406; Guideline 96/54/EC, Method B.6.; US-EPA 712-C-98-197, OPPTS 870.2600; The test item contains commercial products known to be stable and homogenous both undiluted and in ready-to-use dilution with water. Therefore, analytical determinations of the stability and homogeneity of the formulations in physiological saline solution for administration were not performed. This deviation did not limit the assessment of the results.**
GLP/GEP: **yes**

I. Materials and methods

A. Materials

1. Test material: YRC 2894 240 OD
Development no.: 30-00260399
Description: white liquid
Lot/Batch no: 07690/0086(0082)
Content: 237.22 g/L
Stability of test compound: guaranteed for study duration; expiry date: 2003-03-25

2. Vehicle: sterile physiological saline solution

3. Test animals:
Species: guinea pig
Strain: Crl: HA
Age: 4 weeks
Weight at dosing: 283 – 378 g
Source: [redacted] Germany
Acclimatisation period: at least 5 days

Diet:	pelleted standard diet "[redacted] 3420 – Maintenance Diet for Guinea Pigs", [redacted] AG, *ad libitum*
Water:	tap water, *ad libitum*
Housing:	adaptation period: conventionally in Makrolon type IV cages, in groups of 5 guinea pigs/cage; study period: in groups of 2 or 3 guinea pigs/cage; bedding: low-dust wood shavings ([redacted], Germany)

B. Study design and methods

1. Animal assignment and treatment:

Dose	
Intradermal induction:	2.5% (10 mg test item/animal)
Topical induction:	12% (60 mg test item/animal)
Challenge:	6% (30 mg test item/animal)
Application route:	intradermal, dermal
Application volume:	intradermal induction: 0.1 mL/injection topical induction, challenge: 0.5 mL/patch
Exposure:	- topical induction (performed 1 week after intradermal induction): 48h - challenge (performed 3 weeks after intradermal/2 weeks after topical induction): 24h
Group size:	42 females (test item: 20, control: 10, range finding: 10 (induction concentration), 2 (challenge concentration))
Observations:	clinical signs, skin reactions, body weight (at start/termination of study)

II. Results and discussion

A. Findings

Appearance and behaviour of the test item group animals were not different from the control group animals. Animal no. 15 (test item group) showed clinical signs (labored, irregular breathing, pallor, uttering sounds (cold like) and piloerection) from day 15 to 18 of the study. According to the author of the study the reason for these findings was unknown. However, these transient signs could be indicative for a respiratory infection.

After intradermal induction the control animals displayed red wheal after 48 h, while the test item group animals showed red wheal and encrustation at this examination time point.

After 7 days, the injection sites in the control and test item group animals showed wheals and encrustations. After the second (topical) induction the test item group animals had encrustations on the treatment area in places from day 10-12.

The challenge, which was conducted using a 6% formulation of the test item in physiological saline solution, produced grade 1 skin effects in 2 of 20 animals of the test item group (10%) as well as in 1 of 10 animals of the control group (10%).

At the end of the study, the mean body weight of the test item group animals was in the same range than that of the control group animals.

Table 7.1.6-1 Number of animals exhibiting skin effects

	Test item group (20 animals)					Control group (10 animals)				
	Test item patch			Control patch		Test item patch			Control patch	
Hours	48	72	Total	48	72	48	72	Total	48	72
Challenge 6%	2	1	2	0	0	1	1	1	0	0

The guinea pig maximization test methodology was checked for reliability in a test on female guinea pigs using alpha hexyl cinnamic aldehyde at the concentrations indicated below. After the intradermal induction with a 5% test item formulation and the topical induction with a 25% formulation, the challenge with a 12% test item formulation led to grade 1-3 skin effects in 100% of the test animals , while no skin effects were observed in control group animals. The sensitivity as well as the reliability of the experimental technique was thus confirmed by this study. ([redacted], H. W., 2002, document no. AT00083 [M-069646-01-1])

III. Conclusion

Under the conditions of the maximization test and with respect to the evaluation criteria thiacloprid OD 240 exhibits no skin sensitising potential.

The study result triggers the following classification/labelling:
- Regulation (EC) No 1272/2008 (CLP): none

CP 7.1.7 Supplementary studies on the plant protection product

Not applicable according to Commission Directive (EU) No 284/2013. No synergistic or additive toxicological effects are known for the active ingredient thiacloprid nor for other components of thiacloprid OD 240.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No supplementary studies were performed.

~~CP 7.2 Data on exposure~~

~~The exposure of operator to thiacloprid when using Biscaya® 240 OD was not evaluated as part of the EU review of the active substance. Therefore, all relevant data and risk assessments are provided here and are considered adequate.~~

~~Biscaya® 240 OD is an oil dispersion formulation containing 240 g a.s./kg thiacloprid. The product is used as an insecticide for spray application in oilseed rape. Non-dietary exposure is estimated and subsequent risk assessments are made for operators, bystanders/residents and workers. Exposure estimations are based on the respective critical use conditions (cGAP) for each relevant scenario providing the highest exposure estimate. Dossier part D1 contains the detailed use information.~~

~~CP 7.2.1 Operator exposure~~

~~Exposure of operators is estimated using the UK POEM and the German Model. A summary of the cGAP used for operator risk assessment is presented in Table 7.2.1-1.~~

~~Table 7.2.1-1 Summary of critical GAP for operator exposure evaluations~~

~~Crop~~	~~F/G~~	~~Application method~~	~~UK-POEM~~		~~German Model~~
			~~Max. dose rate (kg a.s./ha)~~	~~Min. water volume (L/ha)~~	~~Max. dose rate (kg a.s./ha)~~
~~Oilseed rape~~	~~F~~	~~Field crop sprayer~~	~~0.072~~	~~100-300~~	~~0.072~~

~~The method of application will be tractor mounted/ trailed boom spraying using hydraulic nozzles (field crop sprayer). The critical GAP when using the UK POEM results from a combination of dose rate (0.072 kg a.s./ha) with lowest water volume (100 L/ha). When using the German Model the maximum application rate determines the cGAP (0.072 kg a.s./ha).~~

~~AOEL:~~

~~The Review Report for thiacloprid (SANCO/ 4347/2000- Final, 13 May 2004) is considered to provide the relevant scientific information for the review of the product. An AOEL of 0.02 mg/kg bw/d was established from the rabbit developmental study (maternal toxicity) and a SF of 100.~~

~~Dermal absorption:~~

~~A dermal absorption study was performed with the OD 240 formulation *in vitro* using human skin. The *in vitro* study indicated that the mean percentage of [^{14}C]-thiacloprid considered to be absorbable over a period of 24 hours was~~

- ~~0.2% for the neat formulation (240 g a.s./L)~~

- ~~6% for the intermediate spray dilution (0.74 g a.s./L) and~~
- ~~14% for the low spray dilution (0.1 g/L).~~

~~These values are proposed for use in occupational and residential exposure assessments (for details see CP 7.3).~~

~~Since the dermal absorption depends on the concentration used in the field the cGAP must be determined from two potential use scenarios when using the UK-POEM. The use of 0.072 kg a.s./ha in 100 L results in a spray concentration of 0.072 g a.s./L for which a dermal absorption of 6% is appropriate to be used. The use of 0.072 kg a.s./ha in 300 L results in a spray concentration of 0.24 g a.s./L for which a dermal absorption of 14% is appropriate to be used~~[1].

~~The UK-POEM calculations for the cGAP are therefore conducted using dermal absorption values of 0.2% for the concentrate and 6% for the spray dilution.~~

~~The German model calculations for the cGAP are conducted using dermal absorption values of 0.2% for the concentrate and 14% for the spray dilution.~~

~~Summary~~

~~A summary of the exposure estimates resulting from the critical GAP is presented in the following table.~~

~~Table 7.2.1-2: Predicted operator exposure~~

~~Crops~~	~~F/G~~	~~Application method~~	~~PPE~~	~~Systemic exposure* (mg/kg bw/day)~~		~~% of AOEL (0.02 mg/kg bw/day)~~	
				~~UK-POEM~~	~~German Model~~	~~UK-POEM~~	~~German Model~~
~~Oilseed rape~~	~~F~~	~~Field crop sprayer~~	~~No~~[1]	~~0.0330~~	~~0.0069~~	~~165~~	~~34~~
			~~With~~[2]	~~0.0056~~	~~0.0005~~	~~28~~	~~2~~

~~[1] No PPE: UK-POEM: Coverall, no gloves, German model: T-shirt and shorts, no gloves~~
~~[2] With PPE: UK-POEM and German model: Coverall and gloves during mixing/loading and application~~
~~* Dermal absorption of 2% (concentrate) and 6%(UK-POEM, spray)/14% (German model, spray), 100% absorption *via* inhalation route~~

~~Assessment~~

~~Exposure estimates predict acceptable exposures for operators handling the product.~~

[1] Although the concentration of 0.72 g a.s./L is slightly lower than the intermediate concentration in the dermal absorption study (0.74 g a.s./L) the value of 6% established from the latter is chosen for the risk assessment. This is done because the deviation of the a.s. concentration in the dilution differs for a factor of <2 and a transmissibility of the results can be assumed. In the present case the tested dilution is 1:324 (0.74 g a.s./L) compared to the dilution under evaluation of 1:333 (0.72 g a.s./L)). This approach is based on the EU guideline (SANCO/12638/2001) for the evaluation of significant changes of the chemical composition of plant protection products. Changes of ± 100 % for concentrations ≤ 0.5% are acceptable according to the guideline.

~~The UK POEM indicates that exposure of unprotected operators is above the AOEL (165%). However, it demonstrates a safe use for operators wearing gloves (28% of the AOEL). The German Model demonstrates a safe use for unprotected operators wearing T-shirt and shorts (34% of the AOEL). When gloves are worn during mixing/loading and application exposure will be 2% of the AOEL.~~

~~**Conclusion**~~

~~Overall, it is concluded that the use of Thiacloprid OD 240 does not result in an unacceptable risk for operators.~~

~~CP 7.2.1.1 Estimation of operator exposure~~

~~Exposure estimations are made using the UK POEM and the German model. The product is applied in oilseed rape using vehicle mounted/trailed field crop sprayers. Exposure is calculated based on the eGAP (see Table 7.2.1-1). Detailed calculations are presented in the following tables.~~

~~Table 7.2.1.1-1: UK-POEM calculations~~

THE UK PREDICTIVE OPERATOR EXPOSURE MODEL (POEM)

Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles		
Product	**Thiacloprid OD 240**	Active substance	**Thiacloprid**
Formulation type	organic solvent-based	a.s. concentration	**240** mg/ml
Dermal absorption from product	**2** %	Dermal absorption from spray	**6** %
Container	5 litres 45 or 63 mm closure		
PPE during mix/loading	Gloves	PPE during application	Gloves
Dose	**0.3** l/ha	Work rate/day	**50** ha
Application volume	**100** l/ha	Duration of spraying	**6** h

EXPOSURE DURING MIXING AND LOADING

Container size	5	litres	
Hand contamination/operation	0.01	ml	
Application dose	0.3	litres product/ha	
Work rate	50	ha/day	
Number of operations	3	/day	
Hand contamination	0.03	ml/day	
Protective clothing	None		Gloves
Transmission to skin	100	%	10 %
Dermal exposure to formulation	0.030	ml/day	0.003 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	0.030	41.550 ml/day	0.003	6.450 ml/day
Concen. of a.s. product or spray	240	0.72 mg/ml	240	0.72 mg/ml
Dermal exposure to a.s.	7.200	29.916 mg/day	0.720	4.644 mg/day
Percent absorbed	6	%	2	6 %
Absorbed dose	0.144	1.795 mg/day	0.014	0.279 mg/day

INHALATION EXPOSURE DURING SPRAYING

Inhalation exposure	0.01	ml/h	
Duration of exposure	6	h	
Concentration of a.s. in spray	0.72	mg/ml	
Inhalation exposure to a.s.	0.0432	mg/day	
Percent absorbed	100	%	
Absorbed dose	0.0432	mg/day	

PREDICTED EXPOSURE	No PPE		With PPE	
Total absorbed dose	1.9822	mg/day	0.3362	mg/day
Operator body weight	60	kg	60	kg
Operator exposure	0.0330	mg/kg bw/day	0.0056	mg/kg bw/day

~~Table 7.2.1.1-2: German Model calculations~~

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

Product:	Calypso OD 240				
Active substance:	Thiacloprid		a.s. concentration:	240	[g/l or kg]
Formulation:	Liquid		PPE during mix/loading:	Respiration:	None
Dose [l or kg/ha]:	0.3			Hands:	Gloves
Work rate [ha/day]:	20		PPE during application:	Respiration:	None
Body weight [kg]:	70			Hands:	Gloves
Inhalation absorption [%]	100			Head:	None
Dermal absorption [%]	2.0	(concentrate)		Body:	Standard protective coverall
	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	1.44	0.000012	1.0	0.000012	I = Inhalation D = Dermal
$D_{M(H)}$ =	2.4	1.44	0.0494	0.01	0.000494	M = Mix/loading
I_A =	0.001	1.44	0.000021	1.0	0.000021	A = Application
$D_{A(C)}$ =	0.06	1.44	0.0012	1.0	0.001234	H = Hands
$D_{A(H)}$ =	0.38	1.44	0.0078	0.01	0.000078	C = Head
$D_{A(B)}$ =	1.6	1.44	0.0329	0.05	0.001646	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	0.049371	0.000987	0.000494	0.00001
	Application	14.0	0.041966	0.005875	0.002958	0.000414
Inhalation:	Mix/Loading	100	0.000012	0.000012	0.000012	0.000012
	Application	100	0.000021	0.000021	0.000021	0.000021
			Total:	**0.006896**		**0.000457**

~~CP 7.2.1.2 Measurement of operator exposure~~

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

~~CP 7.2.2 Bystander and resident exposure~~

~~The evaluation of bystander and resident exposure is performed according to the UK Regulatory Update: 10/2008, issued: 22 April 2008.~~

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

~~Bystanders are persons:~~

- ~~who are located within or directly adjacent to the area where pesticide application or treatment is in process or has been made~~
- ~~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
- who are not wearing protective clothing and/or perhaps little ordinary clothing e.g. short sleeved shirt and short trousers

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 pesticides 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 per day

The assessment is performed for the following three scenarios:

1. Exposure from spray drift at the time of application
2. Exposure from inhalation of pesticide which volatilises from the crop or soil surface after the application has been made
3. 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

Table 7.2.2-1 - Summary of critical GAP for bystander/resident exposure evaluations

Application scenario	Exposure scenario	Critical parameters
Field crop sprayer	Spray drift	Conc. of 0.72 g a.s./L (72 g a.s. in 100 L) and using relevant dermal absorption of 6%
	Volatilization	1 µg/m³/24 h, arable crops
	Drift fallout	1% (at 3 m), 2 appl. with 0.072 kg a.s./ha

The cGAP for bystander exposure from spray drift is justified from a comparison of exposure calculated for the two scenarios considering spray concentration and relevant dermal absorption. If the highest spray concentration of 0.72 g a.s./L (72 g a.s. in 100 L water) is considered the relevant dermal absorption is 6% (see chapter CP 7.3). If the lowest spray concentration of 0.24 g a.s./L (72 g a.s. in 300 L water) is considered the relevant dermal absorption is 14%. The worst case exposure via spray drift is calculated for a spray concentration of 0.72 g a.s./L and a dermal absorption of 6%.

The worst case for volatilization will be given by using the highest time weighted average estimate of 1µg/m³/24h (from studies conducted in Germany) during application using field crop sprayers..

The highest exposure for a child playing on a lawn is calculated for the highest drift fallout and maximum dose rate. This is the case for a 1% drift fallout during field crop spraying (at 3 m) and a

dose rate of 0.072 kg a.s./ha, 2 applications. A dermal absorption of 14% is calculated for the worst case.

Summary

A summary of the exposure estimates resulting from the critical GAP is presented in the following table. Detailed calculations are presented in CP 7.2.2.1.

Table 7.2.2-2: Predicted systemic bystander/resident exposure as a proportion of the AOEL

	Field crop sprayer	
	Systemic exposure (mg/kg bw/day)	% of AOEL (0.02 mg/kg bw/day)
Bystander – spray drift Adult	0.00014	0.7
Residents – vapour exposure Adult Child	0.000253 0.0006	1.2 3
Children's exposure due to drift fallout	0.00008	0.4

Conclusion

Exposure of bystanders to thiacloprid from spray drift during application using field crop sprayers is 0.7% of the AOEL. Resident exposure to volatile material is 1.2% (adult) and 3% (child) of the AOEL. Exposure of a small child playing on the lawn is 0.4% of the AOEL.

It is predicted that all exposures are within acceptable levels and an unacceptable risk for bystanders and residents is not anticipated.

Additional exposure evaluation is performed using experimental data of a bystander study performed with Biscaya® 240 OD (see chapter CP 7.2.2.2). Exposure of adult and child bystanders was monitored during spray application of Biscaya® 240 OD in oilseed rape using standard and drift reducing nozzles ([redacted], 2012). The trial was compliant with GLP and carried out within OECD guidelines. The study is considered to be acceptable in terms of design and validation. A summary of the exposure assessment based on these data is presented in the following table.

Table 7.2.2-3: Bystander exposure (spray drift) and % of AOEL based on experimental data

	Distance (m)	% of AOEL (0.02 mg/kg bw/day)			
		Child		Adult	
		Standard nozzle	Drift red. nozzle	Standard nozzle	Drift red. nozzle
Potential exposure	3	2.66	0.14	1.00	0.03
	8	0.72	0.12	0.39	0.02

	13	0.34	0.06	0.09	0.02
Actual exposure	3	2.04	0.12	0.61	0.02
	8	0.51	0.09	0.20	0.02
	13	0.18	0.06	0.04	0.01

Potential dermal exposure represents a person not wearing any clothing. Actual exposure represents a person assuming wearing little clothing (T-shirt and shorts). Highest exposure is measured for a child bystander at 3 m distance to the spray boom equipped with standard nozzles (about 3% of the AOEL for potential exposure, about 2% of the AOEL for actual exposure). Adult exposure is 1% of the AOEL or less. Any larger distance (8 m or 13 m) or the use of drift-reducing nozzles will reduce exposure to ≤1% of the AOEL.

CP 7.2.2.1 Estimation of bystander and resident exposure

1. Exposure from spray drift at the time of application

An estimate of bystander exposure is presented based on a study conducted by Lloyd and Bell[2] (1983) which reports direct measurements of simulated bystander exposure from applications with field crop sprayers. In this study, a single pass of the sprayer resulted in a mean potential dermal exposure (PDE) of 0.1 ml of spray solution on a bystander positioned 8 m downwind from the edge of the treatment area. Mean potential inhalation exposure (PIE) was 0.006 ml of spray solution.

Total systemic exposure from spray drift is estimated as follows:

Systemic exposure = (PDE x SC x DA + PIE x SC x 100%)/BW

Where:

PDE	=	potential dermal exposure (ml spray)
PIE	=	potential inhalation exposure (ml spray)
SC	=	concentration of active substance in spray
DA	=	% dermal absorption
BW	=	bodyweight (60 kg)

ml spray dermal mg/ml % absorbed ml inhaled mg/ml

$$\frac{(0.1 \times 0.72^{*} \times 6\% + 0.006 \times 0.72)}{60} = 0.00014 \text{ mg/kg bw/day}$$

= 0.7% of AOEL

*0.072 kg a.s./100 L water

The highest exposure is calculated if the highest concentration is taken into account (72 g a.s./ha in 100 L/ha water). The relevant dermal absorption to be used for this concentration is 6%. Exposure is lower if lowest concentration (72 g a.s./ha in 300 L/ha water) and dermal absorption of 14% is used. Therefore, a calculation for the latter scenario is not presented here.

[2] Lloyd G.A. and Bell G.J. (1983). Hydraulic nozzles: comparative spray drift study (MAFF/ADAS).

~~Assuming an application of 0.072 kg thiacloprid in 100 litres water, no protection from clothing and 100% inhalation, retention and absorption of PIE, the estimated bystander exposure is 0.00014 mg/kg bw/day. This is equivalent to 0.7% of the AOEL (0.02 mg/kg bw/day).~~

~~Further evaluations considering negligible exposure from spray drift are contained in document J (see 'Measurement of exposure').~~

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

~~For applications made using field crop (boom) sprayers, exposure to vapour post application is predicted from studies conducted in Germany, where lindane (vapour pressure = 5.6 x 10^{-3} Pa at 25 °C), parathion (1.3 x 10^{-3} Pa at 25 °C) and pirimicarb (4 x 10^{-3} Pa at 25 °C) were applied in field trials to provide measurements of residues in air adjacent to treated crops (Siebers et al 2000). Each active substance was applied at the same rate (g a.s./ha) 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/m³ (lindane), 0.07 and 0.12 µg/m³ (parathion) and <0.02 and 0.04µg/m³ (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 (2 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/m³ to predict bystander exposure from vapour after application of the spray.~~

~~Using these data, the indicative exposure can be estimated as follows:~~

~~Systemic exposure = Max 24h TW level x LTIR/BW~~

~~Where:~~

~~Max 24h TW~~	=	~~maximum 24 hour time weighted level (air concentration)~~
~~LTIR~~	=	~~long term inhalation rate (15.2 m³/day adult, 8.3 m³/day child)~~
~~BW~~	=	~~body weight (60 kg adult, 15 kg child)~~

~~Adult:~~	~~Child:~~
~~Max 24h TW LTIR~~	~~Max 24h TW LTIR~~
~~$\frac{(1 \times 15.2)}{60}$ = 0.000253 mg/kg bw/day~~	~~$\frac{(1 \times 8.3)}{15}$ = 0.0006 mg/kg bw/day~~
~~= 1.2% of AOEL~~	~~= 3% of AOEL~~

~~An adult weighing 60 kg and a 3-5 year old child weighing 15 kg, breathing 15.2 m³/day and 8.3 m³/day, respectively, of air containing this residue level, would potentially be exposed to 0.000253 and 0.0006 mg/kg bw/d. This amounts to 1.2% and 3% of the AOEL, respectively.~~

~~Further considerations on negligible resident vapour exposure is contained in document J.~~

Evaluations of exposure from inhalation of pesticide which may volatilise from the crop or soil surface (see CP 7.2.2.1) were made with a default air concentration of 1 µg/m³. This value is an indicative value derived from studies (range <0.02 µg/m³ – 0.58 µg/m³) using volatile active substances (lindan, parathion, pirimicarb). It is appropriate to assume that vapour exposure is a function of volatilization which itself depends on the compound's vapour pressure. Vapour pressures of the three above mentioned compounds are 1.3 - 5.6 x 10^{-3} Pa at 25 °C. Thiacloprid has a vapour pressure of 8 x 10^{-10} Pa at 25 °C which is about seven orders of magnitude lower than any of the underlying compounds used in the Tier 1 assessment. Realistic resident exposure to thiacloprid vapour is therefore likely much lower than indicated in the worst case Tier 1 calculation (probably far less than 1% of the AOEL and may be confirmed in additional studies).

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 become 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[3]. 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). The highest exposure is calculated using a dermal absorption of 14%.

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

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

Where:

SE(d)	=	systemic exposure via the dermal route
AR	=	field application rate, 0.072 kg a.s./ha x 2 applications = 1.44 µg/cm²
DF	=	drift fallout value, i.e. about 1% from field crop (boom) sprayer applications at 3 m
TTR	=	turf transferable residues – the EPA value of 5% is used
TC	=	transfer coefficient – the standard EPA value of 5200 cm²/h is used
H	=	exposure duration for a typical day (hours) – this has been assumed to be 2 hours which matches the 75th percentile for toddlers playing on grass in the EPA Exposure Factors Handbook
DA	=	dermal absorption (i.e. 14%)
BW	=	body weight – 15 kg which is the average of UK 1995-7 Health Surveys for England values for males and females of 2 and 3 yrs.

AR		DF		TTR		TC		H		DA		
(1.44	x	1%	x	5%	x	5200	x	2	x	14%)	=	0.000055 mg/kg bw/day

[3] 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.

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b. Children's hand-to-mouth exposure

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

$$SE(h) = \frac{(AR \times DF \times TTR \times SE \times SA \times Freq \times H)}{BW}$$

Where:

SE(h) = systemic exposure via the hand-to-mouth route
AR = field application rate, 0.072 kg a.s./ha x 2 applications = 1.44 µg/cm²
DF = drift fallout value, i.e. about 1% from field crop (boom) sprayer applications at 3 m
TTR = turf transferable residues – the EPA value of 5% is used
SE = saliva extraction factor – the default value is 50%
SA = surface area of the hands – the assumption is that 20 cm² of skin area is contacted each time a child puts a hand in his or her mouth
Freq = frequency of hand to mouth events/hour – for short-term exposures the value of 20 events/hour is used, this is the 90th percentile of observations that ranges from 0 to 70 events/hour
H = exposure duration (hours) – 2 hours is assumed
BW = body weight – 15 kg which is the average of UK 1995-7 Health Surveys for England values for males and females of 2 and 3 yrs.

$$\frac{(AR \times DF \times TTR \times SE \times SA \times Freq \times H)}{BW} = \frac{(1.44 \times 1\% \times 5\% \times 0.5 \times 20 \times 20 \times 2)}{15} = 0.000019 \text{ mg/kg bw/day}$$

c. Children's object-to-mouth exposure

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

$$SE(o) = \frac{(AR \times DF \times TTR \times IgR)}{BW}$$

Where:

SE(o) = systemic exposure via mouthing activity
AR = field application rate, 0.072 kg a.s./ha x 2 applications = 1.44 µg/cm²
DF = drift fallout value, i.e. about 1% from field crop (boom) sprayer applications at 3 m
TTR = turf transferable residues – the default value is 20% transferability for object to mouth assessments
IgR = ingestion rate for mouthing of grass/day – assumed to be equivalent to 25 cm² of grass/day
BW = body weight – 15 kg which is the average of UK 1995-7 Health Surveys for England values for males and females of 2 and 3 yrs.

$$\frac{(AR \times DF \times TTR \times IgR)}{BW} = \frac{(1.44 \times 1\% \times 0.20 \times 25)}{15} = 0.000005 \text{ µg/kg bw/day}$$

Children total exposure is estimated as the sum of the different route exposures, which is

Dermal exposure:	0.000055 mg/kg bw/day (dermal)
Hand-to-mouth exposure:	0.000019 mg/kg bw/day (hand-to-mouth)
Object-to-mouth exposure:	0.000005 mg/kg bw/day (object-to-mouth)
Total systemic exposure:	**0.000079 mg/kg bw/day**

On the basis of these estimates, the level of systemic exposure to thiacloprid is 0.000079 mg/kg bw/day which is 0.4% or less of the systemic AOEL).

CP 7.2.2.2 Measurement of bystander and resident exposure

A bystander exposure study was performed under representative use conditions and is submitted here to confirm the model data.

Exposure of adult and child bystanders was monitored during spray application of Biscaya® 240 OD in oilseed rape ([redacted], 2012). The trial was compliant with GLP and carried out within OECD guidelines. The study is considered to be acceptable in terms of design and validation.

Report:	[redacted]; [redacted]; 2012; M-439075-01-1
Title:	Exposure of bystanders / residents to thiacloprid from spray applications with Biscaya OD 240 in oilseed rape
Report No.:	MR-11/087
Document No.:	M-439075-01-1
Guidelines:	**OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997** **Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E); not specified**
GLP/GEP:	**yes**

~~**Material and methods**~~

~~Plant protection product:~~	~~Biscaya OD 240®~~
	~~Oil Dispersion~~
	~~Active substance: thiacloprid (240 g/L)~~
~~Field study location:~~	~~Germany,~~ [redacted]~~.~~
~~Application:~~	~~April 2012~~
~~Crop:~~	~~Oilseed rape~~
~~Quantity a.s. applied:~~	~~0.3 L/ha (nominal 72 g a.s./ha)~~
~~Bystanders:~~	~~9 adult and 9 child mannequins~~

~~The dermal and inhalation exposure of bystanders was measured while applying Biscaya® OD 240 (a 240 g/L oil dispersion formulation of thiacloprid) and Brilliant Blue FCF® (erioglaucine, E 133, a triarylmethane dye food additive) to an oilseed rape field in Germany. The spray applications were performed with a commercial field crop boom sprayer with 28 m boom width. The spray was applied in two swaths parallel to the length of the pre defined spray drift area. Biscaya® OD 240 was applied with the label specific rate of 0.3 L/ha (nominal 72 g a.s./ha thiacloprid) using a TeeJet AI 11004 nozzle. This nozzle is classified in Germany as a 75% drift reducing air injection nozzle. Brilliant Blue FCF® was applied in parallel under the same climatic conditions but using standard nozzles (TeeJet XR 110 04). Dose rate was 0.8 kg/ha. A water volume of 200 L/ha was applied in both scenarios.~~

~~Spray applications with Biscaya OD 240 and Brilliant Blue FCF were performed under identical conditions using the same tractor and sprayer at the same field plot and the same day under comparable climatic conditions. The trial design allows the comparison of adult and child exposures from drift using either standard nozzles or drift reduction nozzles at various spray distances.~~

~~A total of 18 mannequins representing 9 adult and 9 child bystanders/residents were monitored. The site provided an even, not sloped and homogeneous oilseed rape field of sufficient size at full flowering growth stage (BBCH 65) to perform sequential spray swaths. It allowed to position replicates of mannequins at various distances downwind in order to monitor a range of potential distances where bystanders or residents may be exposed during application.~~

~~The dermal exposure was determined with whole body dosimeters. Each mannequin wore dosimeters consisting of a short sleeved T-shirt and shorts above long underwear (long johns and shirt) and a ski mask covering the head. The long sleeves of the shirts were worn to also cover the hand. An additional hand dosimeter was therefore not included. This clothing scheme allowed the determination of potential dermal exposure representing a person with virtually no clothing as well as actual dermal exposure representing a lightly dressed person wearing only little clothing. Inhalation exposure was determined by the use of a personal air sampling pump connected to an IOM sampler with glass fibre filter, located in the virtual breathing zone of the adult and child dummy.~~

~~**Results**~~

~~Potential dermal, actual dermal and inhalation exposure was calculated from residues in/on each bystander's dosimeters for both nozzle types. Potential dermal exposure is the sum of residues on outer dosimeters (short sleeved T-shirt and shorts), inner dosimeters (long sleeved T-shirt and long johns) and ski mask. This scenario represents a person not wearing any clothing. Actual exposure is the sum of residues on inner cotton dosimeters and ski mask assuming a person wearing little clothing (T-shirt and shorts).~~

Adult and child exposure to spray (mL spray/person) was determined from the amount of residues found in/on dosimeters (µg/sample). Breathing rate factors (29 L/min for an adult and 16.7 L/min for a child) are additionally used to adjust pump flow rates for adult and child inhalation exposure.

Exposure to thiacloprid is calculated for both nozzle types in mg a.s./person. Figures for the drift reducing nozzle are taken directly from the measured thiacloprid residues on the dosimeters. Figures for the standard nozzle are based on the spray volume measured for the food dye tracer and the thiacloprid concentration in the spray. Results are presented in the following table.

Table 7.2.2.2-1: Bystander exposure to thiacloprid

		Adult		Child	
Distance	Type	Drift red. nozzle	Standard nozzle	Drift red. nozzle	Standard nozzle
Potential dermal exposure (mg a.s./person)					
3m	95th perc.	0.0027	0.0836	0.0016	0.0323
8m	95th perc.	0.0019	0.0311	0.0014	0.0087
13m	95th perc.	0.0012	0.0062	0.0007	0.0038
Actual dermal exposure (mg a.s./person)					
3m	95th perc	0.0016	0.0502	0.0014	0.0243
8m	95th perc.	0.0012	0.0153	0.0011	0.0061
13m	95th perc.	0.0010	0.0027	0.0007	0.0018
Inhalation exposure (mg a.s./person)					
3m	95th perc.	0.000036	0.000292	0.000022	0.000269
8m	95th perc.	0.000026	0.000281	0.000011	0.000069
13m	95th perc.	0.000023	0.000153	0.000009	0.000073

Conclusion

The experimental conditions are analogous with those prevalent during typical spray applications of Biscaya® OD 240 to oilseed rape.

Risk assessment:

Taking as surrogates the 95th percentile values the following systemic bystander exposure results are obtained for the risk assessment.

Potential exposure: SE = ((PDE x DA) + IE)/BW
Actual exposure: SE = ((ADE x DA) + IE)/BW

Where:
SE = Systemic exposure (mg/kg bw/day)
PDE = Potential dermal exposure (mg/person)
ADE = Actual dermal exposure (mg/person)
DA = dermal absorption (14%)
IE = Inhalation exposure (mg/person)
BW = Body weight (60 kg adult, 9 kg child)

Table 7.2.2.2-2: Systemic bystander exposure to thiacloprid

-	-	Systemic exposure* (mg/kg bw/day)			
	Distance (m)	Child		Adult	
		Standard nozzle	Drift red. nozzle	Standard nozzle	Drift red. nozzle
Potential exposure	3	0.000532	0.000027	0.000200	0.000007
	8	0.000143	0.000023	0.000077	0.000005
	13	0.000067	0.000012	0.000017	0.000003
Actual exposure	3	0.000408	0.000024	0.000122	0.000004
	8	0.000103	0.000018	0.000040	0.000003
	13	0.000036	0.000012	0.000009	0.000003

* 14% dermal absorption, 60 kg adult, 9 kg child

Table 7.2.2.2-3: Risk assessment

-	-	% of AOEL (0.02 mg/kg bw/day)			
	Distance (m)	Child		Adult	
		Standard nozzle	Drift red. nozzle	Standard nozzle	Drift red. nozzle
Potential exposure	3	2.66	0.14	1.00	0.03
	8	0.72	0.12	0.39	0.02
	13	0.34	0.06	0.09	0.02
Actual exposure	3	2.04	0.12	0.61	0.02
	8	0.51	0.09	0.20	0.02
	13	0.18	0.06	0.04	0.01

CP 7.2.3 Worker exposure

The determination of the cGAP for worker re-entry is based on the recommendation provided in the EUROPOEM II report[4] for worker exposure for four different harvesting scenarios with bare hands:

Crop group	Transfer Coefficient (cm^2/h)
Fruits (from trees):	4500
Vegetables:	2500
Ornamentals:	5000
Strawberries:	3000

The worker risk assessment is made for the intended uses of thiacloprid OD 240. A summary of the critical GAP used for worker risk assessment is presented in the following table.

[4] EUROPOEM II project FAIR3-CT96-1406; Post Application Exposure of Workers to Pesticides in Agriculture, Report of the Re-entry Working Group; December 2002

Table 7.2.3-1: Critical GAPs for worker exposure

Crop grouping	Re-entry task	Duration (h)	Max. dose rate		No of appl.	Min. interval (days)	Min. PHI (days)
			(L/ha product)	(kg a.s./ha)			
Oilseed rape	Scouting	2	0.3	0.072	2	10	n.a.

- Summary

Predicted exposures are calculated from a cumulative foliar deposit based on the maximum number of applications, the maximum dose rate and 2 hours/day contact with the foliage. Exposure is compared with the AOEL. Exposure estimates and proportions of the AOEL accounted for by the estimates are summarised in the following table.

Table 7.2.3-2: Predicted worker exposure

Crop grouping	Re-entry task	Systemic exposure* (mg/kg bw/day)	% of AOEL (0.02 mg/kg bw/day)
Oilseed rape	Scouting	0.0101	50

* 14% dermal absorption, 60 kg worker

- Conclusions

Exposure of workers entering treated areas is within acceptable levels. Calculations reflect standard work clothing worn by adult workers (shoes, socks, long-legged pants, and long sleeves) working with bare hands. The maximum number of applications and no residue decline is assumed. Exposure is 50% of the AOEL and an unacceptable risk is therefore not anticipated.

Additional exposure estimates are calculated in a tiered approach using experimentally determined DFR data (see chapter CP 7.2.2.2).

A summary of the refined exposure assessments is presented in the following table.

Table 7.2.3-3: Summary of predicted worker exposure (tiered approach)

	Source	Exposure (mg/kg bw/day)	% of AOEL (0.02 mg/kg bw/day)
Tier 1	Defaults	0.0101	50
Tier 2	Experimental DFR	0.0012-0.0017	6-9

Calculations reflect standard work clothing worn by adult workers (shoes, socks, long-legged pants, and long sleeves) working with bare hands. In a 2nd Tier, exposure is calculated based on experimental DFR data (see chapter CP 7.2.2.2). A fast DFR decline was observed in the experimental studies with DT_{50} of 1.2 – 3.7 days. Residues were always below the LOQ three days after the application. Exposure of workers re-entering oilseed rape directly after the last treatment is 6%-9% of the AOEL.

It is concluded that realistic exposure to thiacloprid does not present an unacceptable risk for re-entry workers during scouting in oilseed rape.

CP 7.2.3.1 Estimation of worker exposure

The exposure calculation is performed according to the following equation:

S = DFR x N x TC x WR x AR x P / BW x DA

Where: S: Systemic exposure
DFR: Dislodgeable foliar residues (default 3 µg as/cm²)
N: Number of applications (2 appl.)
TC: Transfer Coefficient (activity specific; 5000 cm²/person/h)
WR: Work rate (8 hours/day)
AR: Application rate (crop specific; 0.072 kg a.s./ha)
P: Protection factor for PPE (1, no PPE)
BW: Body weight (60 kg/person)
DA: Dermal absorption (14%)

Exposure is calculated with the maximum dose rate and 2 hours contact with foliage per day for scouting activities. The higher of the dermal absorption values from concentrate or dilution is applied (14%). Where sequential applications are performed a worst case is assumed considering re-entry after the final treatment and potential accumulation of DFR from successive treatments without residue decline.

Re-entry for scouting in oilseed rape:

S	=	DFR	x	N	x	TC	x	WR	x	AR	x	P	/	BW	x	DA
	=	3	x	2	x	5000	x	2	x	0.072	x	1	/	60	x	14%
	=	0.01008 mg/kg bw/day														
	=	50% of AOEL														

If the worst-case approach would be to assume that no dissipation occurs DFR_0 would be used for calculations, i.e. the residue available directly after the last application and accumulation of residues on foliage. Worker exposure during re-entry of oilseed rape would be 0.0101 mg/kg bw/day i.e. 50% of the AOEL. An unacceptable risk is therefore not anticipated.

Tier 2 refinement using experimentally determined DFR data

Dislodgeable Foliar Residues (DFR) studies were conducted under actual use conditions. Detailed summaries of three DFR trials are reported below. The highest DFR values observed in the course of the experiments are considered in the exposure assessment (see following table).

Table 7.2.3.1-1: Experimentally derived maximum DFR values

Crop	Country	Report no., document no.	Formulation	Study conditions (no. of appl. / appl. Rate in kg a.s./ha)	cGAP (no. of appl. / appl. Rate in kg a.s./ha)	Max. DFR_M (µg/cm²)	Observed on
Bean	Germany	11-2908, M-433739-01-1	OD 240	3 / 0.096	2 / 0.072	0.258	0 days after 1st appl., DAFT 0
Potato	Germany	11-2900, M-433623-01-1	OD 240	3 / 0.120	2 / 0.072	0.338	0 days after 1st appl., DAFT 0
Potato	France	11-2906, M-433626-01-1	SC 480	3 / 0.096	2 / 0.072	0.225	0 days after 2nd appl., DAFT 14

DAFT = days after 1st treatment

Bean, potato and oilseed rape are smooth-leaf field crops. Therefore, the DFR data from these crops are taken to make estimations of DFR on oilseed rape.

It is noted that the DFR trials were conducted with three applications using the maximum dose rate of 0.096 kg a.s./ha (bean, Germany, and potato, France) up to 0.120 kg a.s./ha (potato, Germany) whereas the cGAP under evaluation considers only two applications and 0.072 kg a.s./ha. The measured maximum DFR values (DFR_M) from these trials are not normalized. They therefore constitute highly conservative estimates for the worker exposure evaluation.

The above mentioned equation changes to:

$S = (DFR_M \times TC \times WR \times P)/BW \times DA$

Where: DFR_M = Measured dislodgeable foliar residues (µg as/cm²)

Calculation of worker exposure during re-entry in oilseed rape:

Calculations are made with the DFR_M from the three individual trials.

1. DFR_M is taken from trials conducted in bean (Germany, report 11-2908). As the trial was conducted with 3 applications and with the maximum dose rate of 0.096 kg a.s./ha it is considered to cover the cGAP with 2 applications and the dose rate of 0.072 kg a.s./ha.

$S = (DFR_M \times TC \times WR \times P)/BW \times DA$

$= (0.258\ \mu g/cm^2 \times 1100\ cm^2/h \times 2\ h \times 1)/60\ kg \times 14\%$

$= 0.0013$ mg/kg bw/day

= 7% of AOEL

Re-entry exposure directly after application is 7% of the AOEL.

2. DFR_M is taken from trials conducted in potato (Germany, report 11-2900). As the trial was conducted with 3 applications and with the maximum dose rate of 0.120 kg a.s./ha it is considered to cover the cGAP with 2 applications and the dose rate of 0.072 kg a.s./ha.

$S = (DFR_M \times TC \times WR \times P)/BW \times DA$

$= (0.338\ \mu g/cm^2 \times 1100\ cm^2/h \times 2\ h \times 1)/60\ kg \times 14\%$

$= 0.0017$ mg/kg bw/day

$= 9\%$ of AOEL

Re-entry exposure directly after application is 9% of the AOEL.

3. DFR_M is taken from trials conducted in potato (France, report 11-2906). As the trial was conducted with 3 applications and with the maximum dose rate of 0.096 kg a.s./ha it is considered to cover the cGAP with 2 applications and the dose rate of 0.072 kg a.s./ha.

$S = (DFR_M \times TC \times WR \times P)/BW \times DA$

$= (0.225\ \mu g/cm^2 \times 1100\ cm^2/h \times 2\ h \times 1)/60\ kg \times 14\%$

$= 0.0012$ mg/kg bw/day

$= 6\%$ of AOEL

Re-entry exposure directly after application is 6% of the AOEL.

Summary of DFR studies

Thiacloprid dislodgeable foliar residues were determined in three studies following foliar spray treatment in the field in bean (Germany) and potato (Germany and France). Summaries of the studies are presented in the following.

DFR study kidney bean (Germany):

Report:	[redacted]; [redacted]; [redacted]; 2012; M-433739-01-1
Title:	Determination of the dislodgeable foliar residues (DFR) of thiacloprid in/on kidney bean after spraying of thiacloprid OD 240 in the field in Germany
Report No.:	01.11.2908
Document No.:	M-433739-01-1
Guidelines:	**US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a)); not specified**
GLP/GEP:	**yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on kidney bean leaf foliage in northern Europe after three spraying applications with

Thiacloprid OD 240. The study included one supervised residue trial conducted in the field in Germany during the 2011 season.

Table 7.2.3.1-3: Application parameters

Country	Application				
	Type	No	Growth stage (BBCH)	Interval (days)	Rate (kg a.s./ha)
Germany	Spraying	3	61-65	7	0.096

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co; El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-4: Amounts of dislodgeable foliar residues of thiacloprid on kidney bean leaves in Germany [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT[#]	Sampling interval (DAT)	Thiacloprid DFR (µg/cm²)
-0	0	< 0.01
0	**0**	**0.258**
1	1	0.135
3	3	< 0.01
7	7	< 0.01
7	**0**	**0.223**
8	1	0.012
10	3	< 0.01
14	7	< 0.01
14	**0**	**0.219**
15	1	0.101

~~17~~	~~3~~	~~< 0.01~~
~~21~~	~~7~~	~~< 0.01~~
~~24~~	~~10~~	~~< 0.01~~

~~#:DAFT: day after first treatment; DAT: day after treatment~~

~~A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 1.2 days (see Appendix).~~

~~III Conclusion~~

~~The maximum DFR value is 0.258 µg/cm² observed at day 0 after the 1st application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3 onwards after each single application. Residues decline with a DT_{50} of 1.2 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.~~

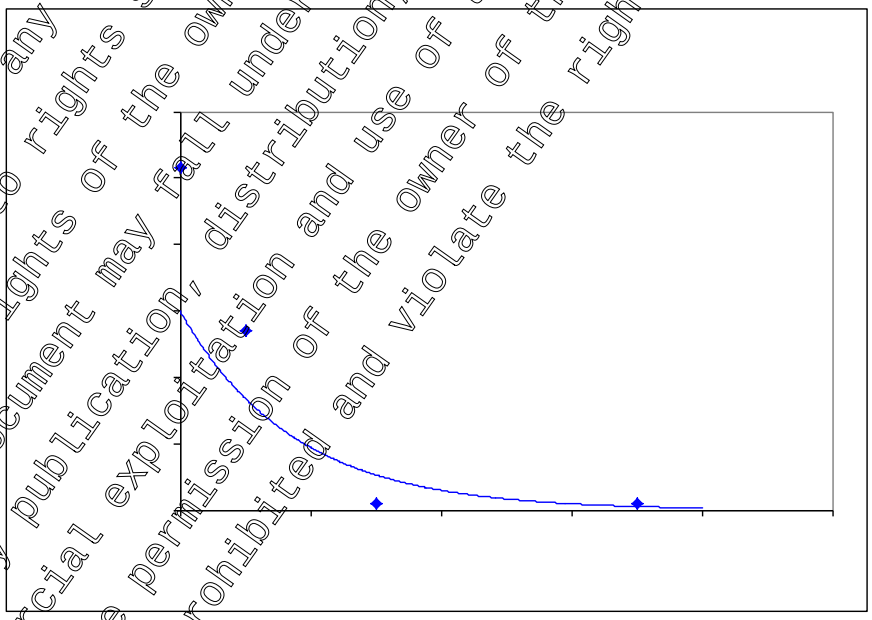
~~Appendix~~

Thiacloprid, DFR on kidney bean, Germany, 2011

Report: 11-2908

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.258
1	0.135
3	0.005
7	0.005



$$C = C_0 \times e^{-k t} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}} t}$$

C_0	0.149648564
k	0.577822578
$t_{1/2}$	**1.199584798**
R^2	0.72108961

DT_{50}(days):	1.2

~~DFR study potato (Germany):~~

Report:	[redacted]$;[redacted];[redacted]; 2012; M-433623-01-1
Title:	Determination of the dislodgeable foliar residues (DFR) of thiacloprid in/on potato after spraying of thiacloprid OD 240 in the field in Germany
Report No.:	01.11.2900
Document No.:	M-433623-01-1
Guidelines:	**US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a)); not specified**
GLP/GEP:	**yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on potato leaf foliage in northern Europe after three spraying applications with thiacloprid OD 240. The study included one supervised residue trial conducted in the field in Germany during the 2011 season.

Table 7.2.3.1-5: Application parameters

Country	Application				
	Type	No	Growth stage (BBCH)	Interval (days)	Rate (kg a.s./ha)
Germany	Spraying	3	71-81	10	0.120

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co, El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-6: Amounts of dislodgeable foliar residues of thiacloprid on potato leaves in Germany [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT[#]	Sampling interval (DAT)	Thiacloprid DFR (µg/cm^2)
-0	-0	< 0.01

0	**0**	**0.338**
1	1	0.028
3	3	0.011
7	7	< 0.01
10	10	< 0.01
10	**0**	**0.308**
11	1	< 0.01
13	3	< 0.01
17	7	< 0.01
20	10	< 0.01
20	**0**	**0.279**
21	1	0.011
23	3	< 0.01
27	7	< 0.01
30	10	< 0.01
34	14	< 0.01
41	21	< 0.01

#: DAFT: day after first treatment; DAT: day after treatment

A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 2.0 days (see Appendix).

III Conclusion

The maximum DFR value is 0.338 µg/cm² observed at day 0 after the 1st application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3-7 onwards after each single application. Residues decline with a DT_{50} of 2.0 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.

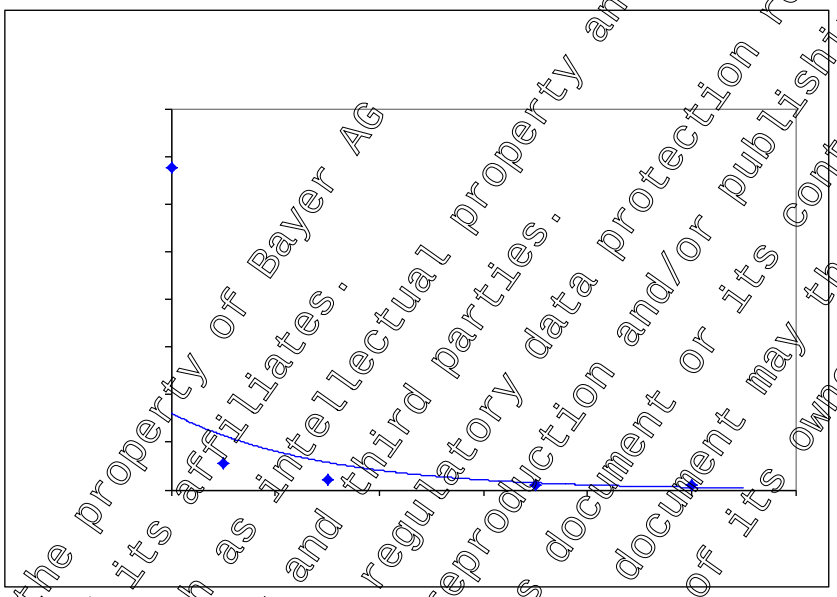
Appendix

Thiacloprid, DFR on potato foliage, Germany, 2011

Report: 11-2900

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.338
1	0.028
3	0.011
7	0.005
10	0.005



$$C = C_0 \times e^{-k\,t} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}}t}$$

C_0	0.080430751
k	0.341188637
$t_{1/2}$	**2.031565844**
R^2	0.670097702

DT_{50}(days):	2.0

~~DFR study potato (France):~~

~~**Report:**~~ [redacted]; 2012; M-433626-01-1
~~Title:~~ ~~Determination of the dislodgeable foliar residues (DFR) of thiacloprid on potato after spraying of YRC 2894 SC480 in the field in France (South)~~
~~Report No.:~~ ~~01-FR-2906~~
~~Document No.:~~ ~~M-433626-01-1~~
~~**Guidelines:**~~ ~~**US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1(a)); not specified**~~
~~**GLP/GEP:**~~ ~~**yes**~~

~~I Material and methods~~

~~The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on potato leaf foliage in southern Europe after three spraying applications with thiacloprid SC 480. The study included one supervised residue trial conducted in the field in France during the 2011 season.~~

Table 7.2.3.1-7: Application parameters

Country	Application				
	Type	No	Growth stage (BBCH)	Interval (days)	Rate (kg a.s./ha)
Germany	Spraying	3	24 - 38	14	0.096

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co, El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-8: Amounts of dislodgeable foliar residues of thiacloprid on potato leaves in France [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT#	Sampling interval (DAT)	Thiacloprid DFR (µg/cm²)
-0	0	<0.01
0	**0**	**0.196**
1	1	0.140
3	3	<0.01
7	7	<0.01
14	14	<0.01
14	**0**	**0.225**
15	1	0.177
17	3	<0.01
21	7	<0.01
24	10	<0.01
28	**0**	**0.225**

29	1	0.204
31	3	0.039
35	7	0.01*
42	14	< 0.01
49	21	< 0.01

#:DAFT: day after first treatment; DAT: day after treatment
* average result set to 0.010 µg/cm² as worst case due to residues of 0.01 µg/cm² on sub-plot 1, sub-plot 2+3 were < 0.01 µg/cm²

A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 3.7 days (see Appendix).

III Conclusion

The maximum DFR value is 0.225 µg/cm² observed at day 0 after the 3rd application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3-7 onwards after each single application. Residues decline with a DT_{50} of 3.7 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.

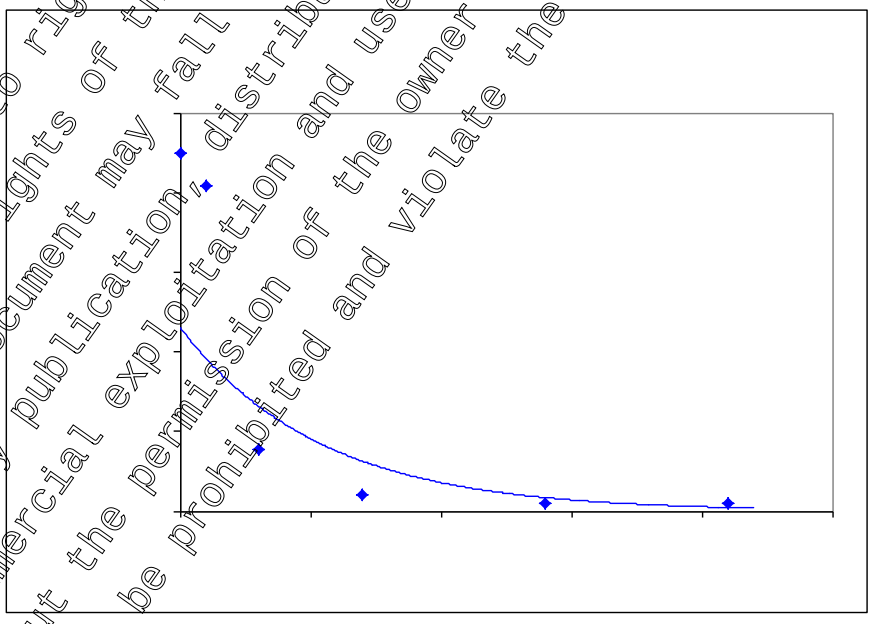
Appendix

Thiacloprid, DFR on potato foliage, France 2011

Report: 11-2906

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.225
1	0.204
3	0.039
7	0.01
14	0.005
21	0.005



$C = C_0 \times e^{-k t} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}} t}$

C_0	0.115357862
k	0.186282433
$t_{1/2}$	3.720947655
R^2	0.774075866

DT_{50}(days):	3.7

~~CP 7.2.3.2 Measurement of worker exposure~~

~~Since the exposure estimate carried out indicated that the AOEL will not be exceeded under practical conditions of use, a study to provide a measure of worker exposure was not necessary and was therefore not carried out.~~

CP 7.2 Data on exposure

BCS has submitted a dossier for the re-approval of Thiacloprid as requested according to the EU Regulation 1107/2009. Because Thiacloprid was classified after dossier submission by the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) among others with Repro. 1B; H360FD for effects on fertility and developmental toxicity, an accompanying dossier is submitted to obtain re-approval based on point 3.6.4 of annex II of Regulation 1107/2009.

This document provides information that the non-dietary exposure of humans to the active substance thiacloprid in the plant protection product formulated as FS 400, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans. A guidance document on negligible non-dietary exposure has not been finalized yet. This document refers to the (draft) EU Commission guidance version of November 2015[5].

According to this guidance two aspects are considered:

- Available risk mitigation measures will be considered for all relevant routes of exposure and will be applied for the proposed uses of the product, with the aim to minimize exposure of humans to the active substance as much as technically possible;
- A decision making framework is proposed which includes risk calculations and consideration of exposure studies in order to verify if the scenarios of use proposed are leading to negligible exposure.

Mitigation measures are evaluated to achieve the lowest possible exposure of operators, bystanders/residents and workers during handling the 240 OD formulation or as a consequence of its use. In the following, use scenarios are identified in which exposure is reduced ensuring the least possible contact between human beings and the plant protection product (PPP).

The representative use of Thiacloprid 240 OD is the spray application in oilseed rape. A summary of the use conditions is presented in the following table.

Table 7.2-1: Critical GAP determined by the application parameters

Crop	Application method	Formulation	Growth stage (BBCH)	No. of appl.	Interval (days)	Max. dose rate (kg a.s./ha)	Water volume (L/ha)
Oilseed rape	Field crop sprayer	240 OD	30-59	1-2	10	0.072	100-300

[5] Brussels, XXX, SANCO-2014-12096, […](2015) XXX draft, Commission Notice, Technical guidance on points 3.6.3. to 3.6.5 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the demonstration of negligible exposure to an active substance in a plant protection product under realistic conditions of use, REVISED DRAFT - November 2015

In order to minimize exposure of operators, bystanders, residents and workers as much as possible the following engineering control measures and safety recommendations are proposed:

Operators:

	Mixing/loading:	closed system transfer and use of appropriate PPE
		Points 3.6.3 / 3.6.4 / 3.6.5 (human exposure) of Annex II of Regulation (EC) No 1107/2009 state that as a pre-requisite the product is used in closed systems or in other conditions excluding contact with humans. From a technical point of view, it is not possible to define absolutely closed systems. A 'closed system' may only relate to a certain phase in the life of a PPP (e.g. a system may be 'closed' during mixing and loading but not during application).
	Application:	drift reducing nozzles and use of appropriate PPE
Bystander/resident:		drift reducing nozzles, buffer zone
Workers:		restricted re-entry interval/waiting periods and use of appropriate PPE

Decisions on negligible exposure are considered to imply risk calculations and consideration of exposure studies performed under the conditions of the proposed scenario of use.

One possibility to demonstrate a quantifiable level for negligible exposure is to apply an additional and protective "threshold" or safety factor to the relevant toxicological reference value (AOEL) establishing an exposure level which is far below the level which is of no risk even for the most vulnerable groups. The level of the additional safety margin has been proposed - under the advisory procedure described in Article 4 of Regulation (EU) No 182/2011 – to be 10.

In a 1st tier, risk assessments including effects of additional engineering control measures on exposure are therefore presented as % of AOEL and the additional safety margins achieved.

In a 2nd tier, the risk margins to the specific hazards relevant for the classification of thiacloprid under Regulation (EC) No 1272/2008 are considered for decision making. These margins are often higher than the standard factor of 100 when comparing the NOAEL from the study critical for classification for carcinogenicity or reproduction toxicity (fertility or development) and the toxicological reference value (AOEL) set under Regulation (EC). The comparison with the specific hazard AOEL provides an additional Margin of Exposure - and therefore a higher level of safety - beyond the threshold already considered as safe. For the purpose of demonstrating negligible exposure, a safety margin i.e. MoE of at least 1000 is considered sufficient. The risk assessment is therefore presented for both alternative approaches.

Relevant toxicological reference values:

Established AOEL

The Review Report for thiacloprid (SANCO/ 4347/2000- Final, 13 May 2004) is considered to provide the relevant scientific information for the review of the product. An AOEL of 0.02 mg/kg bw/d was established from the rabbit developmental study (maternal toxicity) and a SF of 100.

Hazard specific AOELs

Negligible exposure has to be shown for thiacloprid and due to its recent classification by ECHA RAC as a Cat. 1B reproductive toxin based on effects on fertility and developmental toxicity in animal studies.

For the adverse effects of thiacloprid on fertility and developmental toxicity, which were the basis for this classification, hazard specific AOELs can be derived. This was done by review of the whole toxicological data base on thiacloprid and identification of the overall NOAEL for each respective finding. The respective hazard specific AOEL was then calculated by division of the overall NOAEL of the specific finding with an additional safety factor of 100.

The calculation of benchmark doses was not considered to be possible for the respective effects. This was due to missing dose response (dystocia, increased incidences of stillbirth at lower doses) or the fact, that clear effects in the study were only observed at one dose level (reduced pup weights, increased incidences of post-implantation loss, stillbirth and cannibalized pups). Therefore, the hazard specific AOELs were derived from the lowest NOAEL of the respective effect in the available studies.

The respective hazard specific AOELs for the adverse effects on fertility and developmental toxicity (as discussed during the RAC discussions) are presented in Table 7.2-2 below.

It can be seen that even the lowest hazard specific AOEL of 0.1 mg/kg bw/day is higher than the systemic AOEL of 0.02 m/kg bw/day in the EU.

Table 7.2-2: Overview on hazard specific AOELs for thiacloprid and their derivation

Hazard / specific endpoint	**Overall LOAEL [mg/kg bw/day]**	**Overall NOAEL [mg/kg bw/day]**	**Hazard specific AOEL (safety factor: 100) [mg/kg bw/day]**
Fertility (for details see Appendix II)			
Dystocia, rat	22	20	0.2
Developmental Toxicity (for details see Appendix II)			
Reduced pup weights (observed on day 4 and 7, resp.)	43	20	0.2
Increased incidences of post- implantation loss	45	10	0.1
Increased incidences of stillbirths	35	17.5	0.18
Increased incidences of cannibalized and missing pups	43	22	0.2

<u>AAOEL</u>

The EFSA guidance[6] on assessment of operator, worker, bystander and resident exposure has proposed a number of changes to current practice in assessing exposure to pesticides. These changes include the introduction of acute risk assessments for pesticides which are acutely toxic by means of establishing an AAOEL value (Acute Acceptable Operator Exposure Level) - a term used to describe a reference value against which acute non-dietary exposures i.e. those that might be incurred in a single day could be assessed.

[6] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Following the noting at the Standing Committee meeting in May, the Commission has published a guidance[7] relating to the implementation of EFSA's non-dietary exposure guidance document. This guidance notes that the derivation of acute acceptable operator exposure values (AAOELs) is unresolved and pending development of a harmonized approach to the setting of an Acute Acceptable Operator Exposure Level (AAOEL) applicants are not required to undertake acute non-dietary exposure assessments.

However, a new draft guidance is available from the EU Commission[8] that refers to formal derivation of an AAOEL by using the ARfD as a surrogate. Acute exposure is therefore calculated and estimates are compared with the ARfD of 0.03 mg/kg bw which is proposed based on the acute neuroxicity study.

The EFSA guidance does not contain suitable information to estimate acute worker exposure. Acute risk assessment is therefore performed only for the operator and the bystander and worker risk assessment only considers the AOEL.

Dermal absorption:

Dermal absorption of thiacloprid in the representative formulation was evaluated *in vitro* using the representative 240 OD formulation and human skin. The *in vitro* study indicated that the mean percentage of $[^{14}C]$-thiacloprid considered to be absorbable over a period of 24 hours was

- 0.2% for the neat formulation (240 g a.s./L)
- 6% for the intermediate spray dilution (0.74 g a.s./L) and
- 14% for the low spray dilution (0.1 g/L).

The use of 0.072 kg a.s./ha in 100 L results in a spray concentration of 0.72 g a.s./L for which a dermal absorption of 6% is appropriate to be used[9]. The use of 0.072 kg a.s./ha in 300 L results in a spray concentration of 0.24 g a.s./L for which a dermal absorption of 14% is appropriate to be used. The latter proposed for use in risk assessments (for details see CP 7.3) to cover all situations.

[7] European Commission, Commission Guidance Document, SANTE-10832-2015, Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, 29 May 2015.

[8] European Commission, Commission Guidance Document, SANTE-10832-2015 rev. 1.1, Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products, Xxxx2016,

[9] Although the concentration of 0.72 g a.s./L is slightly lower than the intermediate concentration in the dermal absorption study (0.74 g a.s./L) the value of 6% established from the latter may be chosen for the risk assessment. This is done because the deviation of the a.s. concentration in the dilution differs for a factor of <2 and a transmissibility of the results can be assumed. In the present case the tested dilution is 1:324 (0.74 g a.s./L) compared to the dilution under evaluation of 1:333 (0.72 g a.s./L)). This approach is based on the EU guideline (SANCO/12638/2001) for the evaluation of significant changes of the chemical composition of plant protection products. Changes of ± 100 % for concentrations ≤ 0.5% are acceptable according to the guideline.

CP 7.2.1 Operator exposure

The EFSA guidance on non-dietary exposure (EFSA model)[10] is used for the exposure assessment in this dossier as it allows for a harmonised risk assessment. Details of model calculations are presented in Appendix 1.

An experimental operator exposure study has additionally been conducted to provide exposure data when using a closed transfer system during mixing/loading. Data are taken for a higher tier assessment and replace the modelling approach where appropriate. A default body weight of 60 kg/person is assumed for all calculations. A water volume of 300 L/ha is assumed resulting in a worst case (14% dermal absorption).

The measures taken to reduce exposure of operators to the active substance as much as technically possible consider the relevant routes of exposure.

Exposure of operators to thiacloprid in the 240 OD formulation is evaluated for the following work activities and mitigation options:

- During mixing/loading: closed system transfer equipment

  Specific engineering control measures such as closed transfer system during mixing/loading are not included in the EFSA model due to lacking public data. Therefore, an exposure study has been conducted with operators using closed transfer system equipment. The study is used for the risk assessment.

- During application: drift reducing nozzles

  The EFSA model provides an exposure scenario for drift reduction nozzles during spray applications in arable crops. The risk assessment is performed using this exposure mitigation option.

Summary

In a 1st tier, the level of exposure resulting from the critical GAP (300 L/ha spray volume) is compared with the toxicological reference value (AOEL) and an additional safety margin of 10 (Table 7.2.1-1).

In a 2nd tier, the Margin of Exposure to the study which is critical for the relevant classification under Regulation (EC) No 1272/2008 is calculated (Table 7.2.1-2).

A summary of the risk assessment is presented below.

Table 7.2.1-1: Assessment of negligible exposure using the toxicological reference values (AOEL/AAOEL) and additional safety margin of 10

Crop (method)	**Source** (experimental study / model)	**Systemic exposure**∞ [mg/kg bw/day]		**% of AOEL** (0.02 mg/kg bw/day) / **MoE**[1]	**% of AAOEL** (0.03 mg/kg bw/day) / **MoE**[1]	**Add. Margin of Exposure ≥10?**
		Longer-term	**Acute**			

[10] EFSA (European Food Safety Authority), 2014. Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874, 55 pp., doi:10.2903/j.efsa.2014.3874

Oilseed rape (spray application)	Mixing/loading: Closed transfer system, work wear, no gloves (source: exposure study, M-521971-01-1, easyFlow system)	8.3×10^{-10}	8.3×10^{-10}			
	Application: Drift reduction nozzle, with PPE[2] (source: EFSA calculator)	0.000056	0.000206			
	Total	0.000056	0.000206	0.3% 35714	0.7% 14563	Yes

∞ 60 kg person, dermal absorption of 0.2% (concentrate) and 14% (300 L/ha spray), 100% absorption *via* inhalation route
[1] Margin of Exposure (MoE): NOAEL/exposure; $NOAEL_{longer-term}$ = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity); $NOAEL_{acute}$ = 3 mg/kg bw/day based neurotoxicity study
[2] With PPE: Working coverall and protective gloves during application

The risk calculations for negligible exposure include mitigation measures for the relevant routes of exposure. Longer-term systemic exposure of operators is 0.000056 mg/kg bw/day. This estimate equates to 0.3% of the AOEL and MoE of 35714. Acute systemic exposure of operators is 0.000206 mg/kg bw/day. This estimate equates to 0.7% of the AOEL and MoE of 14563.

Table 7.2.1-2: Margin of exposure to the study which is critical for the relevant classification of thiacloprid under Regulation (EC) 1272/2008*

Exposure scenario	**Exposure mitigation**	**Systemic exposure**∞ longer-term (acute) [mg/kg bw/day]	**Hazard specific overall NOAEL (hazard/specific endpoint)** [mg/kg bw/day]	**Margin of Exposure**° longer-term (acute)
Spray application (oilseed rape)	Mixing/loading: Closed transfer system, no PPE (source: exposure study, M-521971-01-1, easyFlow system) Application (incl. cleaning): Drift reduction nozzle, with PPE[1] (source: EFSA calculator)	0.000056 (0.000206)	Fertility: 20 (dystocia, rat)	357143 (97087)
			Developmental toxicity:	
			10 (increase in post implantation loss)	178571 (48544)
			17.5 (increase in stillbirths)	312500 (84951)
			22 (increase in cannibalized & missing pups)	392857 (106796)
			20 (reduced pup weights)	357143 (97087)

∞ 60 kg person, dermal absorption of 0.2% (concentrate) and 14% (300 L/ha spray), 100% absorption *via* inhalation route
° Margin of Exposure = hazard specific NOAEL/systemic exposure
[1] With PPE: Coverall, protective gloves during mixing/loading and application

The evidence of negligible exposure using the critical effect NOAEL for the risk assessment is shown with the high margins of exposure. The risk assessment demonstrates that the toxicological reference values are orders of magnitude of 5-6 higher than the experimentally determined systemic exposures.

Conclusion

The term 'negligible exposure' is not finally defined by the EU Member States/Commission. A proposal is made to demonstrate negligible exposure to the active substance thiacloprid in the plant protection product Thiacloprid OD 240 under realistic and practical conditions of use involving professional risk mitigation measures.

The results demonstrate that exposure is far beyond the threshold already considered as safe (additional safety factor >>10 to the AOEL). Margins of Exposure of 5-6 orders of magnitude – and therefore a higher level of safety – exist considering the threshold values for the specific hazards relevant for the classification of thiacloprid.

The applicant therefore considers that exposure of operators to thiacloprid can be mitigated to negligibly low levels under realistic conditions of use.

CP 7.2.1.1 Estimation of operator exposure

Operator exposure estimates are performed using the EFSA model for the application using vehicle-mounted/trailed downward spray equipment (boom). Detailed calculations are presented in Appendix 1, Table A1/A2.

The database of arable crop spraying in the EFSA model contains data with open and closed cabs but no data for EN 15695 certified closed cabs. Prior to proof of additional quantification of mitigation in future exposure studies the certified cabs type 3 or 4 are considered here only as an option to replace assigned PPE during the operator's stay in the closed cabin. As the EFSA model already demonstrates a very low exposure when using drift reduction nozzles during application the additional exposure mitigation via certified closed cabins was not measured in an additional operator exposure study.

The database in the EFSA model contains exposure data for the cleaning of the equipment. Exposure during cleaning was measured in operator exposure studies which are included in the Agricultural Operator Exposure Model (AOEM)[11] that constitutes the operator part in the EFSA model. The AOEM database contains monitoring data of applicators who cleaned the spray equipment as part of the exposure study. When cleaning was performed it was usually not monitored separately but included in the application task. In some studies separate hand exposure values for cleaning were recorded. However, as cleaning was assumed to be part of the application task, hand exposure from both cleaning as well as application was combined in the model as total hand exposure during application. Cleaning of the equipment was included in less than half of the trials. Of all the 344 replicates monitored during application 144 replicates performed a cleaning. 97 replicates were monitored during Low Crop Tractor Mounted (LCTM) application of which 43 performed a cleaning. The contribution of the cleaning exposure was analysed by the AOEM working group for modelling purpose. The statistical analysis revealed that cleaning was not a major factor for exposure. The total hand exposure of operators was similar regardless of whether a cleaning operation was conducted or not. Therefore, cleaning was not considered further as a modelling factor.

[11] Großkopf et al. (2013): Joint development of a new Agricultural Operator Exposure Model, Project Report, Federal Institute for Risk Assessment, Berlin 2013 (BfR-Wissenschaft 07/2013). M-525532-01-1

The operator model of the AOEM was transferred into the EFSA guidance on the assessment of exposure of operators. Since the exposure evaluation in this document is performed using the EFSA calculator the exposure during cleaning is included in this assessment as part of the application data.

Exposure is calculated for an operator wearing work wear (cotton/polyester 35%/65%) and chemical resistant gloves (nitrile type). Calculations include spray equipment with drift reduction nozzle.

Detailed exposure calculations are presented in Annex I, Table A1.

Assuming a 60 kg person and dermal absorption of 0.2% for the product and 14% for the diluted spray (300 L/ha) the following exposures are calculated:

Table 7.2.2.1-1: Operator exposure as a proportion of AOEL and AAOEL

	Systemic exposure (mg/kg bw/day)	
	Longer-term	Acute
Mixing/loading	0.000102	0.000569
Application	0.000056	0.000206
Total	**0.000158**	**0.000775**

Total systemic longer-term exposure is 0.000158 mg/kg bw/day. This corresponds to 0.8% of AOEL. Total systemic acute exposure is 0.000775 mg/kg bw/day. This corresponds to 3% of AAOEL.

CP 7.2.1.2 Measurement of operator exposure

Although an exposure lower than 10% of the AOEL/AAOEL can be demonstrated with the EFSA model, reduction of operator exposure can be achieved by using a closed transfer system (easyFlow) during mixing/loading. A description of the application method is provided in chapter 'Method of application (KCP 3.5); 1.3 Closed transfer system / easyFlow'.
Exposure during mixing/loading was measured in an operator exposure study using the easyFlow closed transfer system. The objective of this study was to establish generic hand exposure data when the closed transfer system easyFlow is used. The study was conducted under GLP by Bayer CropScience in Germany.

A summary of the study design and the results is briefly presented below:

Report:	[redacted]q;[redacted];2015;M-521971-01
Title:	Measurement of hand exposure when loading a product using the closed transfer system easyFlow
Report No:	SA15019
Document No:	M-521971-01-1
Guidelines:	**O.E.C.D. Series on testing and Assessment N° 9, Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application (2002).;not specified**
GLP/GEP:	**yes**

Material and method

The study took place at the Bayer CropScience AG's headquarter in D-40789 Monheim am Rhein, Alfred-Nobel-Str. 50, Germany in the Application Technology Unit building (building 5910) on the 4th of February 2015.

The easyFlow system consists of two adapters, one is fixed to the tank and the other one is fixed to the product container.
The study was performed using a dye tracer (Brilliant Blue G) formulated in a liquid formulation consisting of 83% w/w Glycerin, 0.5% w/w Brilliant Blue G and 16.5% w/w water (Batch No 2014-014269). This formulation was provided in 5 L canisters. The concentration of the dye in the formulation was 0.5% which gave a dark blue colour to the formulation.

Five operators (two Bayer employees and three farmers) were involved in the study. Only one Bayer employee had worked with the easyFlow closed transfer system before.

As it was not possible to cover the quantity of product used for all plant protection products, the exposure was measured for the complete loading of one container, which is called in the following one operation.

During one operation the operators performed the following tasks: loading of one five litre canister, cleaning of the canister and the easyFlow system and exchange of the easyFlow adapter on a new canister. Briefly, the operator opened the canister, screwed the adapter on it and performed the loading of the product. When the canister was completely emptied into the tank, the operator cleaned the canister and the closed transfer system with the flushing water supply line provided with the tank adapter. The operator then removed the canister from the tank, unscrewed the adapter from the canister and placed it on a new one.

Fortification of unexposed gloves with known quantities of Brilliant Blue G were performed during the study and showed that the residues were stable.

Residues of Brilliant Blue G were extracted from samples and quantified using LC/MS/MS detection system.

The Limit Of Quantification (LOQ) was 0.1 µg/sample (one pair of gloves)

The Limit Of Detection (LOD) calculated was 0.05 µg/sample (one pair of gloves)

Findings
The system allows loading the product into the tank and cleaning the canister without contact with the product. The efficacy of the canisters' cleaning is shown on Figure 1.

The formulation of Brilliant Blue G is a dark blue liquid, therefore any contamination with this formulation is very easy to visualize. No blue spots were seen neither on the gloves nor on the system itself or on the surface of the tank and of the canister. The gloves looked dry and clean at the end of the task.

Figure 7.2.1.2-1: Efficacy of the canister cleaning

The residues of Brilliant Blue G on the gloves were found to be all below the LOD (0.05 µg/sample) as presented in the Table below.

Table 7.2.1.2-2: Hand exposure of operators using easyFlow

Operator	LOQ [µg/sample]	Residue of Brilliant Blue G [µg/sample]
OA	0.1	< LOD
OB		< LOD
OC		< LOD
OD		< LOD
OE		< LOD

LOQ = Limit of quantification
LOD = Limit of detection, LOD calculated = 0.05 µg/sample

Conclusion

The study demonstrate that the operator is not in contact with the product during the loading of the product and the cleaning of the canister when using the closed transfer system easyFlow.

As no residues were detected in the study (all samples were < LOD of 0.05 µg/sample) exposure on the hands is practically zero. As a convention in exposure assessment ½ of the detection level is taken for the exposure estimation resulting in hand exposure of 0.025 µg/person x day. Assuming a body weight of 60 kg/person the calculated potential hand exposure is 0.0004166 µg/kg bw/day.

Hand exposure is the main source of contamination during mixing/loading. As no residues were detected in any of the gloves samples additional dermal exposure of other body parts or inhalation exposure is implausible.

Assessment

Potential hand exposure is 0.0004166 µg/kg bw/day (using ½ LOD). Systemic exposure is calculated with dermal absorption of 0.2% for the neat formulation. This results in systemic exposure of 8.3×10^{-10} mg/kg bw/day for an unprotected operator when using the closed transfer system. Protected hands would furthermore reduce the hand exposure. A theoretical calculation for this additional exposure mitigation is considered to be dispensable and is therefore not made. When hand exposure is < LOD a potential for body exposure is considered to be unlikely.

These results show that an operator using the easyFlow system during mixing/loading has no exposure to the product during this phase. The exposure can be described as being negligible.

CP 7.2.2 Bystander and resident exposure

The EFSA guidance on non-dietary exposure (EFSA model) is used for exposure assessment in this dossier as it allows for a harmonised risk assessment. Details of the model calculations are presented in Appendix 1.

An experimental bystander/resident exposure study has been conducted to support the exposure modelling. Also, DFR studies with the representative formulation have been conducted. The experimental studies are taken for a higher tier exposure assessment of bystanders/residents and replace the modelling approach where appropriate. A default body weight of 60 kg/person (adult) and 10 kg/person (child) is assumed for all calculations. A spray volume of 300 L/ha is considered (worst case, dermal absorption 14%).

The measures taken to reduce exposure of bystanders/residents to the active substance as much as technically possible consider the relevant routes of exposure. The following exposure mitigation is considered:

- During application: drift reducing nozzles

Longer-term exposure is calculated for the resident. Acute (short-term) exposure is calculated for the bystander. The exposure values are compared with the established AOEL (0.02 mg/kg bw/day) for the resident risk assessment and with the proposed AAOEL (0.03 mg/kg bw/day) for the bystander risk assessment.

Summary

Alternative approaches are applied to verify that the exposure is negligible. In a 1st tier, the level of exposure resulting from the critical GAP (300 L/ha spray volume) is compared with the toxicological reference valuew (AOEL/AAOEL) and an additional safety margin of 10 (Table 7.2.2-1). In a 2nd tier, the Margin of Exposure to the study which is critical for the relevant classification under Regulation (EC) No 1272/2008 is calculated (Table 7.2.2-2).

A summary of the risk assessment is presented below.

Table 7.2.1-1: Assessment of negligible resident/bystander exposure using the toxicological reference values (AOEL/AAOEL) and additional safety margin of 10

Exposure scenario	**Target group**	**Systemic exposure**∞ [mg/kg bw/day]	**% of AOEL** [0.02 mg/kg bw/day]	**% of AAOEL** [0.03 mg/kg	**MoE**[1]	**Add. Margin of Exposure ≥10?**

					bw/day]		
Oilseed rape (spray appl.)	Resident[2]	Adult	0.000672	3.4	-	2976	Yes
		Child	0.001253	6.3	-	1592	Yes
	Bystander[3]	Adult	0.000807	-	2.7	3717	Yes
		Child	0.001484	-	4.9	2022	Yes

∞ 60 kg person (adult), 10 kg/person (child), dermal absorption of 14% (300 L/ha spray), 100% absorption *via* inhalation, drift reduction nozzle
[1] MoE: NOAEL/exposure; longer-term NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity), acute NOAEL = 0.03 mg/kg bw/day based on neurotoxicity study
[2] All pathways
[3] Worst case single exposure pathway 'entry into treated crops'

The risk calculations for negligible exposure include engineering control measures (drift reduction nozzles). Systemic exposure of adult and child residents during spray application in oilseed rape is 0.0007 mg/kg bw/day and 0.0013 mg/kg bw/day, respectively. These estimates equate to 6.3% and 3.4% of the AOEL and MoE of 2976 and 1592, respectively. Systemic exposure of adult and child bystanders for the worst case single exposure pathway 'entry into treated crops' is 0.0008 mg/kg bw/day and 0.0015 mg/kg bw/day, respectively. These estimates equate to 2.7% and 4.9% of the AAOEL and MoE of 3717 and 2022, respectively. A buffer zone would furthermore reduce the exposure. As exposure is already very low without a buffer zone additional calculations for buffer zones are considered to be dispensable.

Table 7.2.1-2: Margin of exposure to the study which is critical for the relevant classification of thiacloprid under Regulation (EC) 1272/2008*

Exposure scenario	**Target group**		**Systemic exposure**∞ [mg/kg bw/day]	**Hazard specific overall NOAEL (hazard/specific endpoint)** [mg/kg bw/day]	**Margin of Exposure**°
Spray application (oilseed rape)	Resident	Adult	0.000672	Fertility: 20 (dystocia, rat)	29762
				Developmental toxicity:	
				10 (increase in post implantation loss)	14881
				17.5 (increase in stillbirths)	26042
				22 (increase in cannibalized & missing pups)	32738
				20 (reduced pup weights	29762
		Child	0.001253	Fertility: 20 (dystocia, rat)	15962

				Developmental toxicity:	
				10 (increase in post implantation loss)	7980
				17.5 (increase in stillbirths)	13966
				22 (increase in cannibalized & missing pups)	17558
				20 (reduced pup weights	
Spray application (oilseed rape)	Bystander	Adult	0.000807	Fertility: 20 (dystocia, rat)	24783
				Developmental toxicity:	
				10 (increase in post implantation loss)	12391
				17.5 (increase in stillbirths)	21685
				22 (increase in cannibalized & missing pups)	27261
				20 (reduced pup weights	24783
		Child	0.001484	Fertility: 20 (dystocia, rat)	13477
				Developmental toxicity:	
				10 (increase in post implantation loss)	6739
				17.5 (increase in stillbirths)	11792
				22 (increase in cannibalized & missing pups)	14825
				20 (reduced pup weights	13477

∞ 60 kg person, dermal absorption 14% (300 L/ha spray), 100% absorption *via* inhalation route
° Margin of Exposure = hazard specific NOAEL/systemic exposure

Conclusion

The results demonstrate that exposure is far beyond the threshold already considered as safe (additional safety factor >>10 to the AOEL). Margins of Exposure of 4-5 orders of magnitude – and therefore a higher level of safety – exist considering the threshold values for the specific hazards relevant for the classification of thiacloprid.

The applicant therefore considers that exposure of adult and child bystanders to thiacloprid can be mitigated to negligibly low levels under realistic conditions of use.

CP 7.2.2.1 Estimation of bystander and resident exposure

The EFSA guidance on non-dietary exposure is used to estimate the exposure. The exposure is evaluated for a downward spray scenario using drift reduction equipment but without buffer zone.

Four pathways of exposure are considered:

- spray drift (at the time of application)
- vapor (may occur after the PPP has been applied)
- surface deposits
- entry into treated crops

For the resident exposures, 75th percentiles are considered for the single pathways and the total exposure from all pathways is calculated as mean value. For the bystander exposures, 95th percentiles are considered for the single pathways only (no total exposure calculation from single pathways). Exposures are calculated for the use of drift reduction nozzles.

Summaries of the exposure calculations using the EFSA calculator are presented below. Detailed calculations are presented in Appendix 1, Table A2.

Table 7.2.2.1-1: Resident exposure calculation (using the EFSA calculator)

Substance	Thiacloprid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.24 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 0.2	Dermal for in use dilution = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0005	% of RVNAS	2.27%
	Vapour (75th percentile) mg/kg bw/day	0.0011	% of RVNAS	5.35%
	Surface deposits (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	0.92%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0031	% of RVNAS	15.26%
	All pathways (mean) mg/kg bw/day	0.0039	% of RVNAS	19.44%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.54%
	Vapour (75th percentile) mg/kg bw/day	0.0002	% of RVNAS	1.15%
	Surface deposits (75th percentile) mg/kg bw/day	0.0001	% of RVNAS	0.31%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0017	% of RVNAS	8.48%
	All pathways (mean) mg/kg bw/day	0.0017	% of RVNAS	8.39%

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	0.0010	% of RVAAS	3.44%
	Vapour (95th percentile) mg/kg bw/day	0.0011	% of RVAAS	3.57%
	Surface deposits (95th percentile) mg/kg bw/day	0.0005	% of RVAAS	1.79%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.0031	% of RVAAS	10.17%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	0.0003	% of RVAAS	0.93%
	Vapour (95th percentile) mg/kg bw/day	0.0002	% of RVAAS	0.77%
	Surface deposits (95th percentile) mg/kg bw/day	0.0002	% of RVAAS	0.62%
	Entry into treated crops (95th percentile) mg/kg bw/day	0.0017	% of RVAAS	5.65%

The evaluations based on the EFSA calculator results in total child resident exposure of 0.0039 mg/kg bw/day from all pathways (19% of the AOEL) and in a total adult resident exposure of 0.0017 mg/kg bw/day from all pathways (8% of the AOEL).

The EFSA model represents a Tier 1 calculation based on default values. Experimental data from bystander exposure drift study and DFR studies using the OD 240 formulation are available to calculate realistic exposures for all pathways. Data and exposure refinements are presented in the following chapter.

CP 7.2.2.2 Measurement of bystander and resident exposure

This chapter presents experimental data to refine the four exposure pathways

- spray drift (at the time of application)
- vapor (may occur after the PPP has been applied)
- surface deposits
- entry into treated crops

A bystander/resident study has been conducted using the Thiacloprid 240 OD formulation to measure the exposure via spray drift. The data are used to refine the 'Spray drift' scenario as calculated in the EFSA model. The requirements to measure bystander and resident exposure are laid down in Commission Regulation No 284/2013[12]. The study was performed under realistic exposure conditions taking into account the proposed conditions of use. The experimental study is therefore considered to be the best representation of bystander and resident spray drift to thiacloprid using the OD 240 formulation in oilseed rape.

A comparison of application parameters and environmental conditions pertaining to the sets of data in the EFSA model (BREAM studies) and the bystander/resident study performed with the OD 240 formulation is presented in the following table.

Table 7.2.2.2-1: Comparison of bystander spray application details

Parameter	Thiacloprid bystander drift study	BREAM calculator input	Notes

[12] COMMISSION REGULATION (EU) No 284/2013, of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market

	with OD 240		
Test item	Thiacloprid OD 240	Tracer (Brillant Blue)	Formulation effects on drift are not confirmed but product specific data should be used if available to exclude any potential impact from the formulation that is used.
Crop/target	Oilseed rape, BBCH 65	Bare soil / lawn	OD 240 is sprayed on tall oilseed rape (BBCH 65, flowering) but not on bare soil or lawn. The crop has filter effects especially if tall crops are considered.
Nozzle	AI 110-04	FF03110	75% drift reduction nozzle was used in the OD 240 study. Drift was measured. The BREAM data are based on use of conventional flat fan nozzle. At the time of model compilation it was the only dataset available. The EFSA model considers an adjustment for drift reduction by considering 50% as a reliable factor. However, measured data are preferred to calculated data.
Nozzle type	75% drift reduction	Regular	
Number of nozzles	56	48	OD 240 study represents two passes of a 28-m boom collecting all relevant particles of 2 swaths. BREAM study represents single pass of a 24-m boom. It is noted that further upwind passes could possibly contribute additional drift, but the wind conditions would not be identical and the additional contribution from including more upwind nozzles or passes is considered to be relatively small
Crop height	1.4 m	0 – 0.05 m (bare soil or short/cut grass)	Crop height, boom height and boom height above crop under representative conditions (bystander study with OD 240) are relevant for risk assessment. Boom height of 0.7 m above bare soil does not represent the use conditions of the OD 240 formulation in oilseed rape. The optimum height is 0.5 m. Spray drift increases with boom height. The EFSA guidance notes that the model does not yet support estimation of exposure from spraying other crops. Boom heights higher than 0.5 m would create spray overlaps from single nozzles. A double pattern overlap will result when boom height is 0.7 m which should be avoided in practice.
Boom height	1.9 m	0.7 m	
Boom height above crop	0.5m	0.7 m	
Forward speed	9 km/h	12.6 km/h	Good Agricultural Practice enabling a safe drift potential requires a forward speed of maximum 8 km/h because distribution problems increase with speed above this level. The EFSA considered a speed to be the upper end of the current "average" in the UK based on expert opinion (i.e. 3.5 m/s, hence 12.6 km/h). A 2004 UK survey showed that between 15 and 20 % of the area treated by large or self-propelled sprayers was done using average speeds in the range 13–16 km/h
Spray concentration	0.35 g a.s./L spray	1 g a.s./L spray	EFSA model uses 1 g a.s./L to generate unit values which can be adjusted by product-specific values. 0.35 g a.s./L is the representative product-specific value.
Wind speed	2.6 – 4 m	2.7 m/s	2.7 m/s is upper limit of what is considered acceptable for spraying in the UK Code of Practice.

The experimental study is considered to be the best representation of bystander and resident spray drift exposure. The main reasons are:

1. The experimental study is crop specific, while data in the model (EFSA/BREAM) only consider application on bare ground/grassland. Crops have filter effects capable to impact on spray drift.

2. Study is performed with the formulation under evaluation, while the model is based on a tracer in surfactant + water.

3. Experimental data (measurements) achieved with the formulation under evaluation are more relevant than calculated data from modelling. The BREAM model uses an empirical relationship between bystander dermal exposure and airborne spray concentrations. It takes the output from the mechanistic Silsoe spray drift model, which predicts airborne spray, and determines the potential dermal exposure of a resident or bystander standing downwind of the spray application. The empirical data in the model is very variable, and when this is included in a probabilistic model such as BREAM, it determines the variability of the model output, and therefore unrealistic high values of the upper centiles (worst case x worst case assumptions). Analysis of the BREAM model has shown that the calculated exposures at the 95th percentile level do not match with the measured BREAM data as they exceed the measured data by a factor of 5-10.

Additional DFR studies have been conducted with the 240 OD formulation to determine the extent and decline of dislodgeable foliar residues. These data are used to refine the 'Surface deposits' scenario and the 'Entry into treated crops' scenario. For consistency reasons, refinement for the vapor exposure is also presented here based on biocide guidance information.

1 Spray drift

Exposure of adults and children via spray drift was monitored during spray application of Biscaya® 240 OD in oilseed rape ([redacted], 2012). Applications were performed according to the critical GAP. The study was compliant with GLP and carried out within OECD guidelines. The study is considered acceptable in terms of design and validation.

Report:	[redacted]0; [redacted]; 2012; M-439075-01-1
Title:	Exposure of bystanders / residents to thiacloprid from spray applications with Biscaya OD 240 in oilseed rape
Report No.:	MR-11/087
Document No.:	M-439075-01-1
Guidelines:	**OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997** **Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E); not specified**
GLP/GEP:	**yes**

Material and methods

Plant protection product:	Biscaya 240 OD® Oil Dispersion Active substance: thiacloprid (240 g/L)
Field study location:	Germany, [redacted]
Application:	April 2012
Crop:	Oilseed rape

Quantity a.s. applied: 0.3 L/ha (nominal 72 g a.s./ha)
Bystanders: 9 adult and 9 child mannequins

The dermal and inhalation exposure was measured using adult and child mannequins while applying Biscaya® 240 OD and and the tracer Brilliant Blue FCF® (erioglaucine, E 133, a triarylmethane dye food additive) to an oilseed rape field in Germany. The spray applications were performed with a commercial field crop boom sprayer with 28 m boom width. The spray was applied on an even, not sloped and homogeneous oilseed rape field of sufficient size at full flowering growth stage (BBCH 59) in two swaths parallel to the length of the pre-defined spray drift area. Crop canopy reached an average height of 1.4 m. The spray was applied with the boom 0.5 m above canopy height. Biscaya® 240 OD was applied with the label specific rate of 0.3 L/ha (nominal 72 g a.s./ha thiacloprid) using a TeeJet AI 11004 nozzle. This nozzle is classified in Germany as a 75% drift reducing air injection nozzle. Brilliant Blue FCF® was applied in parallel under the same climatic conditions but using standard nozzles (TeeJet XR 110 04). Dose rate was 0.8 kg/ha. A water volume of 200 L/ha was applied in both scenarios.

Spray applications with Biscaya 240 OD and Brilliant Blue FCF were performed under identical conditions using the same tractor and sprayer at the same field plot and the same day under comparable climatic conditions. The trial design allows the comparison of adult and child exposures from drift using either standard nozzles or drift reduction nozzles at various spray distances.

A total of 18 mannequins representing 9 adult and 9 child bystanders/residents were monitored. The site provided an even, not sloped and homogeneous oilseed rape field of sufficient size at full flowering growth stage (BBCH 65) to perform sequential spray swaths. It allowed to position replicates of mannequins at various distances downwind in order to monitor a range of potential distances where bystanders or residents may be exposed during application.

Fig. 7.2.2.2-1: Mannequin positioning in bystander/resident exposure study

The dermal exposure was determined with whole-body dosimeters. Each mannequin wore dosimeters consisting of a short-sleeved T-shirt and shorts above long underwear (long johns and shirt) and a ski mask covering the head. The long sleeves of the shirts were worn to also cover the hand. An additional hand dosimeter was therefore not included. This clothing scheme allowed the determination of potential dermal exposure representing a person with virtually no clothing as well as actual dermal exposure representing a lightly dressed person wearing only little clothing. Inhalation exposure was determined by the use of a personal air sampling pump connected to an IOM-sampler with glass fibre filter, located in the virtual breathing zone of the adult and child dummy.

Results

Results are summarized in the following tables.

Table 7.2.2.2-2: Residues on outer dosimeters (shorts and short sleeved T-shirt)

Distance	Adult Sample ID	Residues (µg/sample)*		Child Sample ID	Residues (µg/sample)*	
		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)
3 m	A1	0.784	358	a1	0.190	101
	A2	0.809	332	a2	0.509	78.0
	A3	1.069	80	a3	0.206	31.2
8 m	B1	0.350	173	b1	0.292	27.4
	B2	0.741	37.8	b2	0.281	7.16
	B3	0.372	19.8	b3	0.055	8.23

13 m	C1	0.265	35.2	c1	0.195	23.0
	C2	0.248	33.3	c2	0.042	4.00
	C3	0.222	8.50	c3	0.053	3.38

* corrected for field recovery

Table 7.2.2.2-3: Residues on inner dosimeters (long johns + long sleeved T-shirt) and ski mask

Distance	Adult Sample ID	Residues (µg/sample)*		Child Sample ID	Residues (µg/sample)*	
		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)
3 m	A1	0.853	356	a1	0.869	99.3
	A2	1.05	521	a2	0.944	260
	A3	1.697	40.3	a3	1.450	37.2
8 m	B1	1.11	167	b1	0.781	66.0
	B2	1.20	26.3	b2	1.16	22.8
	B3	1.11	20.2	b3	0.494	14.0
13 m	C1	0.220	27.4	c1	0.366	18.4
	C2	0.803	21.6	c2	0.230	9.58
	C3	0.975	13.0	c3	0.706	10.2

* corrected for field recovery

Table 7.2.2.2-4: Residues on IOM-filters (pump flow rate: 2 L/min)

Distance	Adult Sample ID	Residues (µg/filter)		Child Sample ID	Residues (µg/filter)	
		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)		Thiacloprid (drift reduction nozzle)	Erioglaucine (standard nozzle)
3 m	A1	0.00163	0.209	a1	0.00142	0.102
	A2	0.00147	0.071	a2	0.00133	0.339
	A3	0.00256	0.147	a3	0.00274	0.210
8 m	B1	0.00185	0.210	b1	0.00138	0.0605
	B2	0.0005*	0.061	b2	0.00111	0.0855
	B3	0.00125	0.042	b3	0.00100	0.0674
13 m	C1	0.00173	0.077	c1	0.00108	0.0645
	C2	0.0005*	0.110	c2	0.00108	0.0905
	C3	0.0005*	0.033	c3	0.0005*	0.0336

* ½ LOQ

Conclusion

The experimental conditions are representative for typical spray applications of Biscaya® 240 OD in flowering oilseed rape. Spray applications were performed with vehicle trailed spray booms using drift reduction nozzles when applying Thiacloprid (OD 240) and standard nozzles (no drift reduction) when applying the tracer erioglaucin (Brillant Blue). The spray application resulted in exposure of adult and child mannequins wearing outer and inner dermal dosimeters and respiratory filters. Considerable lower residues were observed when drift reduction nozzles were used. The results are considered appropriate to be used for bystander and resident risk assessment.

Refinement of the 'spray drift' scenario (based on measurements):

Potential dermal, actual dermal and inhalation exposure is calculated from residues in/on each dosimeters for both nozzle types. Potential dermal exposure is the sum of residues on outer dosimeters (short sleeved T-shirt and shorts), inner dosimeters (long sleeved T-shirt and long johns) and ski mask. This scenario represents a person not wearing any clothing. Actual exposure is the sum of residues on inner cotton dosimeters and ski mask assuming a person wearing little clothing (T-shirt and shorts).

Inhalation exposure of the resident is calculated by adjusting the residues obtained with the pump flow rate of 2 L/min to a breathing rate of an adult resident of 0.23 m^3/day/kg (9.6 L/min for a 60 person) and a child resident of 1.07 m^3/day/kg (7.4 L/min for a 10 kg child).

Example:

Distance	*Adult Sample ID*	*Residues (µg/filter) Thiacloprid*
3 m	*A1* *A2* *A3*	*0.00163* *0.00147* *0.00256*

0.00163 µg/filter x 9.6 L/min/2 L/min = 0.0078 µg/person
0.00147 µg/filter x 9.6 L/min/2 L/min = 0.0071 µg/person
0.00256 µg/filter x 9.6 L/min/2 L/min = 0.0123 µg/person

= 0.000012 mg/person (95th perc.) or
= 0.000009 mg/person (mean)

Inhalation exposure of the bystander is calculated accordingly by adjusting the residues obtained with the pump flow rate of 2 L/min to a breathing rate of an adult bystander of 0.04 m^3/h/kg (40 L/min for a 60 person) and a child bystander of 0.19 m^3/h/kg (31.7 L/min for a 10 kg child).

Exposure to thiacloprid is calculated for the use of drift reduction nozzle. Values for the drift reducing nozzle are taken directly from the measured thiacloprid residues on the dosimeters.

For the resident, both the 95th percentiles and the mean values are calculated. The 95th percentile values are taken to refine the 'Spray drift' pathway. The mean values are taken to calculate the contribution for 'All pathways'. This approach follows the EFSA guidance on operator, worker and bystander exposure calculations. For the bystander, only the 95th percentiles are calculated.

The systemic exposure is calculated for the 3m distance only (no buffer strip). The following equations are used.

Potential syxtemic exposure: SE = ((PDE x DA) + IE)/BW
Actual systemic exposure: SE = ((ADE x DA) + IE)/BW

Where:

SE	=	*Systemic exposure (mg/kg bw/day)*
PDE	=	*Potential dermal exposure (mg/person)*
ADE	=	*Actual dermal exposure (mg/person)*
DA	=	*dermal absorption (14%, 200 L/ha spray volume used in study)**
IE	=	*Inhalation exposure (mg/person)*
BW	=	*Body weight (60 kg adult, 10 kg child)*

worst case, 6% dermal absorption for 100 L/ha spray volume is not calculated

Table 7.2.2.2-5: Resident exposure to spray drift ; 3m distance, breathing rate: 0.23 m^3/day/kg (adult) and 1.07 m^3/day/kg (child), drift reduction nozzle

	Exposure (mg a.s./person), 95th perc.			
	Adult		Child	
	Drift red. nozzle	Standard nozzle	Drift red. nozzle	Standard nozzle
Potential	0.0027	0.0836	0.0016	0.0323
Actual	0.0016	0.0502	0.0014	0.0243
Inhalation	0.000012	0.000097	0.000010	0.000120
	Systemic exposure* (mg/kg bw/day)			
Potential	0.0000064	0.0001966	0.0000239	0.0004637
Actual	0.0000040	0.0001188	0.0000206	0.0003519
Mean	Exposure (mg a.s./person)			
	Adult		Child	
	Drift red. nozzle	Standard nozzle	Drift red. nozzle	Standard nozzle
Potential	0.0021	0.0560	0.0014	0.0201
Actual	0.0012	0.0304	0.0011	0.0132
Inhalation	0.000009	0.000068	0.000007	0.000080
	Systemic exposure* (mg/kg bw/day)			
Potential	0.0000050	0.0001317	0.0000201	0.0002896
Actual	0.0000030	0.0000721	0.0000159	0.0001921

* 14% dermal absorption, 60 kg adult, 10 kg child,

Table 7.2.2.2-6: Bystander exposure to spray drift (3m distance, breathing rate: 0.04 m^3/h/kg (adult) and 0.19 m^3/day/kg (child), drift reduction nozzle

	Exposure (mg a.s./person), 95th perc.			
	Adult		Child	
	Drift red. nozzle	Standard nozzle	Drift red. nozzle	Standard nozzle
Potential	0.0027	0.0836	0.0016	0.0323
Actual	0.0016	0.0502	0.0014	0.0243
Inhalation	0.000049	0.000403	0.000041	0.000514
	Systemic exposure* (mg/kg bw/day)			
Potential	0.0000071	0.0002017	0.0000270	0.0005031
Actual	0.0000046	0.0001239	0.0000237	0.0003913

* 14% dermal absorption, 60 kg adult, 10 kg child,

The actual systemic exposure values are considered for the exposure assessment of the ‘Spray drift’ scenario. A summary of the exposure via spray drift is presented below.

Resident:

- Adult
  - Spray drift (95th perc.): 0.000004 mg/kg bw/day
  - Spray drift (mean): 0.000003 mg/kg bw/day
- Child
  - Spray drift (95th perc.): 0.000021 mg/kg bw/day

- Spray drift (mean): 0.000016 mg/kg bw/day

Bystander:

- Adult - Spray drift (95th perc.): 0.000005 mg/kg bw/day
- Child - Spray drift (95th perc.): 0.000024 mg/kg bw/day

2 Vapour

Exposure of adults and children via vapor is one driver of exposure when using the EFSA model (5.35% of AOEL for child exposure and 1.15% of AOEL for adult exposure). The vapor exposure in the model is calculated using the indicative exposure of 1 µg/m³ for residues in air adjacent to treated crops. This value is derived from field data of application of the moderately volatile compound parathion applied at high rate in Germany. The vapor pressure of parathion is 5.0 x 10^{-3} Pa at 20°C. The vapor pressure of thiacloprid is seven orders of magnitude lower (3 x 10^{-10} Pa at 20°C for thiacloprid). It is practically non-volatile. Assuming that the level of volatile active substance in the air mainly depends on its vapor pressure it can be assumed that the concentration of thiacloprid in air after application in the field is practically zero.

Refinement of the 'Vapour' scenario:

A refinement of the 'Vapour' scenario is made considering the HEEG guidance on assessment of inhalation exposure of volatilised biocide active substance[13].

The exposure from inhaled vapor can be derived by considering the saturated vapor concentration (SVC) for 24 hours per day, the molecular weight and the vapor pressure. It can be assumed that a person is exposed to the saturated vapor concentration of the active substance for 24 hours a day. This is the worst-case scenario as it is not possible for the air to hold more than the saturated vapor concentration of the active substance at a given ambient temperature and it is not possible for a person to be exposed more than 24 hours per day.

The guidance considers the following parameters for the computations:

Parameter	Symbol	Value	Justification
Gas constant	R	8.31451 J mol^{-1} K^{-1}	Physical constant
Temperature	T	293 K	Assumed room temperature = 20 ºC
Toddler inhalation rate	Ir	8 m^3/24h	The toddler will represent a worst case [this inhalation rate and body weight are in the current HEEG Opinion On Default Human Factors]
Toddler body weight	bw	10 kg	

(a) The saturated vapor concentration (SVC) of an active substance is calculated as follows:

[13] EU-Commission, HEEG Opinion 13, HEEG opinion on Assessment of Inhalation Exposure of Volatilised Biocide Active Substance, Ispra, 12/10/2011.

$$SVC = \frac{mw[g/mol] \times vp[Pa]}{R[J \times mol^{-1} \times T[K]} = 0.41 \times mw \times vp [mg/m^3]$$

(b) The inhalation exposure of an infant, toddler, child and adult over a total of 24 hours can then be calculated as follows:

$$Exposure = SVC[mg/m^3] \times \frac{ir[m^3/24h]}{bw[kg]} = 0.41 \times \frac{mw \times vp \times ir}{bw} [mg/kg\ bw/24h]$$

(c) Comparing exposure to AOEL and substituting the value for the toddler (which represents the worst case) from table above gives

$$\frac{Exposure}{AOEL} = \frac{0.410 \times mw[g/mol] \times vp[Pa] \times ir[m3/24h]}{AOEL[mg/kg] \times bw[kg]} = 0.328 \times \frac{mw \times vp}{AOEL}$$

As a Tier-1 screening tool whether inhalation exposure can be neglected or should be included into the risk assessment, the following screening test is proposed which is based on the toddler representing the worst case.

Let *mw* and *vp* denote the molecular weight (in g/mol) and the vapour pressure (in Pa). For toddler (based on an inhalation rate of 8 m³/24 hr and bw of 10 kg) and using an AOEL in mg a.s./kg bw/d, if

$$0.328 \times \frac{mw \times vp}{AEL_{long\text{-}term}} \leq 1$$

then risk from inhalation exposure for the toddler is negligible, otherwise inhalation exposure should be included in the risk assessment. If the inhalation risk for the toddler is negligible then the inhalation risk for the infant, child and for the adult can also be considered to be negligible.

The molecular weight of thiacloprid is 252.73 g/mol, the vapour pressure is 3 x 10^{-10} Pa at 20ºC. Inhalation exposure of a resident child (toddler) from volatilized thiacloprid is

$$0.328 \times \frac{253 \times (3 \times 10^{-10})}{0.02} = 3.8 \times 10^{-6} \leq 1$$

The test does take into account that an infant and an adult can be exposed for 24 hours in a day. Professionals are included as well. The proposed screening test results in a value ≤ 1, this means, a risk for residents and bystanders from inhalation exposure can be excluded.

3 Surface deposits

The exposure refinement for adult and child residents/bystanders via ‘surface deposits’ is made based on experimental determination of the half-life (DT_{50}) of thiacloprid on leaf foliage. Thiacloprid DT_{50}

was determined in three DFR field studies following foliar spray treatment in bean (Germany) and potato (Germany and France).

Summaries of the studies are presented in the chapter Worker Exposure (KCP 7.2.3).

Applications were performed according to the critical GAP. The studies are compliant with GLP and carried out within OECD guidelines. The studies are considered to be acceptable in terms of design and validation.

A summary of the three experimental studies conducted with thiacloprid is presented in the following table.

Table 7.2.2.2-7: Summary of DFR studies performed with thiacloprid

Crop	Country	Formulation	Study conditions (appl. rate/ no. of appl. in kg a.s./ha)	Max. DFR_M ($\mu g/cm^2$)	Max. DFR_M ($\mu g \cdot cm^2/kg$ a.s. applied/ha)	Observed on	DT_{50} (days)
Bean	Germany	240 OD	0.096 / 3	0.258	2.7	0 days after 1st appl., DAFT 0	1.2
Potato	Germany	240 OD	0.120 / 3	0.338	2.8	0 days after 1st appl., DAFT 0	2.0
Potato	France	SC 480	0.096 / 3	0.225	2.3	0 days after 2nd appl., DAFT 14	3.7

It is noted that the DFR trials were conducted

- with three applications and
- using the maximum dose rate of 0.096 kg a.s./ha in bean (Germany) and potato (France) and 0.120 kg a.s./ha in potato (Germany)

whereas the cGAP under evaluation considers only two applications and 0.072 kg a.s./ha. The DFR values were measured directly after the application (day 0) and 1, 3, 7 and 10 days after the application. The individual study DT_{50} of 1.2, 2.0 and 3.7 days were calculated with a mean of 2.3 days. This indicates fast degradation and explains why no accumulation of residues is found after sequential application and the maximum DFR are found either after the 1st or after the 2nd application.

The mean DT_{50} of 2.3 days is used in the EFSA calculator to refine the 'surface deposits' scenario. The refinement is justified by the specific decline of thiacloprid residues under environmental field conditions.

Refinement of the 'surface deposits' scenario:

The Tier 1 exposure of the 'surface deposits' scenario was calculated in the EFSA calculator assuming a default DT_{50} = 30 days and 2 applications. This results in a Multiple Application Factor (MAF) of 1.79. The refinement is done considering a DT_{50} = 2.3 days and 2 applications. This results in a Multiple Application Factor (MAF) of 1.05 used in the equation. The worst case is calculated

considering a dermal absorption of 14% when using a spray volume of 300 L/ha. The detailed calculation is presented in Appendix 1, Table A3.

Table 7.2.2.2-8: Exposure refinement via 'surface deposits' (DT50 = 2.3 days, MAF = 1.05):

		Systemic exposure [mg/kg bw/day]	
		75th perc.	Mean
Resident	Child	0.0001077	0.0000788
	Adult	0.0000360	0.0000264
		95th perc.	-
Bystander	Child	0.000314	-
	Adult	0.000109	-

4 Entry into treated crops

A refinement for adult and child resident exposure via 'entry into treated crops' is made using experimental DFR data. Thiacloprid dislodgeable foliar residues were determined in three field studies following foliar spray treatment in bean (Germany) and potato (Germany and France).

Summaries of the studies are presented in the chapter Worker Exposure (KCP 7.2.3).

Applications were performed according to the critical GAP. The studies are compliant with GLP and carried out within OECD guidelines. The studies are considered to be acceptable in terms of design and validation.

A summary of the experimental conditions and the results of the three DFR studies conducted with thiacloprid are presented in the following table:

Table 7.2.2.2-9: Summary of DFR studies performed with thiacloprid

Crop	Country	Formulation	Study conditions (no. of appl. / appl. Rate in kg a.s./ha)	Max. *DFR$_M$* (µg/cm²)	Max. *DFR$_M$* (µg/cm²/kg a.s. applied/ha)	Observed on	DT$_{50}$ (days)
Bean	Germany	240 OD	3 / 0.096	0.258	2.7	0 days after 1st appl., DAFT 0	1.2
Potato	Germany	240 OD	3 / 0.120	0.338	2.8	0 days after 1st appl., DAFT 0	2.0
Potato	France	SC 480	3 / 0.096	0.225	2.3	0 days after 2nd appl., DAFT 14	3.7

A justification that the DFR data from these studies can be used for oilseed rape is given by the US-EPA recommendation for choosing relevant crops group for re-entry evaluation[14].

Because of the agricultural diversity of crops and their varieties a method of clustering crops into groups is proposed by EPA that are expected to result in comparable re-entry exposure. It is desirable that DFR studies used for the assessment be representative of the growth form and crop architectures of the registered uses. The US-EPA re-entry evaluation for scouting in rape (canola) is based on DFR and exposure studies (to establish transfer coefficients) performed in peas (dry). This crop is grouped in the crop group ‘Field / row crops, low / medium’ and the cluster ‘Smooth-leaf field crops: scouting in solid stand conditions’. This crop group include inter alia beans (string and dry), soybeans, peas and rape (canola). Potato is also grouped in the a.m. guidance in the cluster ‘Smooth-leaf field crops: but scouting in row conditions.

It is therefore considered that the DFR studies conducted with thiacloprid in beans and potato are appropriate to be used for rape and evaluation of exposure due to entry into treated crops.

It is noted that the DFR trials were conducted

- with three applications and
- using the maximum dose rate of 0.096 kg a.s./ha thiacloprid in bean (Germany) and potato (France) and 0.120 kg a.s./ha in potato (Germany)

whereas the cGAP under evaluation considers only two applications and 0.072 kg a.s./ha. The maximum DFR values were measured on day 0 i.e. directly after the application (0.258 μg/cm^2, 0.338 μg/cm^2 and 0.225 μg/cm^2). The very low DT_{50} of 1.2, 2.0 and 3.7 days (mean: 2.3 days) indicates fast degradation and explains why no accumulation of residues is found after sequential application and the maximum DFR are found either after the 1st or after the 2nd application.

As the dose rates in the DFR studies were higher than the dose rate under evaluation (0.096 kg a.s./ha and 0.120 kg a.s./ha vs. 0.072 kg a.s./ha) the values are normalized to 0.072 kg a.s./ha (no normalization is made for higher number of applications because of the low DT_{50}. Thus, the maximum DFR is 0.1884 μg/cm^2 (mean of 0.1935 μg/cm^2, 0.2028 μg/cm^2 and 0.1688 μg/cm^2) for sequential applications of Thiacloprid 240 OD with a dose rate of 0.072 kg a.s./ha.

These values are used to refine the ‘entry into treated crop’ scenario in the EFSA calculator. The refinement is justified by the specific decline of thiacloprid residues under environmental field conditions.

<u>Refinement of the ‘entry into treated crops’ scenario:</u>

The Tier 1 exposure of the ‘entry into treated crops’ scenario was calculated in the EFSA calculator with defaults for DFR (3 µg/cm^2/kg a.s.) and residue decline (DT_{50} = 30 days). The refinement is done based on the DFR of 0.1884 μg/cm^2. The worst case is calculated considering a dermal absorption of 14% when using a spray volume of 300 L/ha. The calculation is made according to the algorithm presented in the EFSA calculator:

[14] Agricultural Transfer Coefficients, U.S. EPA / Office of Pesticide Programms / Health Effects Division, Science Advisory Council for Exposure (ExpoSAC), Policy Number: 3, March 1, 2012. M-525540-01-1

$$\left[\left[\text{TC entry into treated crops 75}^{th}\text{ perc.-child (cm}^2\text{/hour)} \times \text{Duration (h)} \times \text{Dose rate (kg a.s./ha)} \times \text{DFR (µg/cm}^2\text{)} \times \text{MAF}\right] / 1000 \times \text{Max. dermal absorption (\%)}\right] / \text{Body weight (kg)} =$$

The calculation of the exposure via 'entry into treated crops' is identical for the resident and the bystander. For the resident, the mean exposure is also calculated. This value is used to calculate the exposure from 'all pathways'.

Resident:

Child:	75th perc.:	((2250 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/10 = 0.001484 mg/kg bw/day
	Mean:	((1794 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/10 = 0.001158 mg/kg bw/day
Adult:	75th perc.:	((7500 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/60 = 0.000807 mg/kg bw/day
	Mean:	((5980 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/60 = 0.000643 mg/kg bw/day

Bystander:

Child:	75th perc.:	((2250 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/10 = 0.001484 mg/kg bw/day
Adult:	75th perc.:	((7500 x 0.25 x 1[1] x 0.1884 x 1[2])/1000 x 0.14)/60 = 0.000807 mg/kg bw/day

[1] dose rate is considered by the experimental DFR
[2] MAF is considered by the experimental DFR

Summary of all pathways:

Refinements were presented above for all for exposure pathways (spray drift, vapor, surface deposits and entry into treated crops). A summary of all exposure calculations is presented below.

For the resident, the 75th perc. values are used for the single pathways. The mean values are used for 'All pathways'. For the bystander, the 95th perc. values are used for the single pathways.

Table 7.2.2.2-10: Resident and bystander exposure

Resident		Systemic exposure (mg/kg bw/day	% of AOEL (0.02 mg/kg bw/day)	MoE
Child	Spray drift (95th perc.) Spray drift (mean)	0.000021 0.000016	0.11	95 238
	Vapour	0	0.00	∞
	Surface deposits (75th perc.) Surface deposits (mean)	0.000108 0.000079	0.54	18 519
	Entry into treated crops (75th perc.) Entry into treated crops (mean)	0.001484 0.001158	7.42	1 348
	All pathways (mean)	**0.001253**	**6.28**	**1 592**
Adult	Spray drift (95th perc.) Spray drift (mean)	0.000004 0.000003	0.02	500 000
	Vapour	0	0.00	∞
	Surface deposits (75th perc.) Surface deposits (mean)	0.000036 0.000026	0.18	55 555
	Entry into treated crops (75th perc.) Entry into treated crops (mean)	0.000807 0.000643	4.04	2 478

	All pathways (mean)	**0.000672**	**3.36**	**2 976**
Bystander		Systemic exposure (mg/kg bw/day	% of AAOEL (0.03 mg/kg bw/day)	MoE
Child	Spray drift (95th perc.)	0.000024	0.08	125 000
	Vapour	0	0.00	∞
	Surface deposits (95th perc.)	0.000314	1.05	9 554
	Entry into treated crops (95th perc.)	0.001484	4.95	2 021
Adult	Spray drift (95th perc.)	0.000005	0.02	600 000
	Vapour	0	0.00	∞
	Surface deposits (95th perc.)	0.000109	0.36	27 523
	Entry into treated crops (95th perc.)	0.000807	2.69	3 717

Substance: = Thiacloprid
Formulation = 240 OD
Application rate = 0.072 kg a.s. /ha
Spray dilution = 0.72 g a.s./l (100 L/ha), 0.24 g a.s./L (300 L/ha)
Vapour pressure = 3 x 10^{-10} Pa at 20°C = non-volatile
Application method= Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction
Crop = Oilseed rape
Growth stage = BBCH 65 (full flowering)
Buffer strip = 3 m
Dermal abs. = Dermal of in use dilution = 14% (300 L/ha spray volume)
Inhalation abs. = 100%
Oral abs. = 100%
DFR = 0.1884 µg a.s./cm² per 0.072 kg a.s./ha
AOEL = 0.02 mg/kg bw/day
AAOEL (ARfD) = 0.03 mg/kg bw/day
NOAEL$_{long-term}$ = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)
NOAEL$_{acute}$ = 3 mg/kg bw/day based on neurotoxicity study
MoE = NOAEL/exposure;

Assessments involve mitigation via drift reduction nozzles (but no buffer zone). Buffer zones would further reduce the spray drift exposure. Exposure calculations are based on exposure studies to evaluate the effect of drift reduction nozzles and on experimental DFR data.

The total exposure (all pathways, mean) of a resident child for a spray application using up to 300 L/ha water (14% dermal absorption) is 0.001253 mg/kg bw/day. The total exposure (all pathways) of a resident adult is 0.000672 mg/kg bw/day. This is 6.3% and 3.4% of the established AOEL, respectively, and equates to MoE of 1592 (child) and 2976 (adult) to the established NOAEL (2 mg/kg bw/day). The overall exposure is very low, however, it is noted that the resident exposure is not determined by the spray drift, vapor or surface deposits but mainly driven by the exposure pathway 'entry into treated crops'. This exposure accounts for about 90% of the total child exposure and 95% of the total adult exposure.

The worst exposure route for bystanders is via entry into treated crops. The bystander child is exposed to 0.001484 mg/kg bw/day. The bystander adult is exposed to 0.000808 mg/kg bw/day. This is 4.9% and 2.7% of the surrogate AAOEL, respectively, and equates to MoE of 2021 (child) and 3717 (adult) to the respective NOAEL (3 mg/kg bw/day).

CP 7.2.3 Worker exposure

The EFSA guidance on non-dietary exposure (EFSA model) is used for exposure assessment in this dossier as it allows for a harmonised risk assessment. Details of model calculations are presented in Appendix 1.

Experimental DFR studies have been conducted to support the modelled exposure assessment. The data are taken for a higher tier assessment and replace the modelling approach where appropriate. A default body weight of 60 kg/person is assumed for all calculations. A spray volume of 300 L/ha is considered (worst case, dermal absorption 14%).

The measures taken to reduce exposure of workers to the active substance as much as technically possible consider the relevant routes of exposure.

Exposure of bystanders/residents to thiacloprid in the 240 OD formulation is evaluated for the following work activities and mitigation options:

- Inspection/scouting
  - restricted entry interval (REI)
  - work wear, no gloves
  - work wear, single use gloves

Summary

Alternative approaches are applied to verify that the exposure is negligible. In a 1st tier, the level of exposure resulting from the critical GAP (300 L/ha spray volume) is compared with the toxicological reference value (AOEL) and an additional safety margin of 10 (Table 7.2.3-1). In a 2nd tier, the Margin of Exposure to the study which is critical for the relevant classification under Regulation (EC) No 1272/2008 is calculated (Table 7.2.3-2).

A summary of the risk assessment is presented below.

Table 7.2.1-1: Assessment of negligible exposure using the toxicological reference value (AOEL) and additional safety margin of 10

Crop (re-entry activity)	Worker exposure scenario	Systemic exposure∞ [mg/kg bw/day]	% of AOEL (0.02 mg/kg bw/day)	MoE[1]	Add. Margin of Exposure ≥10?
Oilseed rape (scouting)	REI[2] of 3 days (work wear, no gloves)	0.00003	0.2	61 350	Yes
	Directly after last application (work wear, no gloves)	0.00129	6.4	1 553	Yes
	Directly after last application (work wear, single-use gloves)	0.00074	3.7	2 717	Yes

∞ 60 kg person, dermal absorption of 14% (300 L/ha spray), 100% absorption *via* inhalation, based on DFR studies
[1] MoE: NOAEL/exposure; NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)
[2] REI = Restricted Entry Interval (based on DFR studies)

Systemic exposure of workers during scouting in oilseed rape is 0.00003 mg/kg bw/day (work wear, no gloves) if a re-entry interval of 3 days is considered, 0.00129 mg/kg bw/day directly after application (work wear, no gloves) and 0.00074 mg/kg bw/day directly after applicaton (work wear, single-use gloves). These estimates equate to 0.2%, 6.4% and 3.7% of the AOEL, respectively.

Table 7.2.1-2: Margin of exposure to the study which is critical for the relevant classification of thiacloprid under Regulation (EC) 1272/2008*

Crop (re-entry activity)	Worker exposure scenario	Systemic exposure[∞] [mg/kg bw/day]	Hazard specific overall NOAEL (hazard/specific endpoint) [mg/kg bw/day]	Margin of Exposure[º]
Oilseed rape (scouting)	REI[2] of 3 days (work wear, no gloves)	0.00003	Fertility: 20 (dystocia, rat)	666 667
			Developmental toxicity:	
			10 (increase in post implantation loss)	333333
			17.5 (increase in stillbirths)	583333
			22 (increase in cannibalized & missing pups)	733333
			20 (reduced pup weights	666667
	Directly after last application (work wear, no gloves)	0.00129	Fertility: 20 (dystocia, rat)	15 587
			Developmental toxicity:	
			10 (increase in post implantation loss)	7752
			17.5 (increase in stillbirths)	13566
			22 (increase in cannibalized & missing pups)	17054
			20 (reduced pup weights	15504
	Directly after last application (work wear, single-use gloves)	0.00074	Fertility: 20 (dystocia, rat)	27 174
			Developmental toxicity:	
			10 (increase in post implantation loss)	13514
			17.5 (increase in stillbirths)	23649
			22 (increase in cannibalized & missing pups)	29730
			20 (reduced pup weights)	27027

∞ 60 kg person, dermal absorption 14% (300 L/ha spray), 100% absorption *via* inhalation route
º Margin of Exposure = hazard specific NOAEL/systemic exposure

The evidence of negligible exposure using the critical effect NOAEL for the risk assessment is demonstrated by the high margins of exposure. The risk assessment shows that the toxicological reference values are 4-5 orders of magnitude higher than the experimentally determined systemic exposures.

Conclusion

The term 'negligible exposure' is not finally defined by the EU Member States/Commission. A proposal is made to demonstrate negligible exposure to the active substance thiacloprid in the plant protection product Thiacloprid OD 240 under realistic and practical conditions of use involving professional risk mitigation measures.

The results demonstrate that exposure is far beyond the threshold already considered as safe (additional safety factor >>10 to the AOEL). Margins of Exposure of 4-5 orders of magnitude – and therefore a higher level of safety – exist considering the threshold values for the specific hazards relevant for the classification of thiacloprid.

The applicant therefore considers that exposure of workers to thiacloprid can be mitigated to negligibly low levels under realistic conditions of use.

CP 7.2.3.1 Estimation of worker exposure

The measures taken to reduce exposure of workers to the active substance as much as technically possible consider the relevant routes of exposure. The EFSA guidance on non-dietary exposure is followed to allow for a harmonized risk assessment.

Worker exposure is evaluated as follows:

1. Evaluation according to EFSA guidance on non-dietary exposure (DT_{50} = 30 days)
2. Measurement of DFR and determination of DT_{50} no gloves
3. Mitigation via single-use gloves

A summary of the critical GAP for worker exposure evaluation is presented in the following table.

Table 7.2.3.1-1 Summary of critical GAP for worker exposure evaluation

Crop grouping	Re-entry task	Duration (h)	Max. dose rate		No of appl.	Min. interval (days)	Min. PHI (days)
			(L/ha product)	(kg a.s./ha)			
Oilseed rape	Inspection/ scouting	2	0.3	0.072	2	10	n.a.

Exposure of workers is estimated for activities that involve contact with treated crops. This will mainly occur when manual work is necessary. The EFSA guidance notes that exposure calculations for inspection/scouting activities are to be evaluated for a duration of 2 hours/day.

1) Evaluation according to EFSA guidance on non-dietary exposure

A summary of the exposure calculations for the critical GAP using the EFSA calculator is presented below. Detailed calculations are presented in Appendix 1, Table A4 (worst case: 300 L/ha scenario, 14% dermal absorption).

Table 7.2.3.1-2: Worker exposure calculation (using the EFSA calculator), 300 L/ha spray

Substance	Thiacloprid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.72 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 0.2	Dermal for in use dilution = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	30 days	
Worker - Inspection, irrigation	Potential exposure mg/kg bw/day		0.022601	% of RVNAS	113.00%
	Working clothing mg/kg bw/day		0.002531	% of RVNAS	12.66%
	Working clothing and gloves mg/kg bw/day			% of RVNAS	

The evaluation using the EFSA calculator results in a worker exposure of 0.002521 mg/kg bw/day (12.7%) when applications were done with 300 L/ha spray volume.

2. Refinement via experimentally determined DFR and DT_{50}

The calculation with the EFSA calculator is based on default assumptions for the initial DFR (3 µg/cm^2 x kg a.s) and the residue decline (MAF based on DT_{50} = 30 days). In order to calculate realistic values for both parameters DFR studies were conducted with the formulation under evaluation and following worst case use conditions i.e. max. application rate, max. no. of applications and min. interval between applications. This allows to determine the initial dislodgeable foliar residue (DFR_0) directly after the last application and to evaluate the residue decline in order to determine the half-life (DT_{50}) of the active substance on the plant surface.

Summary of DFR studies

Thiacloprid dislodgeable foliar residues were determined in three studies following foliar spray treatment in the field in bean (Germany) and potato (Germany and France). Summaries of the studies are presented in the following.

DFR study kidney bean (Germany):

Report: [redacted]2;[redacted];[redacted];2012;M-433739-01
Title: Determination of the dislodgeable foliar residues (DFR) of thiacloprid in/on kidney bean after spraying of thiacloprid OD 240 in the field in Germany
Report No: 11-2908
Document No(s): Report includes Trial Nos.:
11-2908-01
M-433739-01-1
Guidelines: **US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a));not specified**
GLP/GEP: **yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on kidney bean leaf foliage in northern Europe after three spraying applications with Thiacloprid 240 OD. The study included one supervised residue trial conducted in the field in Germany during the 2011 season.

Table 7.2.3.1-3: Application parameters

Country	Application				
	Type	No	Growth stage (BBCH)	Interval (days)	Rate (kg a.s./ha)
Germany	Spraying	3	61-65	7	0.096

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co, El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm². The leaf punches represented a total double-sided leaf surface area of 400 cm². A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-4: Amounts of dislodgeable foliar residues of thiacloprid on kidney bean leaves in Germany [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT#	Sampling interval (DAT)	Thiacloprid DFR (µg/cm²)
-0	0	< 0.01
0	**0**	**0.258**
1	1	0.135
3	3	< 0.01
7	7	< 0.01
7	**0**	**0.223**
8	1	0.012
10	3	< 0.01
14	7	< 0.01
14	**0**	**0.219**
15	1	0.101

17	3	< 0.01
21	7	< 0.01
24	10	< 0.01

#:DAFT: day after first treatment; DAT: day after treatment

A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 1.2 days (see Appendix).

III Conclusion

The maximum DFR value is 0.258 µg/cm² observed at day 0 after the 1st application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3 onwards after each single application. Residues decline with a DT_{50} of 1.2 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.

Thiacloprid, DFR on kidney bean, Germany 2011

Report: 11-2908

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.258
1	0.135
3	0.005
7	0.005

$$C = C_0 \times e^{-k\,t} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}}t}$$

C_0	0.149648564
k	0.577822578
$t_{1/2}$	1.199584798
R^2	0.72108961

DT_{50}(days):	1.2

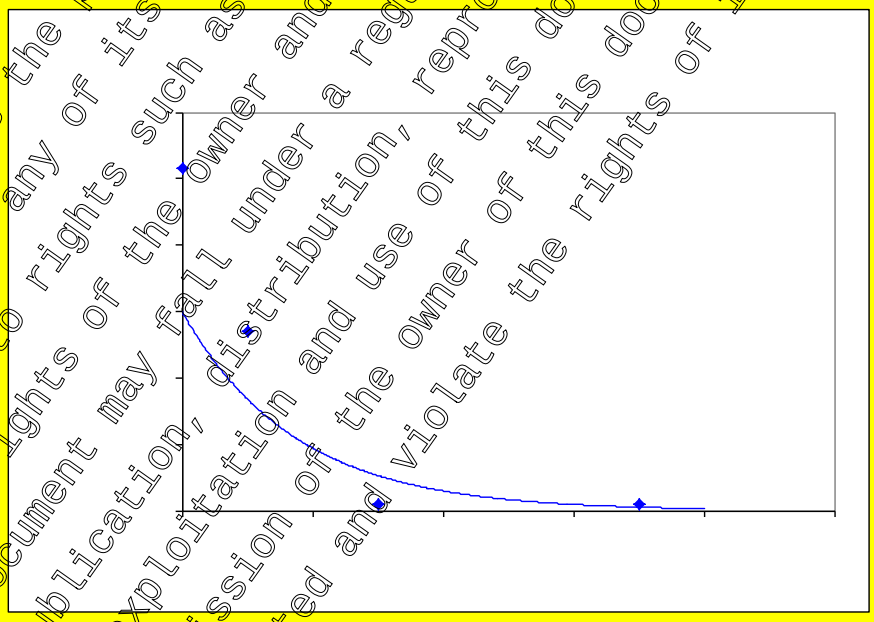


Figure 7.2.3.1-1: Determination of DT_{50} of thiacloprid in kidney bean

DFR study potato (Germany):

Report:	[redacted]8;[redacted];[redacted];2012;M-433623-01
Title:	Determination of the dislodgeable foliar residues (DFR) of thiacloprid in/on potato after spraying of thiacloprid OD 240 in the field in Germany
Report No:	11-2900
Document No(s):	Report includes Trial Nos.: 11-2900-01 M-433623-01-1
Guidelines:	**US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a));not specified**
GLP/GEP:	**yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on potato leaf foliage in northern Europe after three spraying applications with thiacloprid 240 OD. The study included one supervised residue trial conducted in the field in Germany during the 2011 season.

Table 7.2.3.1-5: Application parameters

Country	**Application**				
	Type	**No**	**Growth stage (BBCH)**	**Interval (days)**	**Rate (kg a.s./ha)**
Germany	Spraying	3	71-81	10	0.120

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co, El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-6: Amounts of dislodgeable foliar residues of thiacloprid on potato leaves in Germany [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT#	**Sampling interval (DAT)**	**Thiacloprid DFR (µg/cm^2)**
- 0	- 0	< 0.01

0	**0**	**0.338**
1	1	0.028
3	3	0.011
7	7	< 0.01
10	10	< 0.01
10	**0**	**0.308**
11	1	< 0.01
13	3	< 0.01
17	7	< 0.01
20	10	< 0.01
20	**0**	**0.279**
21	1	0.011
23	3	< 0.01
27	7	< 0.01
30	10	< 0.01
34	14	< 0.01
41	21	< 0.01

#:DAFT: day after first treatment; DAT: day after treatment

A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 2.0 days (see Appendix).

III Conclusion

The maximum DFR value is 0.338 µg/cm² observed at day 0 after the 1st application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3-7 onwards after each single application. Residues decline with a DT_{50} of 2.0 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.

Thiacloprid, DFR on potato foliage, Germany, 2011

Report: 11-2900

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.338
1	0.028
3	0.011
7	0.005
10	0.005

$$C = C_0 \times e^{-kt} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}} t}$$

C_0	0.080430751
k	0.341188637
$t_{1/2}$	**2.031565844**
R^2	0.670097702

DT_{50}(days): 2.0

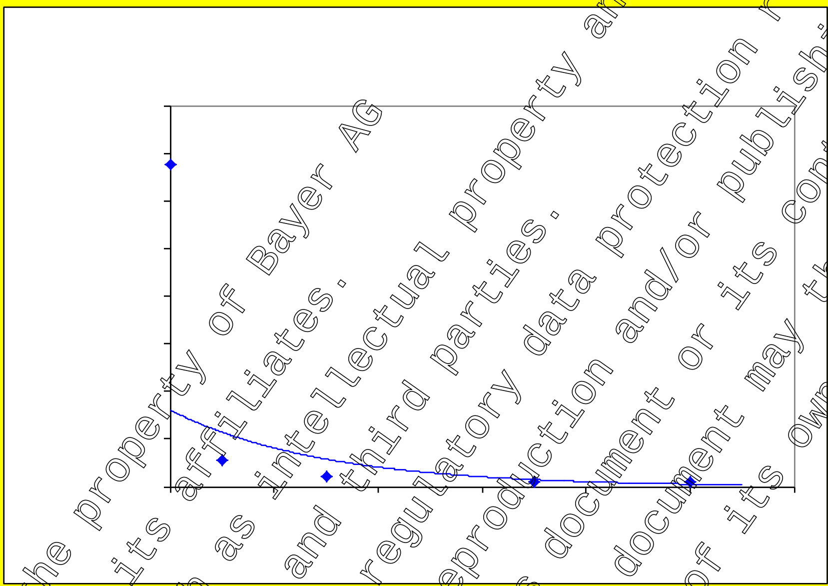


Figure 7.2.3.1-2: Determination of DT_{50} of thiacloprid in potato (Germany)

DFR study potato (France):

Report: [redacted];2012;M-433626-01
Title: Determination of the dislodgeable foliar residues (DFR) of thiacloprid on potato after spraying of YRC 2894 SC480 in the field in France (South)
Report No: 11-2906
Document No(s): Report includes Trial Nos.:
11-2906-01
M-433626-01-1
Guidelines: **US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a));not specified**
GLP/GEP: **yes**

I Material and methods

The purpose of the study was to determine the magnitude of the dislogeable foliar residues of thiacloprid on potato leaf foliage in southern Europe after three spraying applications with thiacloprid SC 480. The study included one supervised residue trial conducted in the field in France during the 2011 season.

Table 7.2.3.1-7: Application parameters

Country	Application				
	Type	No	Growth stage	Interval	Rate

			(BBCH)	(days)	(kg a.s./ha)
Germany	Spraying	3	24 - 38	14	0.096

Samples were collected in a manner designed to obtain representative samples. They were taken, prepared in the field where necessary, transported and stored according to US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation. Leaf punches were collected directly into a pre-labelled poly-propylene jar using a leaf punch sampler (Birkestrand Co; El Monte, CA). Each sample consisted of 40 discs cut with a leaf puncher with 2.523 cm diameter and a disk area of 5 cm^2. The leaf punches represented a total double-sided leaf surface area of 400 cm^2. A sample was collected from each of the three subplots to provide three replicate samplings at each sampling interval. Leaf punches were taken from the potential worker contact zone including upper, middle, and lower portions of the crop foliage and interior and exterior portions of the crop foliage. Control leaf punch samples were collected prior to the first application. Treated samples collected on the day of application were taken after the spray had dried. After each sample was collected, the sampling jar was capped and kept cool for transport to the field site laboratory. Leaf punch samplers were cleaned after each sampling interval. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after collection.

II Results and discussion

The results are summarised in the following table.

Table 7.2.3.1-8: Amounts of dislodgeable foliar residues of thiacloprid on potato leaves in France [µg a.s./cm2], two sided, figures in bold indicate day of treatment

DAFT#	Sampling interval (DAT)	Thiacloprid DFR (µg/cm²)
- 0	0	< 0.01
0	**0**	**0.196**
1	1	0.140
3	3	< 0.01
7	7	< 0.01
14	14	< 0.01
14	**0**	**0.225**
15	1	0.177
17	3	< 0.01
21	7	< 0.01
24	10	< 0.01
28	**0**	**0.225**
29	1	0.204
31	3	0.039
35	7	0.01*
42	14	< 0.01
49	21	< 0.01

#:DAFT: day after first treatment; DAT: day after treatment
* average result set to 0.010 µg/cm² as worst case due to residues of 0.01 µg/cm² on sub-plot 1, sub-plot 2+3 were < 0.01 µg/cm²

A first-order single-exponential dissipation equation was fitted to the set of experimental data. Overall mean dissipation half-life of thiacloprid was 3.7 days (see Appendix).

III Conclusion

The maximum DFR value is 0.225 µg/cm² observed at day 0 after the 3rd application. Thereafter, a fast residue decline is observed with residues < LOQ from day 3-7 onwards after each single application. Residues decline with a DT_{50} of 3.7 days. An accumulation of dislodgeable foliar residues is therefore not anticipated.

Thiacloprid, DFR on potato foliage, France 2011

Report: 11-2906

Calculation of DT_{50} assuming first order kinetics

DALT (Days)	Residues (µg/cm²)
0	0.225
1	0.204
3	0.039
7	0.01
14	0.005
21	0.005

$C = C_0 \times e^{-k \times t} = C_0 \times e^{-\frac{\ln 2}{t_{1/2}} t}$

C_0	0.115357862
k	0.186282433
$t_{1/2}$	**3.720947655**
R^2	0.774075866

DT_{50}(days): 3.7

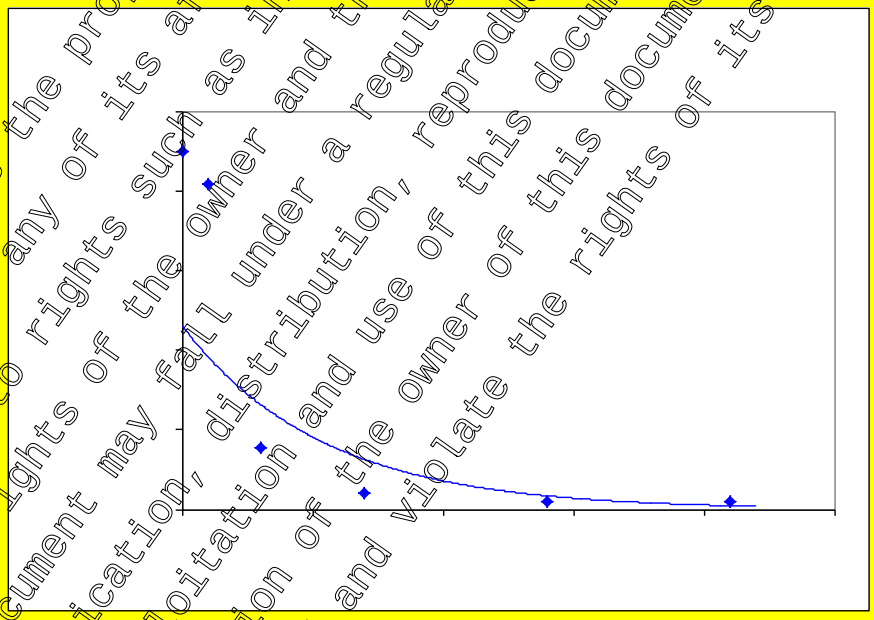


Figure 7.2.3.1-3: Determination of DT_{50} of thiacloprid in potato (France)

Summary

A summary of the experimental conditions and the results of the three DFR studies conducted with Thiacloprid is presented in the following table.

Table 7.2.3.1-9: Summary of DFR studies performed with Thiacloprid

Crop	Country	Formulation	Study conditions (no. of appl. / appl. Rate in kg	Max. DFR_M (μg/cm²)	Max. DFR_M (μg/cm²/kg a.s. applied/ha)	Observed on	DT_{50} (days)

			a.s./ha)				
Bean	Germany	240 OD	3 / 0.096	0.258	2.7	0 days after 1st appl., DAFT 0	1.2
Potato	Germany	240 OD	3 / 0.120	0.338	2.8	0 days after 1st appl., DAFT 0	2.0
Potato	France	SC 480	3 / 0.096	0.225	2.3	0 days after 2nd appl., DAFT 14	3.7

A justification that the DFR data from these studies can be used for oilseed rape is given by the US-EPA recommendation for choosing relevant crops group for re-entry evaluation[15].

Because of the agricultural diversity of crops and their varieties a method of clustering crops into groups is proposed by EPA that are expected to result in comparable re-entry exposure. It is desirable that DFR studies used for the assessment be representative of the growth form and crop architectures of the registered uses. The US-EPA re-entry evaluation for scouting in rape (canola) is based on DFR and exposure studies (to establish transfer coefficients) performed in peas. This crop is grouped in the crop group 'Field / row crops, low / medium' and the cluster 'Smooth-leaf field crops: scouting in solid stand conditions'. This crop group includes inter alia beans (string and dry), soybeans, peas and rape (canola). Potato is also grouped in the a.m. guidance in the cluster 'Smooth-leaf field crops: but scouting in row conditions.

Bean and potato are smooth-leaf field crops. It is therefore considered that the DFR studies conducted with thiacloprid in beans and potato are appropriate to be used for the evaluation of worker inspection/scouting activities in rape.

It is noted that the DFR trials were conducted

- with three applications and
- using the maximum dose rate of 0.096 kg a.s./ha in bean (Germany) and potato (France) and 0.120 kg a.s./ha in potato (Germany)

whereas the cGAP under evaluation considers only two applications and 0.072 kg a.s./ha. The maximum DFR values were measured on day 0 i.e. directly after the application (0.258 $\mu g/cm^2$, 0.338 $\mu g/cm^2$ and 0.225 $\mu g/cm^2$). The very low DT_{50} of 1.2, 2.0 and 3.7 days **(mean: 2.3 days)** indicates fast degradation and explains why no accumulation of residues is found after sequential application and the maximum DFR are found either after the 1st or after the 2nd application. The maximum DFR per kg a.s. applied/ha were 2.7, 2.8 and 2.3 $\mu g/cm^2/kg$ a.s. applied/ha (**mean of maximum values: 2.6 µg/cm²/kg a.s. applied/ha = Initial DFR**).

A fast decline (DT_{50} = 2.3 days) of surface residues of thiacloprid was observed in all DFR studies. The residue was below the level of quantification (LOQ) of 0.01 µg a.s./cm² three days after the application (dose rate of 0.096 kg a.s./ha was used).

[15] Agricultural Transfer Coefficients, U.S. EPA / Office of Pesticide Programms / Health Effects Division, Science Advisory Council for Exposure (ExpoSAC), Policy Number: 3, March 1, 2012. M-525540-01-1

Refinement of worker exposure

The following equation is used to calculate the worker exposure (following EFSA guidance):

$$\text{Worker exposure (mg/kg bw/day)} = \frac{[\text{Transfer coefficient inspection/scouting (cm}^2\text{/hr)} \times \text{Duration (hr)} \times \text{DFR (µg/cm}^2\text{)} \times \text{MAF}]}{1000 \times \text{Dermal absorption (\%)} / \text{Body weight (kg)}}$$

2.1 Worker exposure after re-entry interval (REI) of 3 days, work wear, no gloves

The calculation of the exposure for a re-entry interval of 3 days considers a DFR value of 0.005 µg a.s./cm² (½ LOQ).

Worker exposure (mg/kg bwday)

= (1400 cm²/hr x 2 hr x 0.005 µg/cm² x 1)/1000 x 14%/60 kg
= 0.00003 mg/kg bw/day

This is equivalent to 0.2 % of the AOEL and MoE = 61350.

Re-entry interval of three days provides an additional safety factor resulting in 0.1% of the AOEL and MoE of 61350.

2.2 Worker exposure, work wear, no gloves

The calculation is done using the following changes:

- DFR: 2.6 µg a.s./cm² per kg a.s./applied/ha
- DT_{50} of 2.3 days and 2 applications resulting in Multiple Application Factor (MAF)*: 1.0

** Multiple Application Factor (MAF) when more than one application and assuming DT_{50} of 2.3 days: the MAF used in the above mentioned exposure equation is expressed by the following formula:*

$$MAF_m = \frac{1-e^{-nki}}{1-e^{-ki}}$$

Where:

k = ln(2)/DT_{50} (rate constant)
n = number of applications
i = application interval (d)

A summary of the refined calculations are presented in the tables below. Details are presented in Appendix 1, Table A5.

Table 7.2.3.1-10: Worker exposure calculation (using DFR studies), 300 L/ha spray, work wear, no gloves

Substance	Thiacloprid	Formulation = soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.72 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absorption	Dermal for product = 0.2	Dermal for in use diluation = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	2.6 µg a.s./cm2 per kg a.s./ha		DT50	2.3 days	

Worker - Inspection, irrigation	Potential exposure mg/kg bw/day	0.0115	% of RVNAS	57.28%
	Working clothing mg/kg bw/day	0.0013	% of RVNAS	6.42%
	Working clothing and gloves mg/kg bw/day		% of RVNAS	

A summary of the exposure estimates resulting from the critical GAP, the proportion to the established AOEL and the margins of exposure (MoE) is presented in the following table.

Table 7.2.3.1-11: Worker risk assessment

Re-entry exposure (inspection/scouting)	300 L spray/ha		
	Systemic exposure* (mg/kg bw/day)	% of AOEL[1] (0.02 mg/kg bw/day)	MoE[2]
Work clothing, bare hands	0.001283	6.4	1 559

* 60 kg person, dermal absorption of 0.2% (concentrate) and 14% (300 L/ha spray), 100% absorption *via* inhalation route
[1] AOEL: 0.02 mg/kg bw/day
[2] MoE: NOAEL/exposure; NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)

Systemic exposure of protected re-entry workers wearing long sleeved shirt and long trousers (equivalent to one layer of working clothing) working with protected hands during inspection/scouting in oilseed rape is 0.000736 mg/kg bw/day when 300 L/ha spray is used (14% dermal absorption). This equates to 3.7% of AOEL and MoE of 2577.

2.3 Worker exposure, work wear: single-use gloves

The wearing of single-use gloves poses no hindrance for agronomists to comply with this kind of label requirement for scouting/inspection activities. This is confirmed to the applicant by professional agronomists advising customers and farmers e.g. in the UK and Germany[16].

Thiacloprid 240 OD will be applied during BBCH 30 (stem elongation) and BBCH 59 (first petals visible). The plant surface during this phase is smooth and not abrasive. Gloves such as splash resistant single-use gloves are therefore practicable and feasible for such re-entry work.

The standard to be stipulated should meet at least gloves safety standard EN374-2:2003, Level 2 described in European Directive 89/686 EEC – Manufacturing directive for Complex Design/Conformité Europeene (CE) category III.

The approach of hand protection during re-entry is established in the EFSA guidance on the assessment of exposure of workers in risk assessment for various activities during re-entry. However, hand protection for inspection/scouting is not established. A TC of 1400 cm^2/h is proposed for inspection/scouting in the EFSA guidance assuming that body, arms and legs are covered but hands are unprotected.

[16] Statement on the use of gloves or any other protective equipment during crop inspection activities after application of Thiacloprid-containing PPPs: M-568133-01-1; M-568156-01-1; M-568160-01-1

A proposal is therefore made in the following based on the underlying studies that were used in the EFSA guidance to establish the total TC (body and hands) of 1400 cm^2/h for scouting. The value for unprotected hands was derived from US ARTF data on peas and sweet corn which represent a robust set of data upon which to base the TC value. A detailed consideration and derivation of a TC value for protected hands from these data is shown below.

The studies in question are the ARTF studies ARF009 and ARF021 by Klonne et al. (1999a)[17] and Klonne et al. (1999b)[18]. Both studies are available to CRD[19]. They are therefore not submitted again with this dossier. The studies were conducted to GLP and in accordance with EPA occupational and residential exposure test guidelines - series 875. Full length inner cotton dosimeters were worn underneath the outer dosimeter of cotton long sleeved shirt and long pants. Hand wash and face/neck wipes were undertaken.

The sweet corn study comprised eight workers on three separate re-entry dates (3, 6 and 9 days after the 2nd of two applications of Bravo 500 (chlorothalonil) at the test site in Florida). The working period during re-entry was approx. 4 hours. The corn was typically 152 – 183 cm in height during the re-entry period and considered to be in full foliage. Workers walked through the field and every few feet would inspect plants sometimes removing leaves in the process. Data were gathered on the amount of dermal exposure as well as the amount of foliar residue present on the crop (dislodgeable foliar residue) and the TC value derived in the following way.

TC (cm^2/hr) = adjusted residue value (µg) ÷ DFR (µg/cm^2) ÷ time worked (hours)

The pea study was undertaken in a similar manner except this consisted of 5 workers on 3 separate re-entry dates (2, 4 and 6 days after the second of two applications of Bravo 500 (chlorothalonil) at a test site in Canada). The work period was usually 4 hours although on one day was only 2 hours due to rain. At the time of first application the peas were only 18cm high and by the final day of re-entry were 66cm in height and with full foliage.

A summary of the overall distribution of exposure for both crops can be seen below. In the case of peas, PDE is primarily to the legs which would be expected walking through a relatively low crop compared to sweet corn in which distribution is more even across the body. In both cases, exposure of the hands contributes a relatively small proportion of potential dermal exposure (PDE) but represents the main area of exposure as a % of total actual dermal exposure (ADE).

Table 7.2.3.1-12: Distribution of exposure expressed as a % of TC (geomean)

Body part	Sweetcorn (% TC)		Peas (% TC)	
	PDE*	ADE**	PDE*	ADE**
Legs	36	7	79	17
Body	20	17	2	1
Arms	40	35	11	9
Hands	4	41	8	73
Face/neck	neg.	neg.	neg.	neg.

* Potential dermal exposure = sum of the inner and outer dosimter, face/neck wipe and hands

** Actual dermal exposure = sum of the inner dosimeter, face/neck wipe and hands

[17] Klonne et al. (1999a): Determination of dermal and inhalation exposure to re-entry workers during scouting in sweetcorn, study number ARF009

[18] Klonne et al. (1999b): Determination of dermal and inhalation exposure to re-entry workers during scouting in dry peas, study number ARF021

[19] The studies were already submitted to CRD by ARTF industry member. Therefore, a separate submission by BCS is not considered necessary. BCS herewith expressly indicate its active ARTF membership and note that these studies may be used by CRD for the evaluation of this dossier.

The derived TC value of 1400 cm^2/hr reflects actual total dermal exposure and is the sum of the inner dosimeters, hand wash and face/neck wipes. Both sets of data were log normally distributed and given the relatively small size of the data sets parametric analysis was undertaken to compare to the empirically derived values. The individual values derived from the corn and pea studies are 1033 cm^2/hr and 1180 cm^2/hr respectively being 75^{th} parametric estimates.

The TC for total dermal exposure is the sum of hand and body exposure (sum of inner dosimeter and face/neck wipes). Individual TC for hand and body exposure were calculated from the set of data and are summarized in the following table:

Table 7.2.3.1-13: Summary of TC values (75^{th} parametric estimates)

Route	TC (cm^2/hr)		
	ARF009: Sweetcorn	ARF021: Peas	Combined value
TC hand (unprotected)	409	1037	723
TC body	638	650	644
TC total dermal (assuming arms, body and legs covered)	1033	1732	1383

It is interesting to note that the higher TC values are derived from the pea study because when arms, body and legs are covered it is not the height of the crop that appears to influence exposure so much as the intensity and frequency of contact of bare hands with treated foliage. The US approach of combining corn and pea data is considered sufficiently representative of a range of foliage heights and densities for smooth-leaf field crops in solid stand conditions. Taking into account the factors described above a TC value for scouting in oilseed rape of 1400 cm^2/hr (rounded up parametric 75^{th} centile estimate) is considered appropriate.

A protection factor (PF) of 0.2 (i.e. a 5x reduction of dermal hand exposure) could be applied in the exposure calculation as suggested by CRD Regulatory Update 24/2014[20] for protective single-use gloves. This factor can be applied to the proportion of the transfer coefficient (TC) relating to the hands. The re-calculated TC for protected hand exposure by applying the protection factor of 0.2 to the individual TC hand values is summarized in the following table:

Table 7.2.3.1-14: Summary of TC values protected hands (75^{th} parametric estimates)

Route	TC (cm^2/hr)		
	ARF009: Sweetcorn	ARF021: Peas	Combined value

[20] New arrangements for the use of personal protection gloves to reduce skin exposure in re-entry work after application of plant protection products to crops, Regulatory Update: 24/2014, Issued: 2nd December 2014, http://www.pesticides.gov.uk/guidance/industries/pesticides/News/Collected-Updates/Reg-Updates-2014/December/PPE-gloves-reg-up-2014, M-525563-01-1

TC hand (protected)	82	207	145
TC body	638	650	644
TC total dermal (assuming arms, body, legs and hands covered)	718	898	**803**

The TC of 803 cm²/hr is proposed to be used for the evaluation of worker exposure via protective gloves.

<u>Exposure of workers wearing single-use gloves during scouting in oilseed rape:</u>

The following equation is used to calculate the worker exposure (following EFSA guidance):

$$\text{Worker exposure (mg/kg bw/day)} = \left[\text{Transfer coefficient inspection/scouting } (cm^2/hr) \times \text{Duration (hr)} \times \text{DFR } (\mu g/cm^2) \times \text{MAF} \right] / 1000 \times \text{Dermal absorption (\%)} / \text{Body weight (kg)}$$

The refinement is done using the following changes:

- Dermal transfer coefficient – hand, arms, body and legs covered: 803 cm²/hr
- DFR: 2.6 µg a.s./cm² per kg a.s./applied/ha
- Multiple Application Factor (MAF)*: 1.0 (based on DT_{50} of 2.3 days and 2 applications)

** Multiple Application Factor (MAF) when more than one application and assuming DT_{50} of 2.3 days, the MAF used in the above mentioned exposure equation is expressed by the following formula:*

$$MAFm = \frac{1-e^{-nki}}{1-e^{-ki}}$$

Where:

$k = \ln(2)/DT_{50}$ (rate constant)
n = number of applications
i = application interval (d)

A summary of the refined calculations are presented in the tables below.

Details are presented in Appendix 1, Table A6.

Table 7.2.3.1-15: Worker exposure calculation (based on DFR studies: DFR0, DT50 and assuming single-use gloves are worn

Substance	Thiacloprid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.72 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 0.2	Dermal for in use diluation = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	2.6 µg a.s./cm2 per kg a.s./ha		DT50	2.3 days	

Worker-Inspection, irrigation	Potential exposure mg/kg bw/day	0.0115	% of RVNAS	57.28%
	Working clothing mg/kg bw/day	0.0013	% of RVNAS	6.42%

	Working clothi9ng and gloves mg/kg bw/day	0.0007	% of RVNAS	3.68%

A summary of the exposure estimates resulting from the critical GAP, the proportion to the established AOEL and the margins of exposure (MoE) is presented in the following table.

Table 7.2.3.1-16: Worker risk assessment

Re-entry exposure (inspection/scouting)	300 L spray/ha		
	Systemic exposure* (mg/kg bw/day)	% of AOEL[1] (0.02 mg/kg bw/day)	MoE[2]
Work clothing, single-use gloves	0.0007	3.7	2717

* 60 kg person, dermal absorption of 0.2% (concentrate) and 14% (300 L/ha spray), 100% absorption *via* inhalation route
[1] AOEL: 0.02 mg/kg bw/day
[2] MoE: NOAEL/exposure; NOAEL = 2 mg/kg bw/day based on rabbit developmental study (maternal toxicity)

Systemic exposure of protected re-entry workers wearing long sleeved shirt and long trousers (equivalent to one layer of working clothing) wearing single-use gloves during inspection/scouting in oilseed rape is 0.000736 mg/kg bw/day. This equates to 3.7% of AOEL and MoE of 2717.

CP 7.2.3.2 Measurement of worker exposure

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

CP 7.3 Dermal adsorption

Summary and conclusion on dermal absorption

The extent of dermal absorption of thiacloprid formulated as an OD 240 (Biscaya®) formulation was investigated *in vitro* using human and rat skin. A summary of the study is given in the following section. A conclusion and recommendation regarding the dermal absorption of thiacloprid formulated as an OD 240 is given below.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the neat formulation was 0.12% for the human skin. Applying the new EFSA guidance this value adjusts to 0.2%.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the intermediate dose rate was 4% for human skin. Applying the new EFSA guidance this value adjusts to 6%.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable (directly absorbed plus total remaining at dose site) over a period of 24 hours for the low dose rate was 14.3% for human skin. Applying the new EFSA guidance this value adjusts to 14%.

According to the new EFSA guidance21 there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-thiacloprid in the Biscaya OD 240 formulation:

- 0.2% for the neat formulation (240 g/L)
- 6% for the intermediate dose (0.74 g/L)
- 14% for the low dose (0.1 g/L).

Report:	[redacted]b; [redacted]; 2005; M-249733-01-1
Title:	Thiacloprid SC (Calypso) and Thiacloprid OD (Biscaya) formulations: In vitro dermal absorption study using human skin - Comparison of SC and OD formulations
Report No.:	SA 04295
Document No.:	M-249733-01-1
Guidelines:	**OECD 428; OECD Environmental Health and Safety Publications Series on testing and Assessment No 28. Guidance Document for the Conduct of Skin Absorption Studies; European Commission Guidance Document on Dermal Absorption-Sanco/222/2000 rev. 7; not applicable**
GLP/GEP:	**yes**

Material and methods

Human skin:	[redacted], France. Number and sex: 10 donors, female. Anatomical region: Abdomen. Thickness: 461 to 693 µm.
Test Material:	
Non-radiolabelled:	Batch: M27898. Purity = 99.7%.
Radiolabelled:	[methylene-^{14}C]-thiacloprid Batch: KML 2358. Specific activity: 3.77 MBq/mg. Radiopurity of the formulation: >99%.
Formulation:	The formulation used in this experiment was the thiacloprid OD 240 formulation containing thiacloprid (240 g/L). It was used at three nominal concentrations of thiacloprid: neat, 240 g/L, 0.74 g/L and 0.1 g/L.
Test system:	A flow-through diffusion cell system (Franz's cell modified, Gallas, France)

[21] 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.

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 (Dermalab, Cortex Technology, Denmark) was 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 40 g/hm² were considered potentially damaged and were not used. These samples were replaced by new skin fragments which were also tested for integrity before use in the study.

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

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

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

samples in appropriate scintillation cocktails.

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

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

The study results are presented in Table 7.6.2-1.

Table 7.3-1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- thiacloprid in an OD 240 formulation at the rates of 240 g/L, 0.74 g/L and 0.1 g/L to human skin samples.

Results expressed in terms of percentage of applied radioactivity.

	Distribution of radioactivity (% dose)					
Dose Levels	Neat formulation: High dose (240 g/L)		Dilution: Intermediate dose (0.74 g/L)		Dilution: Low dose (0.1 g/L)	
Species	Human (n=6)		Human (n=5)		Human (n=5)	
	Mean	SD	Mean	SD	Mean	SD
SURFACE COMPARTMENT						
Skin swabs (8h)	97.82	8.73	85.20	2.80	82.46	7.89
Surface Dose (1st two tape-strips)	0.08	0.07	0.49	0.26	1.06	0.30
Donor chamber	0.14	0.03	0.11	0.05	2.49	3.41
Total % non-absorbed	**98.04**	**8.79**	**85.80**	**2.70**	**86.01**	**7.10**
SKIN COMPARTMENT						
Skin [b]	0.05	0.07	0.27	0.25	3.80	3.01
Stratum corneum [c]	0.04	0.04	0.80	0.51	3.25	1.83
Total % at dose site	***0.09***	***0.08***	***1.08***	***0.68***	***7.04***	***1.79***
RECEPTOR COMPARTMENT						
Total % directly absorbed [d]	***0.03***	***0.02***	***2.91***	***1.67***	***7.23***	***2.86***
STUDY: Total % Potentially Absorbable [e]	0.12	0.10	3.98	1.35	14.27	2.63
TOTAL % RECOVERY	**98.16**	**8.88**	**89.78**	**3.87**	**100.3**	**6.09**
Evaluation according to EFSA Guidance						
absorption >75% within half of study duration	No		No		No	
standard deviation >25%	Yes		Yes		No	
recovery <95%	No		Yes		No	
adjusted: Total % Potentially Absorbable [f]	**0.2**		**6**		**14**	

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

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

Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-thiacloprid in the OD 240 formulation was investigated at three concentrations corresponding to the neat product (240 g/L) and to two representative dilutions (0.74 and 0.1 g/L), respectively.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the neat formulation was 0.12% for the human skin. Applying the new EFSA guidance this value adjusts to 0.2%.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the intermediate dose rate was 4% for human skin. Applying the new EFSA guidance this value adjusts to 6%.

The mean percentage of thiacloprid in the OD 240 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 14.3% for human skin. Applying the new EFSA guidance this value adjusts to 14%.

According to the new EFSA guidance[22] there is the provision that when the sampling period is 24 hours (which is the case for this study) and over 75% of the total absorption (material in the receptor fluid at the end of the study) occurred within half of the duration (12 hours) of the total sampling period that the absorption will be taken as the sum of receptor fluid, receptor chamber washes and the skin sample excluding all tape strips. These criteria were not met in this study. There is also the provision that a standard deviation equal to or larger than 25% of the mean of the absorption requires the use of an alternative value or rejection of the study. The guidance prefers the approach of adding the standard deviation to the mean to cover the upper 84th percentile value of the results. Additionally where an overall recovery of less than 95% occurs, a normalisation procedure is to be used by preference. Albeit that the notifier considers that both the value of 25% for the standard deviation limit and the 95% recovery limit to be too conservative, the application of the guidance results in the following values for [^{14}C]-thiacloprid in the Biscaya OD 240 formulation:

- 0.2% for the neat formulation (240 g/L)
- 6% for the intermediate dose (0.74 g/L)
- 14% for the low dose (0.1 g/L).

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information - data provided separately (Document J)

[22] 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.

Appendix I: Exposure calculations

Table A1: Operator exposure calculation for Biscaya 240 OD, outdoor spray application – application using drift reduction nozzles, work wear and protective gloves, 300 L/ha spray (EFSA model)

Operator exposure for Biscaya 240 OD outdoor spray applications

Application rate of active substance	0.072	kg a.s./ha	*i_AppRate*
Assumed area treated	50	ha/day	*d_AreaTreated*
Amount of active substance applied	3.6	kg a.s./day	*i_AmoutAS*
Dermal absorption of the product	0.20%		*i_AbsorpProduct*
Dermal absorption of in-use dilution	14.00%		*i_AbsorInuse*
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.		
Indoor or Outdoor application	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Season	not relevant		

	Exposure values	µg exposure/day mixed and loaded		Reference	Comment
		75th centile	95th centile		
Mixing and loading	Hands	13020	48250	AOEM	
	Body	8778	104496	AOEM	
	Head	187	1024	AOEM	
	Protected hands (gloves)	79	713	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	74	527	AOEM	
	Protected head (hood and face shield)	3	10	AOEM	
	Inhalation	5	30	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Water soluble bag	No		1	

	Exposure values	µg exposure/day applied		Reference	Comment
		75th centile	95th centile		
Application	Hands	226	1423	AOEM	
	Body	46	547	AOEM	
	Head	2	4	AOEM	
	Protected hands (gloves)	7	62	AOEM	
	Protected body (workwear or protective garment and sturdy footwear)	2	5	AOEM	
	Inhalation	2	3	AOEM	
	Protective Equipment	Select for inclusion		Penetration factor	Inhalation Protection factor
	Gloves	Yes		Incl. in AOEM model	
	Clothing	Work wear - arms, body and legs covered		Incl. in AOEM model	
	Head and respiratory PPE	None		1	1
	Closed cab	No		vehicle mounted downward spraying only	

1. Total

	Without RPE/PPE	With RPE/PPE
Longer term		
Total systemic exposure from mixing, loading and application (mg a.s./day)	0.0887127	0.0094527
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0014952	0.0001575
% of RVNAS	7.48%	0.79%
Acute		
Total systemic exposure from mixing, loading and application (mg a.s./day)	0.5477856	0.0465058
Total systemic exposure from mixing, loading and application per kg body weight (mg/kg bw/day)	0.0091298	0.0007751
% of RVANS	30.43%	2.58%

Table A1: (contin.)

2. Longer term exposure

2.1 Mixing and loading

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	26.0404419	0.4340074	*D15*i_AbsorpProduct*
Body	17.5550355	0.2925839	*D16*i_AbsorpProduct*
Head	0.3735618	0.0062260	*D17*i_AbsorpProduct*
Inhalation	5.4194551	0.0903243	*D21*i_AbsorpInhalation*
Sum	49.3884944	0.8231416	
With RPE/PPE (as selected above)			
Hands	0.1585098	0.0026418	*D18*i_AbsorpProduct*
Body	0.1479483	0.0024658	*D19*i_AbsorpProduct or D35*i_AbsorpProduct*F24*
Head	0.3735618	0.0062260	*D20*i_AbsorpProduct or D17*i_AbsorpProduct*F25*
Inhalation	5.4194551	0.0903243	*D21*i_AbsorpInhalation*G25*
Sum	6.0994750	0.1016579	
Water soluble	6.0994750	0.1016579	*C70*F26*

2.2 Application

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	31.6313378	0.5271890	*D30*i_AbsorpInuse*
Body	6.4962172	0.1082703	*D31*i_AbsorpInuse*
Head	0.2591487	0.0043191	*D32*i_AbsorpInuse*
Inhalation	1.9374597	0.0322910	*D35*i_AbsorpInhalation*
Sum	40.3241635	0.6720694	
With RPE/PPE (as selected above)			
Hands	0.9288968	0.0154816	*D33*i_AbsorpInuse*
Body	0.2277533	0.0037959	*D34*i_AbsorpInuse or D31*i_AbsorpInuse*F38*
Head	0.2591487	0.0043191	*D32*i_AbsorpInuse*F39*
Inhalation	1.9374597	0.0322910	*D35*i_AbsorpInuse*G39*
Sum	3.3532585	0.0558876	

3. Acute exposure

3.1 Mixing and loading

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	96.4997879	1.6083298	*E15*i_AbsorpProduct*
Body	208.9913886	3.4831898	*E16*i_AbsorpProduct*
Head	2.0488138	0.0341469	*E17*i_AbsorpProduct*
Inhalation	29.6046534	0.4934076	*E21*i_AbsorpInhalation*
Sum	337.1444437	5.6190741	
With RPE/PPE (as selected above)			
Hands	1.4260870	0.0237681	*E18*i_AbsorpProduct*
Body	1.0530100	0.0175501	*E19*i_AbsorpProduct or E16*i_AbsorpProduct*F24*
Head	2.0488138	0.0341469	*E20*i_AbsorpProduct or E17*i_AbsorpProduct*F25*
Inhalation	29.6046534	0.4934076	*E21*i_AbsorpInhalation*G25*
Sum	34.1323642	0.5688727	
Water soluble	34.1323642	0.5688727	*C104*F26*

2.2 Application

	Systemic exposure [µg a.s. /day]	Systemic exposure [µg a.s./kg bw/day]	Formula
Without RPE/PPE			
Hands	200.6551102	3.3442518	*E30*i_AbsorpInuse*
Body	6.6024062	0.1100401	*E31*i_AbsorpInuse*
Head	0.5535924	0.0092265	*E32*i_AbsorpInuse*
Inhalation	2.8300623	0.0471677	*E35*i_AbsorpInhalation*
Sum	210.6411714	3.5106862	
With RPE/PPE (as selected above)			
Hands	8.7371800	0.1456197	*E33*i_AbsorpInuse*
Body	0.2522794	0.0042097	*E34*i_AbsorpInuse or E31*i_AbsorpInuse*F38*
Head	0.5535924	0.0092265	*E32*i_AbsorpInuse*F39*
Inhalation	2.8300623	0.0471677	*E35*i_AbsorpInhalation*G39*
Sum	12.3734142	0.2062236	

Table A2: Resident exposure calculation (using the EFSA calculator), 300 L/ha spray

1. Total

1.1 1-3 year old child

	Spray drift (75th percentile)	Vapour (75th percentile)	Surface deposits (75th percentile)	Entry into treated crops (75th percentile)	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0045312	0.0107000	0.0018406	0.0305108	0.0388750
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0004531	0.0010700	0.0001841	0.0030511	0.0038875
% of RVNAS	2.27%	5.35%	0.92%	15.26%	19.44%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops	All pathways (mean)
Total systemic exposure (mg a.s./day)	0.0064867	0.0138000	0.0036957	0.1017028	0.1006824
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0001081	0.0002300	0.0000616	0.0016950	0.0016780
% of RVNAS	0.54%	1.15%	0.31%	8.48%	8.39%

2. Resident exposure 75th Percentile

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0045312	0.0004531	((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	d_AirCon*d_BreathRCh*d_BwChild	
Surface deposits				
Dermal	0.0013163	0.0001316	(i_AppRate/100)*C29*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0003435	0.0000344	(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0001808	0.0000181	(i_AppRate/100)*C29*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0305108	0.0030511	(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	
Hand to mouth			(i_AppRate/100)*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0064867	0.0001081	((C15*i_AbsorpInuse*(1-d_ClothAF))+C17)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	d_AirCon*d_BreathRAd*d_BwAdult	
Surface deposits (dermal)	0.0036957	0.0000616	(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*i_AbsorpInuse	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.1017028	0.0016950	(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	

3. Summing of exposure pathways mean

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0025001	0.0002500	((C20*i_AbsorpInuse*(1-d_ClothAF))+C22)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	d_AirCon*d_BreathRCh*d_BwChild	
Surface deposits				
Dermal	0.0009637	0.0000964	(i_AppRate/100)*C30*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0002515	0.0000252	(i_AppRate/100)*C30*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0001324	0.0000132	(i_AppRate/100)*C30*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0243273	0.0024327	(d_TcEntryMeanCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse))	
Hand to mouth			(i_AppRate/100)*1*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			(i_AppRate/100)*1*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0030853	0.0000514	"(C19*i_AbsorpInuse*(1-d_ClothAF))+C21)*d_ConcAS"	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	d_AirCon*d_BreathRAd*d_BwAdult	
Surface deposits (dermal)	0.0027057	0.0000451	(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0810910	0.0013515	(d_TcEntryMeanAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	

Table A2 (contin.): Bystander exposure calculation (using the EFSA calculator), 300 L/ha spray

1. Total

1.1 1-3 year old child

	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.0103286	0.0107000	0.0053680	0.0305169
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0010329	0.0010700	0.0005368	0.0030521
% of RVAAS	3.44%	3.57%	1.79%	10.17%

1.2 Adult

	Spray drift	Vapour	Surface deposits	Entry into treated crops
Total systemic exposure (mg a.s./day)	0.0167290	0.0138000	0.0111421	0.1017028
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0002788	0.0002300	0.0001857	0.0016950
% of RVAAS	0.93%	0.77%	0.62%	5.65%

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0103286	0.0010329	*((C16*i_AbsorpInuse*(1-d_ClothAF))+(C19*d_ConcAS")*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	*d_AirCon*d_BreathRAd*d_BwChild*	
Surface deposits				
Dermal	0.0039958	0.0003996	*(i_AppRate/100)*C24*d_Turf*d_ByTCCh*d_ByExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip="Vehicle-mounted-Drift Reduction",0.5,1)*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0010977	0.0001098	*(i_AppRate/100)*C25*d_Turf*d_SolEst*d_AreqHM*d_ByFreqHM*d_ByExpDur*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0002744	0.0000274	*(i_AppRate/100)*C25*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0305108	0.0030511	*(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	
Hand to mouth			*(i_AppRate/100)*d_MAF*d_Turf*d_SolExt*d_AreqHM*d_ByFreqHM*d_ByExpDur*i_AbsorpOralInuse*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			*(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF*	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0167290	0.0002788	*((C15*i_AbsorpInuse*(1-d_ClothAF)t)+C17)*d_ConcAS*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	*d_AirCon*d_BreathRAd*d_BwAdult*	
Surface deposits (dermal)	0.0111421	0.0001857	*(i_AppRate/100)*C24*d_Turf*d_ByTCAd*d_ByExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip="Vehicle-mounted-Drift Reduction",0.5,1)*	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.1017028	0.0016950	*(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)*	

Table A3: Refinement of resident exposure via 'surface deposits' (using the EFSA calculator, DT_{50} = 2.3 days), 300 L/ha spray)

Substance	Thiacloprid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.24 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications =2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 0.2	Dermal for in use diluation = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	2.3 days	

2. Resident exposure 75th Percentile

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0045312	0.0004531	((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	d_AirCon*d_BreathRCh*d_BwChild	
Surface deposits				
Dermal	0.0007699	0.0000770	(i_AppRate/100)*C29*d_Turf*d_ReTCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0002009	0.0000201	(i_AppRate/100)*C29*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0001058	0.0000106	(i_AppRate/100)*C29*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0178454	0.0017845	(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	
Hand to mouth			(i_AppRate/100)*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0064867	0.0001081	(C15*i_AbsorpInuse*(1-d_ClothAF))+C17)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	d_AirCon*d_BreathRAd*d_BwAdult	
Surface deposits (dermal)	0.0021615	0.0000360	(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*i_AbsorpInuse	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0594846	0.0009914	(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	

3. Summing of exposure pathways mean

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0025001	0.0002500	((C20*i_AbsorpInuse*(1-d_ClothAF))+C22)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	d_AirCon*d_BreathRCh*d_BwChild	
Surface deposits				
Dermal	0.0005636	0.0000564	(i_AppRate/100)*C30*d_Turf*d_RETCCh*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1))	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0001471	0.0000147	(i_AppRate/100)*C30*d_Turf*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0000774	0.0000077	(i_AppRate/100)*C30*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0142287	0.0014229	(d_TcEntryMeanCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse))	
Hand to mouth			(i_AppRate/100)*1*d_Turf*d_MAF*d_SalExt*d_AreaHM*d_ReFreqHM*d_ReExpDur*i_AbsorpOralInuse	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			(i_AppRate/100)*1*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0030853	0.0000514	"(C19*i_AbsorpInuse*(1-d_ClothAF))+C21)*d_ConcAS"	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	d_AirCon*d_BreathRAd*d_BwAdult	
Surface deposits (dermal)	0.0015826	0.0000264	(i_AppRate/100)*C30*d_Turf*d_ReTCAd*d_ReExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip = "Vehicle-mounted-Drift Reduction",0.5,1)	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0474290	0.0007905	(d_TcEntryMeanAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	

Summary surface deposits: Child 75th perc. = 0.0001077 mg/kg bw/day (0.0000770 + 0.0000201 + 0.0000106)
Child mean = 0.0000788 mg/kg bw/day (0.0000564 + 0.0000147 + 0.0000077)
Adult 75th perc. = 0.0000360 mg/kg bw/day
Adult mean = 0.0000264 mg/kg bw/day

Table A3 (contin.): Refinement of bystander exposure via 'surface deposits' (using the EFSA calculator, DT_{50} = 2.3 days), 300 L/ha spray)

Substance	Thiacloprid	Formulation = Soluble concentrates, emulsifiable concentrate, etc.	Application rate-0.072 kg a.s. /ha	Spray dilution = 0.24 g a.s./l	Vapour pressure = low volatile substances having a vapour pressure of
Scenario	Oilseeds / Outdoor / Downward spraying / Vehicle-mounted-Drift Reduction			Buffer = 2-3	Number applications = 2, Application interval = 10 days
Percentage Absoprtion	Dermal for product = 0.2	Dermal for in use diluation = 14	Oral = 100	Inhalation = 100	
RVNAS	0.02 mg/kg bw/day		RVAAS	0.03 mg/kg bw/day	
DFR	3 µg a.s./cm2 per kg a.s./ha		DT50	2.3 days	

2. Details

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
1-3 year old child				
Spray drift	0.0103286	0.0010329	((C16*i_AbsorpInuse*(1-d_ClothAF))+C18)*d_ConcAS)	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0107000	0.0010700	d_AirCon*d_BreathRCh*d_BwChild	
Surface deposits				
Dermal	0.0023371	0.0002337	(i_AppRate/100)*C24*d_Turf*d_ByTCCh*d_ByExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip="Vehicle-mounted-Drift Reduction",0.5,1)	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Hand to mouth	0.0006421	0.0000642	(i_AppRate/100)*C25*d_Turf*d_SalExt*d_AreaHM*d_ByFreqHM*d_ByExpDur*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Object to mouth	0.0001605	0.0000161	(i_AppRate/100)*C25*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops				
Dermal	0.0178454	0.0017845	(d_TcEntryCh*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	
Hand to mouth			(i_AppRate/100)*d_MAF*d_Turf*d_SalExt*d_AreaHM*d_ByFreqHM*d_ByExpDur*i_AbsorpOralInuse	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Object to mouth			(i_AppRate/100)*d_DRP*d_MouthGrass*i_AbsorpOralInuse*d_MAF	Considered only for application on grassland and lawns and for application on golf course, turf or other sports lawns.
Adult				
Spray drift	0.0167290	0.0002788	((C15*i_AbsorpInuse*(1-d_ClothAF)t)+C17)*d_ConcAS	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Vapour	0.0138000	0.0002300	d_AirCon*d_BreathRAd*d_BwAdult	
Surface deposits (dermal)	0.0065169	0.0001086	(i_AppRate/100)*C24*d_Turf*d_ByTCAd*d_ByExpDur*MAX(i_AbsorpProduct,i_AbsorpInuse)*d_MAF*IF(i_AppEquip="Vehicle-mounted-Drift Reduction",0.5,1)	Since drift reducing nozzles are selected a 50% reduction factor has been applied
Entry into treated crops (dermal)	0.0594846	0.0009914	(d_TcEntryAd*0.25*d_DFR*d_MAF)/1000*MAX(i_AbsorpProduct,i_AbsorpInuse)	

Summary surface deposits: Child 95th perc. = 0.000314 mg/kg bw/day (0.0002337 + 0.0000643 + 0.0000161)
Adult 95th perc. = 0.000109 mg/kg bw/day

Table A4: Worker exposure calculation (using EFSA calculator, DT_{50} = 30 days, 300 L/ha spray)

Substance name	Thiacloprid	
Product name	Biscaya 240 OD	
Reference value non acutely toxic active substance (RVNAS)	0.02	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)	0.03	mg/kg bw/day
Crop type	Oilseeds	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	300	L/ha
Maximum application rate of active substance	0.072	kg a.s. /ha
50% Dissipation Time DT50	30	days
Initial Dislodgeable Foliar Residue	3	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.20%	
Dermal absorption of in-use dilution	14.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of < 1*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted/Drift Reduction	
Buffer strip	2-3 m	
Number of applications	2	
Interval between multiple applications	10 days	
Season (upward spraying orchards only)	not relevant	

Worker exposure from residues on foliage for Biscaya 240 OD

Crop type	Oilseeds		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift-Reduction		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.072	kg a.s./ha	*i_AppRate*
Number of applications	2		*i_AppNo*
Interval between multiple applications	10	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	1.8		*d_MAF*
Dermal absorption of the product	0.2%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	14.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.216	µg a.s./cm²	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm²/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm²/hr	*d_DermTcCV1*
Dermal transfer coefficient - Hands, arms, body and legs covered	no TC available for this assessment	cm²/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	1.3560376	0.1518762	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0226006	0.0025313		
% of RVNAS	113.00%	12.66%		

2. Details

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	1.3560376	0.0226006	*d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse*	
Dermal - Work wear - arms, body and legs covered	0.1518762	0.0025313	*d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Dermal - Working wear and gloves	no TC available for this assessment		*d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Inhalation				Na for outdoor activities

Table A5: Worker exposure calculation (DT_{50} = 2.3 days, initial DFR = 2.6 µg/cm², 300 L/ha spray)

Substance name	Thiacloprid	
Product name	Biscaya 240 OD	
Reference value non acutely toxic active substance (RVNAS)	0.02	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)	0.03	mg/kg bw/day
Crop type	Oilseeds	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.	
Miniumum volume water for application (liquids)	300	L/ha
Maximum application rate of active substance	0.072	kg a.s. /ha
50% Dissipation Time DT50	2.3	days
Initial Dislodgeable Foliar Residue	2.6	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.20%	
Dermal absorption of in-use dilution	14.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of < 10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted Drift Reduction	
Buffer strip	2-3	m
Number of applications	2	
Interval between multiple applications	10	days
Season (upward spraying orchards only)	not relevant	

Worker exposure from residues on foliage for Biscaya 240 OD

Crop type	Oilseeds		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted-Drift Reduction		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.072	kg a.s./ha	*i_AppRate*
Number of applications	2		*i_AppNo*
Interval between multiple applications	10	days	*i_AppInt*
Half-life of active substance	2.3	days	*d_HalflifeAS*
Multiple application factor	1.0		*d_MAF*
Dermal absorption of the product	0.20%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	14.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.1872	µg a.s./cm²	*d_DFR*
Working hours	2	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	12500	cm²/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	1400	cm²/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm²/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	0.6873772	0.0769862	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0114563	0.0012831		
% of RVNAS	57.28%	6.42%		

2. Details

	Systemic exposure [mg a.s./day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	0.6873772	0.0114563	*d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse*	
Dermal - Work wear - arms, body and legs covered	0.0769862	0.0012831	*d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Dermal - Working wear and gloves	no TC available for this assessment		*d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse*	
Inhalation				Na for outdoor activities

Table A6: Worker exposure calculation (using proposed TC = 803 cm²/hr for gloves, DT_{50} = 2.3 days, initial DFR = 2.6 µg/cm²) (TCs = 95th param. estimates)

Substance name	Thiacloprid	
Product name	Biscaya 240 OD	
Reference value non acutely toxic active substance (RVNAS)	0.02	mg/kg bw/day
Reference value acutely toxic active substance (RVAAS)	0.03	mg/kg bw/day
Crop type	Oilseeds	
Substance properties		
Formulation type	Soluble concentrates, emulsifiable concentrate, etc	
Miniumum volume water for application (liquids)	300	L/ha
Maximum application rate of active substance	0.072	kg a.s. /ha
50% Dissipation Time DT50	2.3	days
Initial Dislodgeable Foliar Residue	2.6	µg/cm2 of foliage/kg a.s. applied/ha
Dermal absorption of product	0.20%	
Dermal absorption of in-use dilution	14.00%	
Oral absorption of active substance	100.00%	
Inhalation absorption of active substance	100.00%	
Vapour pressure of active substance	low volatile substances having a vapour pressure of <5*10-3Pa	
Scenario		
Indoor or Outdoor application	Outdoor	
Application method	Downward spraying	
Application equipment	Vehicle-mounted, Drift Reduction	
Buffer strip	2-3	m
Number of applications	2	
Interval between multiple applications	10	days
Season (upward spraying orchards only)	not relevant	

Worker exposure from residues on foliage for Biscaya 240 OD

Crop type	Oilseeds		
Indoor or outdoor	Outdoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted, Drift Reduction		
Worker's task	Inspection, irrigation		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	0.072	kg a.s./ha	i_AppRate
Number of applications	2		i_AppNo
Interval between multiple applications	10	days	i_AppInt
Half-life of active substance	2.3	days	d_HalflifeAS
Multiple application factor	1.049		d_MAF
Dermal absorption of the product	0.20%		i_AbsorpProduct
Dermal absorption of the in-use dilution	14.00%		i_AbsorpInuse
Dislodgeable foliar residue (i_AppRate*i_DFR)	0.1872	µg a.s./cm²	d_DFR
Working hours	2	hr	d_WorkHr
Dermal transfer coefficient - Total potential exposure	2500	cm²/hr	d_DermTcUCV
Dermal transfer coefficient - arms, body and legs covered	1400	cm²/hr	d_DermTcCV1
Dermal transfer coefficient - hands, arms, body and legs covered	no TC available for this assessment	cm²/hr	d_DermTcCV2
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	d_InhalTcAut
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	d_InhalTcCut
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	d_InhalTcSort

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	0.6873772	0.0769862	no TC available for this assessment	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0114563	0.0012831		
% of RVNAS	57.28%	6.42%		

2. Details

	Systemic exposure [mg a.s. /day]	Systemic exposure [mg a.s./kg bw/day]	Formula	Comments
Dermal - Potential	0.6873772	0.0114563	d_DermTcUCV*d_WorkHr*i_DFR*i_MAF/1000*i_AbsorpInuse	
Dermal - Work wear - arms, body and legs covered	0.0769862	0.0012831	d_DermTcCV1*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Dermal - Working wear and gloves	no TC available for this assessment		d_DermTcCV2*d_WorkHr*d_DFR*d_MAF/1000*i_AbsorpInuse	
Inhalation				Na for outdoor activities

Dermal-working wear and gloves (using dermal transfer coefficient – hands, arms, body and legs covered = 803 cm²/hr):

$$\text{Worker exposure (mg/kg bw/day)} = \frac{\text{Transfer coefficient inspection/scouting (cm}^2\text{/hr)} \times \text{Duration (hr)} \times \text{DFR (µg/cm}^2) \times \text{MAF}}{1000} \times \frac{\text{Dermal absorption (\%)}}{\text{Body weight (kg)}}$$

Worker exposure (mg/kg bw/day): 803 x 2 x 0.1872 x 1.049/1000 x 14%/60 = 0.000736

Appendix II: Derivation of hazard specific AOELs for thiacloprid

Hazard specific AOELs were derived for those reprotoxicity parameters of thiacloprid, which were the basis for classification of thiacloprid with Repro. 1B; H360FD by the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA), i.e.

1. Dystocia,
2. Reduced pup weights (observed on day 4 and day 7, resp.),
3. Increased incidences of post-implantation loss,
4. Increased incidences of stillbirths & cannibalized pups (possible sign for weak pups)

In the following, the derivation of the hazard specific AOELs is described.

1. Dystocia:

Incidences of dystocia observed in several generation studies on thiacloprid in Sprague-Dawley rats of the breeder Sasco, Inc. (ordered by increasing dose)

Author, Year Reference	Dose [ppm]	Dose* [mg/kg bw/day]	Incidences [% (cases) per pregnant dams]
[redacted], 1998, M-003820-01-1	300	**20**	**0 (0/25)**
[redacted], 1997, M-001304-01-1	300	22	13.3 (4/30)
[redacted], 1997, M-001304-01-1	600	43	10.0 (3/30)
[redacted]-[redacted], 2011, M-403763-01-1	800	54	11.5 (3/26)
[redacted], 1998, M-004253-01-1	800	61**	8.3 (1/12)#
[redacted], 1998, M-003820-01-1	1000	68	4.5 (1/22)
[redacted], 1998, M-004291-01-1	1000	73***	3.3 (1/30)
Historical control data in Sasco Sprague-Dawley rats##			Range: 0 - 11.5 (0/30 - 3/26) Mean incidence: 1.21 (11/906)

*: dose intake determined during gestation
** dose intake determined for pre-mating, gestation and lactation
**: dose intake determined during premating, not determined during gestation
#: There was one additional case of dystocia, but this was obviously caused by big pups (one pup stuck in the birth canal) and is therefore not considered to be related to thiacloprid treatment.
##: Historical control data on dystocia in Sprague-Dawley rats from the breeder Sasco, compiled from 26 one- and two-generation studies (comprising 40 generations) conducted at BCS [redacted] U.S. between 1988 and 1997 (in 1997: switch to Wistar rats) (for details please refer to [redacted], 2014, M-498539-01-1)

Increased incidences of dystocia were observed in generation studies on thiacloprid at dose levels of 22 mg/kg bw/day and higher. Due to the missing dose response, calculation of a benchmark dose was not possible. **Therefore, a hazard specific AOEL of 0.2 mg/kg bw/day was calculated on dystocia based on the NOEL for dystocia of 20 mg/kg bw/day and a safety factor of 100.**

2. Reduced pup weights (observed on day 4 and day 7, resp.):

[redacted], D.A., [redacted], B.F.; A two-generation dietary reproduction study in rats using technical YRC 2894
BCS report 107628; Doc ID M-001304-01-1; 1997-12-08

Rat strain: Sprague-Dawley, Sasco
Study conduct: 1995/1996 at [redacted], Kansas, U.S.
Treatment *via* diet, starting 10 weeks before mating

Dose (during gestation) [ppm] **[mg/kg bw]**		0 **0**	50 **3.8/3.6** **(P/F1)**	300 **23/22** **(P/F1)**	600 **43/43** **(P/F1)**	**Historical control data 1992 – 1997^**
No. of dams P-generation		*30*	*30*	*30*	*30*	
No. of dams F1-generation		*30*	*30*	*30*	*30*	
Pup weights (g), mean F1	at birth	6.6	6.7	6.5	6.5	6.4 – 7.0
	day 7	15.4	15.6	15.0	**14.1*** *(-8.4% of control mean)*	14.9 - 17.6
Pup weights (g), mean F2	at birth	6.6	6.6	6.6	**6.4**	6.5 - 7.1
	day 7	15.6	16.1	**14.8** *(-5.1% of control mean)*	**13.9**** *(-10.9% of control mean)*	15.3 - 17.5

^: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1993-1997 (in 1997 the rat strain was switched from Sprague Dawley to Wistar) were compiled in document M-509754-01-2 ([redacted], 2015).
bw: body weight
M: male
F: female

[redacted] et al., 1995.; A two-generation reproduction range-finding study with YRC 2894 technical in rats
BCS report 107043; Doc ID M-000911-01-1; 1995-06-02

Rat strain: Sprague Dawley, Charles River Crl:CD BR
Study conduct: 1994 at., [redacted], IN, U.S.
Treatment *via* diet, starting at minimum 28 days before mating; F1 pups were raised until week 3 post partum.

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *7*	100 **7.6** *7*	400 **31.1** *7*	1600 **117.1** *7*	**Historical control data 1990-1992[B]**
Pup weights (g), mean at birth day 4	6.0 9.8	6.3 10.4	6.6 10.4	6.0 **8.1*** *(-17.2% of control mean)*	5.8 – 6.5 8.7 – 10.4

Historical control data[B]:
Historical control data from the same lab and the same strain of rats are given in the report on page 89. The data stem from 7 two-generation studies conducted between 1990 and 1992. Further data are not available for this lab and rat strain.
bw: body weight
M: male
F: female

[redacted], D.A.; A one-generation dietary reproduction study in rats using technical grade YRC 2894 to evaluate the reproducibility of Dystocia and an increase in stillbirths in the P generation of a two-generation dietary reproduction study in rats
BCS report 107641; Doc ID M-003820-01-1; 1998-05-12

Rat strain: Sprague-Dawley, Sasco
Study conduct: 1996/1997 at [redacted], Kansas, U.S.
Treatment *via* diet, starting 10 weeks before mating

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *30*	25 **2** *30*	300 **20** *30*	1000 **68** *30*	**Historical control data 1993 - 1997[A]**
Pup weights (g), mean at birth day 4	6.7 10.3	6.6 10.4	6.8 10.2	6.5 **8.9*** *(-13.6% of control mean)*	6.4 – 7.0 9.6 - 10.9

[A]: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1993-1997 (in 1997 the rat strain was switched from Sprague Dawley to Wistar) were compiled in document M-509754-01-2 ([redacted], 2015).
bw: body weight
M: male
F: female

[redacted]n, A.M.; Oral (diet) developmental neurotoxicity study of YRC 2894 in CRL:CD(SD) IGS BR VAF/PLUS
BCS report 110834 Doc ID M-088059-01-1; 2001-09-24

Rat strain: Sprague-Dawley, Charles River Laboratories, Crl:CD (SD) IGS BR VAF/PLUS
Study conduct: 2000 at Argus Research Laboratories, USA
Treatment *via* diet, no treatment before mating

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *25*	50 **4.4** *25*	300 **25.6** *25*	500 **40.8** *25*	**Historical control data**
Pup weights (g), mean /litter PND1 PND5	6.8 10.3	6.8 10.4	7.0 10.2	7.1 10.0	No data

PND: postnatal day

Reduced pup weight (observed on day 4 or 7, respectively) were observed in four generation studies in rats: in the two-generation study by [redacted] & [redacted] (1997, M-001304-01-1), in the dose range finder for the two-generation study by [redacted] et al. (1995, M-000911-01-1), a special one-generation study by [redacted] (1998, M-003820-01-1) and a developmental neurotoxicity (DNT) study by [redacted] (2001, M-088059-01-1). A benchmark dose calculation was not considered adequate in this case, since in the individual studies only the high dose showed a statistically significant effect. Drawing together the effect data from the different studies for a benchmark dose calculation did not seem to be adequate either, because pup weights were determined on different days (on day 7 in the two-generation study ([redacted] & [redacted], 1997, M-001304-01-1), on day 4 in the dose range finder for the two-generation study ([redacted] et al., 1995, M-000911-01-1) and in the special one-generation study ([redacted], 1998, M-003820-01-1), and on day 5 in the DNT study ([redacted], 2001, M-088059-01-1). Furthermore, treatment duration was different in the four studies, starting 10 weeks pre-mating in the two-generation study ([redacted] & [redacted], 1997, M-001304-01-1) and in the special one-generation study ([redacted], 1998, M-003820-01-1), as well as 4 weeks pre-mating in the dose range finder for the two-generation study ([redacted] et al.,1995, M-000911-01-1), while there was no treatment before mating in the DNT study ([redacted], 2001, M-088059-01-1). Treatment duration might have an influence on the magnitude of effect in this case, since no effect was observed on day 5 in the DNT study up to 40.8 mg/kg bw/day, while both generations of the two-generation study showed a reduction of pup weight of approximately -14% on day 7 at 43 mg/kg bw/day. In addition, studies were conducted in three different laboratories with Sprague-Dawley rats from three different breeders (details can be found above in the study specific information). **Therefore, the overall NOAEL of 20 mg/kg bw/day for reduced pup weight on day 4 and 7** (NOAELs: two-generation study (day 7): 23/22 mg/kg bw/day, special one-generation study (day4): 20 mg/kg bw/day) **and a safety factor of 100 were selected as a basis for the respective hazard specific AOEL of 0.2 mg/kg bw/day on reduced pup weight (on day 4 and 7, respectively).**

3. Increased incidences of post-implantation loss:

[redacted], B. (1997), YRC 2894 - Developmental toxicity in rats after oral administration, BCS report 26132, Doc ID M-000832-01-1, 1997-03-25
Rat strain: Wistar rat (Hsd Cpb:WU)
Treatment: daily with gavage from gestation day (GD) 6 to GD19
Study conduct: 1995/1996 at [redacted], Germany

Dose [mg/kg bw] *No. of dams on study* *No. of dams with implantations* *No. of dams with viable fetuses*	**0** *35* *28* *28*	**2** *35* *31* *31*	**10** *35* *32* *32*	**50** *35* *30* *29*	**Historical control data 1992-1999[A]**
Post-implantation loss (%) mean per dam with implantations mean per dam with viable fetuses	 0.9 0.9	 0.9 0.9	 0.5 0.5	 **2.8**** **2.5**	 0.5 – 1.6 0.5 – 1.4

[A]: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1992-1994 were taken from report M-000832-01-1 itself ([redacted], 1997), HCD from 1995-1998 were taken from report M-071988-01-1 ([redacted], 2001)

[redacted], B. (1996), YRC 2894 - Developmental toxicity in rabbits after oral administration, BCS report 24709, Doc ID M-000780-01-1, 1996-01-26

Rabbit strain: Himalayan rabbit (CHBB:HM)
Treatment: daily with gavage from gestation day (GD) 6 to GD28
Study conduct: 1995 at [redacted] in [redacted], Germany

Dose [mg/kg bw] *No. of dams on study* *No. of dams with implantations* *No. of dams with viable fetuses*	**0** *24* *22* *22*	**2** *24* *21* *20*	**10** *24* *24* *24*	**45** *24* *22* *19*	**Historical control data 1992-1998[A]**
Post-implantation loss (%) mean per dam with implantations mean per dam with viable fetuses	 0.9 0.9	 1.0 0.8	 0.3 0.3	 1.8[B] 1.0[B]	 0.1-1.3 0.1-1.3

[A]: Historical control data (HCD) from studies conducted in the same lab and in the same rabbit strain from 1992-1996 were taken from report M-005765-01-1 ([redacted], 1998), HCD from 1997-1998 were taken from report M-026265-01-1 ([redacted], 2000)

[B]: 4/5 female rabbits, which aborted or showed total resorption at the 45 mg/kg level, showed more severe decreases in feed intake than the remaining does; two of these females with total resorptions had shown a very severe body weight loss of 22.5 or 25.5 % of their body weight on day 6 post coitum during treatment.

Increased incidences of post-implantation loss were observed in the developmental toxicity studies on thiacloprid in rat and rabbit at the high dose of 50 or 45 mg/kg bw/day, respectively. Calculation of a benchmark dose was not possible, since the effect was exclusively observed at the high dose. **Therefore, the NOAEL of 10 mg/kg bw/day for this paramenter in rat and rabbit and a safety factor of 100 were taken to derive a hazard specific AOEL of 0.1 mg/kg bw/day on post-implantation loss.**

4. Increased incidences of stillbirths & cannibalized pups (possible sign for weak pups):

[redacted], D.A.; [redacted], B.F.; A two-generation dietary reproduction study in rats using technical YRC 2894
BCS report 107628; Doc ID M-001304-01-1; 1997-12-08

Rat strain: Sprague-Dawley, Sasco
Study conduct: 1995/1996 at [redacted], Kansas, U.S.
Treatment *via* diet, starting 10 weeks before mating

Dose (during gestation) [ppm] [mg/kg bw]	0 **0**	50 **3.8/3.6 (P/F1)**	300 **23/22 (P/F1)**	600 **43/43 (P/F1)**	**Historical control data 1992-1997[A]**
No. of dams P-generation	*30*	*30*	*30*	*30*	
No. of dams F1-generation	*30*				
Total no. of F1 pups born	314	360	290	282	86 - 434
stillborn	2	16	13	16	0 - 16
cannibalized	0	1	0	0	
missing	5	9	6	**17**	
cannibalized & missing	5	10	6	**17**	
Total no. of F2 pups born	306	347	318	313	296 - 372
stillborn	9	**14**	8	**18**	0 - 9
cannibalized	0	0	2	0	
missing	3	2	5	**14**	
cannibalized & missing	3	2	7	**14**	
Fetal incidence of stillbirths (%) F1	0.6	**4.4**[1]	**4.5**[1]	**5.7**[1]	0 - 3.9
F2	2.9	**4.0**[1]	2.5	**5.8**[1]	0 - 2.9
Incidence of stillbirths (dams with stillborns (> 2 stillborns) / total no. of pregnant dams) F1	2 (0) / 28	7 (3) / 29	2 (2) / 24	8 (1) / 27	
F2	4 (1) / 25	7 (3) / 28	8 (0) / 26	8 (2) / 28	
Fetal incidence of cannibalized and missing pups (%) F1	1.59	2.78	2.07	**6.03**	
F2	0.98	0.56	2.20	**4.47**	

A: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1993-1997 (in 1997 the rat strain was switched from Sprague Dawley to Wistar) were compiled in document M-509754-01-2 ([redacted], 2015).
bw: body weight
M: male
F: female
1: In this two-generation study as well as in the whole set of generation studies on thiacloprid the incidences of stillbirths show no consistent dose correlation. Furthermore, there was no increase in the no. of dams with more than 2 stillborn pups. Clearly increased incidences were only observed at high, maternally toxic doses.
*: statistically significantly different from controls, p<0.05
**: statistically significantly different from controls, p<0.01

[redacted] et al., 1995.: A two-generation reproduction range-finding study with YRC 2894 technical in rats
BCS report 107043; Doc ID M-000911-01-1; 1995-06-02

Rat strain: Sprague Dawley, Charles River Crl:CD BR
Study conduct: 1994 at [redacted], [redacted], IN, U.S.
Treatment *via* diet, starting at minimum 28 days before mating; F1 pups were raised until week 5 post partum.

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *7*	100 **7.6** *7*	400 **31.1** *7*	1600 **117.1** *7*	**Historical control data 1990-1992[B]**
Total no. of F1 pups born stillborn found dead (PND 0-4) **No indication for missing & cannibalized pups**	107 6 3	73 1 2	81 1 0	97 3 **16**	170 - 389 0 - 6 1 - 15
Fetal incidence of stillbirths (%)	5.6	1.4	1.2	3.1	0 - 1.6 **concurrent control: 5.6**
Incidence of stillbirths – dams with stillborns (> 2 stillborns) / total no. of pregnant dams	2 (1) / 7	1 (0) / 5	1 (0) / 6	3 (0) / 7	No data
Fetal incidence of cannibalized and missing pups (%) F1	0.0	0.0	0.0	0.0	

Historical control data[B]: Historical control data from the same lab and the same strain of rats are given in the report on page 89. The data stem from 7 two-generation studies conducted between 1990 and 1992. Further data are not available for this lab and rat strain.
bw: body weight
M: male
F: female

[redacted], D.A.; A one-generation dietary reproduction study in rats using technical grade YRC 2894 to evaluate the reproducibility of Dystocia and an increase in stillbirths in the P generation of a two-generation dietary reproduction study in rats
BCS report 107641; Doc ID M-003820-01-1; 1998-05-12

Rat strain: Sprague-Dawley, Sasco
Study conduct: 1996/1997 at [redacted], Kansas, U.S.
Treatment *via* diet, starting 10 weeks before mating

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *30*	25 **2** *30*	300 **20** *30*	1000 **68** *30*	**Historical control data 1993 <1997^A**
Total no. of F1 pups born stillborn found dead	337 13 4	292 5 3	291 **15** 9	198 **15** **14**	86 - 383 0 - 13 0 - 9
cannibalized	1	2	3	0	
missing	3	0	1	15	
cannibalized & missing	4	2	4	**15**	
Fetal incidence of stillbirths (%)	3.9	1.7	**5.2**	**7.6**	0 - 3.9
Incidence of stillbirths dams with stillborns (> 2 stillborns) / total no. of pregnant dams	6 (2) / 27	3 (1) / 25	7 (1) / 25	7 (2) / 20	
Fetal incidence of cannibalized and missing pups (%) F1	1.19	0.68	1.37	**7.58**	

^A: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1993-1997 (in 1997 the rat strain was switched from Sprague Dawley to Wistar) were compiled in document M-509754-01-2 ([redacted], 2015).
bw: body weight
M: male
F: female

[redacted]n, A.M., Oral (diet) developmental neurotoxicity study of YRC 2894 in CRL:CD(SD) IGS BR VAF/PLUS
BCS report 110834 Doc ID M-088059-01-1; 2001-09-24

Rat strain: Sprague-Dawley, Charles River Laboratories, Crl:CD (SD) IGS BR VAF/PLUS
Study conduct: 2000 at Argus Research Laboratories, USA
Treatment *via* diet, no treatment before mating

Dose (during gestation) [ppm] **[mg/kg bw]** *No. of dams P-generation*	0 **0** *25*	50 **4.4** *25*	300 **25.6** *25*	500 **40.8** *25*	**Historical control data**
Total no. of pups born stillborn found dead or presumed cannibalized (PND 1-5)	351 5 4	349 0 5	340 4 4	338 1 4	No data
Fetal incidence of stillbirths (%)	1.4	0.0	1.2	0.3	No data
Fetal incidence of pups found dead or presumed cannibalized (%) F1	1.14	1.43	1.18	1.18	

bw: body weight

[redacted]-[redacted], C.; Thiacloprid - A special one-generation dietary reproduction study in Sprague-Dawley rats
BCS report SA 10007; Doc ID M-403763-01-1; 2011-03-04

Rat strain: Sprague-Dawley, Sasco
Study conduct: 2010-2011 at [redacted], France
Treatment *via* diet, starting 10 weeks before mating,
Study with video-recording of parturition (main group & satellite group (1)) and blood sampling on GD20 (satellite group (1)) and at termination on the day after parturition (main group & satellite group (1)),
as well as blood sampling on GD 21 (satellite group (2)) and on GD22 (satellite group (3))

Dose (during gestation) [ppm] [mg/kg bw] *No. of dams P-generation (main group & satellite group (animals undergoing blood sampling on GD20 & at termination after parturition))*	0 **0** *30* *(24 & 5; pregnant: 20 & 5)*	800 **54** *30* *(24 & 6; pregnant: 23 & 5)*	**Historical control data**
Fetal incidence of stillbirths (%) - F1	2.4	**10.1**	No data
Incidence of stillbirths - F1 (dams with stillborns (> 2 stillborns) / total no. of pregnant dams)	5 (2) / 29 (not recorded in 5 pregnant dams)	15 (6) / 35 (not recorded in 2 pregnant rats)	No data

bw: body weight

[redacted], D.A; A reproduction study in rats to determine if administration of technical YRC 2894 from gestation days 18 to 21 will cause dystocia (Study number II)
BCS report 107640 Doc ID M-002127-01-1; 1998-05-04

Rat strain: CD Sprague-Dawley, Sasco
Study conduct: 1997 at [redacted], Kansas, U.S.
Treatment *via* oral gavage on GD18 to GD21

Dose # **[mg/kg bw]** *No. of dams #*	**0** *27*	**17.5** *9*	**35** *29*	**60** *25*	**Historical control data 1994-1997[A]**
Total no. of pups born stillborn	255 2	109 5	221 **28**	128 **34**	105 - 383 0 - 13
Mean no. of viable pups / dam at birth	12.0	11.3	8.7	7.4	
Fetal incidence of stillbirths (%)	0.8	**4.6**	**12.7**	**26.6**	0 - 3.9
Incidence of stillbirths (dams with stillborns (> 2 stillborns) / total no. of pregnant dams)	3 (0) / 21	2 (1) / 9	11 (4) / 22	7 (3) / 11	

[A]: Historical control data (HCD) from studies conducted in the same lab and in the same rat strain from 1994-1997 (in 1997 the rat strain was switched from Sprague Dawley to Wistar) were compiled in document M-509754-01-2 ([redacted], 2015).

#: Because of toxicity and death observed at the 35 and 60 mg/kg dose, the dose was lowered during the study to 17.5 mg/kg/day. Animals from all dose groups which had not reached gestation day 18, and thus had not previously received vehicle or thiacloprid, were dosed with 17.5 mg/kg/day of thiacloprid.

[redacted], P.; [redacted]: YRC 2894 - Special study for subacute oral toxicity in rats (Toxicokinetics in pregnant and non-pregnant rats)
BCS report 107640 Doc ID M-003821-01-1; 1998-07-14

Rat strain: Sprague-Dawley, Harlan Winkelmann, Borchen, Germany
Study conduct: 1997 at [redacted], Germany
Treatment *via* diet during mating and gestation in pregnant dams and during a comparable time period in non-pregnant female rats

Dose **[ppm]** *No. of pregnant dams* *No. of non-pregnant female rats*	**0** *5* *5*	**1000** *8* *12*	**Historical control data**
Total no. of pups Born Stillborn	54 6	72 15	No data
Mean no. of viable pups / dam at birth	9.6	7.1	No data
Fetal incidence of stillbirths (%)	11.1	**20.8**	No data
Incidence of stillbirths (dams with stillborns (> 2 stillborns) / total no. of pregnant dams)	3 (1) / 5	7 (2) / 8	No data

Stillborn pups:

Increased incidences of stillbirth were observed in some of the generation studies conducted on thiacloprid. The data are not consistent between studies, doses and generations. Also the concurrent controls differed widely between 0.6% in the 1st generation of the two-generation study ([redacted] & [redacted], 1997, M-001304-01-1) and 5.6% in the dose range finder for the two-generation study ([redacted] et al.,1995, M-000911-01-1); in one study with only 5 control animals even 11.1% stillborns were observed ([redacted] & [redacted], 1998, M-003821-01-1).

Slightly increased incidences were seen in the high dose of 43 mg/kg bw/day of the two-generation study ([redacted] & [redacted], 1997, M-001304-01-1) with 5.7 or 5.8%, respectively. The incidences of 4.0 to 4.5% in the low and mid dose of the 1st generation and in the low dose of the 2nd generation were only marginally above the historical control range (up to 3.9%), not clearly dose related and in case of the mid dose not consistent between generations, so that they are still considered to be in the range of the NOAEL. Increased incidences were also reported in the special one-generation study ([redacted], 1998, M-003820-01-1) with 5.2 and 7.6% at 20 and 68 mg/kg bw/day, in the 1-generation study with video recording of parturtition and blood sampling around parturition ([redacted] & [redacted], 2011, M-403763-01-1) at 54 mg/kg bw/day and in the 1-generation study with gavage dosing at gestation days 18-21 ([redacted], 1998, M-002127-01-1) with 12.1% and 26.6% after 35 and 60 mg/kg bw/day. The only marginally increased incidence of 4.6% in comparison to up to 3.9% in historical controls at 17.5 mg/kg bw/day was still considered to be in the range of the NOAEL for this parameter. The apparent increase of stillborn pups after 1000 ppm thiacloprid in the study by [redacted] & Schmidt (1998, M-003821-01-1) with 20.8% vs. 11.1% in controls was no real increase, but caused by the low no. of animals (stillborns in 7/8 dams vs. 3/5 dams in controls).

No increase in stillbirths was noted in the dose range finder for the two-generation study ([redacted] et al.,1995, M-000911-01-1) up to the high dose of 117 mg/kg bw/day and in the DNT study up to 40.8 mg/kg bw/day ([redacted]n, 2001, M-088059-01-1).

Due to the reasons discussed before in the chapter on reduced pup weights, a benchmark dose approach was not considered to be appropriate for this parameter either.

Therefore, the NOAEL of 17.5 mg/kg bw/day from the 1-generation study with gavage dosing at gestation days 18-21 ([redacted], 1998, M-002127-01-1) was taken as a basis for the derivation of the hazard specific AOEL for this parameter. Together with a safety factor of 100 this resulted in a hazard specific AOEL of 0.18 mg/kg bw/day.

Cannibalized and missing pups:

Also data on cannibalized and missing pups were not consistent between studies and doses. Clearly increased fetal incidences were observed in the high dose groups of the two-generation study ([redacted] & [redacted], 1997, M-001304-01-1) with of 6.03 and 4.47% (1st and 2nd generation) at 43 mg/kg bw/day and with 7.58% at 68 mg/kg bw/day in the special one-generation study ([redacted], 1998, M-003820-01-1).

In the dose range finder for the two-generation study ([redacted] et al.,1995, M-000911-01-1) there was no indication for cannibalized and missing pups up to the high dose of 117 mg/kg bw/day, and this is also true for the DNT study up to 40.8 mg/kg bw/day ([redacted]n, 2001, M-088059-01-1).

A benchmark dose calculation was also not considered appropriate in this case.

The hazard specific AOEL of 0.2 mg/kg bw/day for cannibalized and missing pups was therefore based on the overall NOAEL of 22 mg/kg bw/day for this parameter from the two studies (NOAELs: two-generation study: 23/22 mg/kg bw/day, special one-generation study: 20 mg/kg bw/day) **and a safety factor of 100.**